Clinical Approaches and Procedures in Cosmetic Dermatology

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Botulinum Toxins, Fillers and Related Substances

Springer

Clinical Approaches and Procedures in Cosmetic Dermatology

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The series “Clinical Approaches and Procedures in Cosmetic Dermatology” intends to be a practical guide in cosmetic dermatology. Procedures in cosmetic dermatology are very popular and useful in medicine, indicated to complement topical and oral treatments not only for photodamaged skin but also for other dermatoses such as acne, rosacea, scars, etc. Also, full-face treatments using peelings, lasers, fillers and toxins are increasingly being used, successfully substituting or postponing the need for plastic surgeries. Altogether, these techniques not only provide immediate results but also help patients to sustain long-term benefits, both preventing/treating dermatological diseases and maintaining a healthy and youthful skin. Throughout this series, different treatments in cosmetic dermatology will be discussed in detail covering the use of many pharmacological groups of cosmeceuticals, the new advances in nutraceuticals and emerging technologies and procedures.

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With 342 Figures and 21 Tables

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ISSN 2511-820X ISSN 2511-8218 (electronic)
ISBN 978-3-319-16801-2 ISBN 978-3-319-16802-9 (eBook)
ISBN 978-3-319-16803-6 (print and electronic bundle)
https://doi.org/10.1007/978-3-319-16802-9

Library of Congress Control Number: 2018947624

This Springer imprint is published by the registered company Springer International Publishing AG part of Springer Nature
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

When I received the invitation from Maria Claudia Almeida Issa (M.D., Ph.D.) and Bhertha Tamura (M.D., Ph.D.) to write one of the chapters of this marvelous book, I was very happy. Later, the mission to write the prologue of this book – whose editors, having to their credit numerous publications in the international scientific field of cosmetic dermatology, dignify the Brazilian dermatology – left me extremely honored. In this book, some of the leading medical doctors and research scientists from Brazil and a few from other parts of the world present their professional experience in the field of cosmetic dermatology.

Cosmetic dermatology is constantly evolving. Procedures for rejuvenating the skin are actively sought by people nowadays. As dermatology grows as a specialty, an increasing proportion of dermatologists will become proficient in performing different procedures. Even those who do not perform cosmetic procedures must be well versed in the details to be able to guide their patients.

There have been numerous major advances in the field of cosmetic dermatology, including the use of botulinum exotoxin, soft tissue augmentation, chemical peels, cutaneous lasers, and light source–based procedures, and the state of the art of dermatologic and cosmetic prescriptions have been developed and enhanced by dermatologists and plastic surgeons.

Botulinum toxin and fillers are routinely used to bring youthful appearance. Over time, a number of indications and different techniques have been developed, promoting even better results. The knowledge of anatomy related to toxin and filler applications is fundamental to achieve good results with safety. This volume covers all these topics and would serve as a good reference for doctors who already handle these procedures and for those who are planning to begin.

The series "Clinical Approaches and Procedures in Cosmetic Dermatology" offers a wonderful and embracing text. It was a pleasure to contribute to this unique book, along with so many renowned authors.

This work project is certainly a text of inestimable value for those who wish to deepen their knowledge in the field of cosmetic dermatology.

Hoping that you will enjoy learning from this book!

Mônica Manela Azulay

Preface

Nowadays, life expectation has increased, and for a better quality of life, people are looking for ways to enhance physical beauty and aesthetics and improve health. Dermatologists and plastic surgeons who work in the field of cosmetic dermatology can help patients to maintain a healthy and youthful skin. Topical and oral treatments associated with full-face procedures using peelings, lasers, fillers, and toxins are increasingly being used, successfully substituting or postponing the need for plastic surgeries.

This series of books is very special among those already published, as it encompasses all topics related to this area of dermatology. All authors are experts in the field of cosmetic dermatology. Literature review and its correlation with authors' experience is a differential feature of this work.

This work has been divided into four volumes due to the breadth of the topics, which cover skin anatomy, histology, and physiology; patients' approaches; common cosmetic dermatosis; topical and oral treatments; and cosmetic procedures.

Among cosmetic procedures, patients recognize botulinum toxin and fillers as those which bring the best satisfaction in short term. In this volume, authors report minutely the use of botulinum toxin, fillers, and collagen biostimulators. They describe the anatomy related to the use of botulinum toxin and fillers, explaining different techniques according to the region to be treated. Indications, contraindications, and management of possible complications are also discussed.

The series "Clinical Approaches and Procedures in Cosmetic Dermatology" was prepared to be a guide in cosmetic dermatology. It can be considered a complete encyclopedia in the field of cosmetic dermatology, and, for this reason, it is extremely useful for those who already work with cosmetic dermatology as well as for beginners in this field. This is a new reference work project, and we are delighted to have you on board.

August 2018
Brazil

Maria Claudia Almeida Issa
Bhertha Tamura

Acknowledgments

When we were invited to write a book on cosmetic dermatology, we could not imagine the dimension of this work project.

After drawing the program content, we realized that a comprehensive handbook series in this field would be built. Nevertheless, it would not be possible without the efforts and experiences of our invited partners. They deserve our acknowledgment and our deep appreciation.

To all collaborators, our very special thanks.

Maria Claudia Almeida Issa
Bhertha Tamura

Contents

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Dr. Maria Claudia Almeida Issa is among the leading dermatologists in Brazil and Latin America, especially in what regards cosmetic dermatology. Dr. Issa holds a Ph.D. in Dermatology from the Federal University of Rio de Janeiro (2008) and an M.Sc. in Dermatology from the Fluminense Federal University (1997). She is currently an Associate Professor within the Department of Clinical Medicine – Dermatology, at the Fluminense Federal University, Brazil. Her research focuses on photodynamic therapy, non-melanoma skin cancer, lasers, photoaging, and dermal remodeling. Finally, Dr. Issa has an extensive clinical experience in cosmetic dermatology, being registered as a dermatologist at the Brazilian Society of Dermatology since 1995 and member of the American Academy of Dermatology.

Dr. Bhertha Tamura holds M.Sc. and Ph.D. degrees in Dermatology from the Hospital das Clínicas de São Paulo – Universidade de São Paulo. She is a specialist in general surgery and dermatology. She is also a counselor for the Brazilian Society of Dermatologic Surgery and the Brazilian Society of Dermatology, member of the Scientific Commission of the Brazilian Society of Dermatology, Chief of the Department of Dermatology at the Complexo Hospital Heliopolis (São Paulo, Brazil), and member of several international dermatological societies.

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Part I

Anatomy View, Indications, Complications, and Management of Botulinum Toxin

Facial Anatomy View for Aesthetic Botulinum Toxin Injection

Bhertha Tamura

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_1

Abstract

Anatomy has been focused since the first papers of crow's feet and frown lines treated with botulinum toxin (BT). The knowledge and deep understanding of the synergism and antagonism of the muscle contraction still generates a lot of doubts and is essential for an excellent outcome after the injection of BT. We already know that the patients, most of all, are wondering if they will have a natural look after the treatment. Several authors have published the importance of having an individualized analysis in order to achieve great results at absolutely low risk of asymmetries or other complications.

Keywords

Facial anatomy · Botulinum toxin injection · Muscle contraction · Aesthetic

Introduction

If we are chasing a differentiated result for very special patients, it is absolutely imperative that we can classify each muscle, pair of muscle, their location, their action, and their role in the mimics.

There are beauty concept differences between cultures and ethnics, but basically the aim is to get a natural result with a maximum relaxation of the muscles that perpetrates the facial lines. Recently many authors also consider the prophylaxis of the wrinkles when the patients have hyperkinetic movements at specific areas of the facial mimics.

There is not a rule or a standard technique for the injection of botulinum toxin (BT). To reach a natural result, it is necessary to understand facial muscle dynamics.

Facial Muscles

We need to have in mind the synergistic and antagonistic action of the muscle complexes at the face, but first of all, know exactly their location, function, origin, and insertion (Altruda Filho et al. 2005; Gardner et al. 1978; Haddock et al. 2009).

The frontalis and occipitalis venter of the *frontalis* muscle originates at the *galea aponeurotica* of the skull and inserts at the *orbicularis oculi* muscle. At its anterior portion, the muscle divides in pair and is joined by the superficial fascia. This pair can get together at the medial part of the frontal region near the hair implantation; they can extend in different ways, and they are responsible for different patterns of the frontal mimics from one individual to the other changing the botulinum toxin dosage and sites of injection depending on the extension of the muscle. It raises the eyebrows and wrinkles of the frontal area. Figure 1 shows a very good example of the galea aponeurotica between the muscle bundles, area that does not need BT injection in patients that have this muscle pattern.

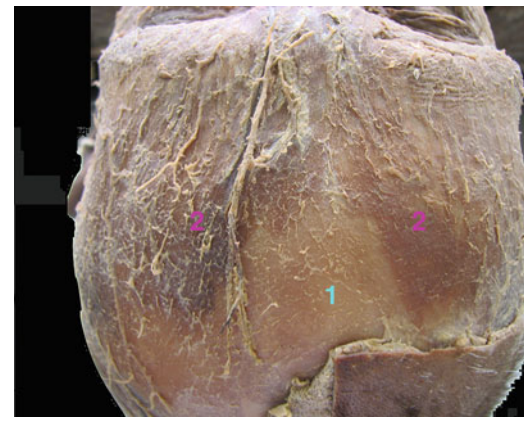

Fig. 1 Figure 1 shows a very good example of the *galea aponeurotica* between the muscle bundles, area that does not need BT injection in patients that have this muscle pattern

Fig. 2 The *corrugator supercilii* pulls the eyebrow together and downward leading to the glabellar hyperkinetic lines – the frown lines

Corrugator Supercilii

The *corrugator supercilii* originates (Gardner et al. 1978) at the internal and anterior orbital margin, superior and medial to the nose, and inserts at the *frontalis* muscle and the superciliary skin. Its contraction pulls the eyebrow together and downward leading to the glabellar hyperkinetic lines – the frown lines (Fig. 2).

They are intimately related to the orbital septum and to the *palpebrae* elevator muscle. And this is the most frequent reason for the lid ptosis after BT treatment near the glabellar area, and this proximity is shown on Fig. 3.

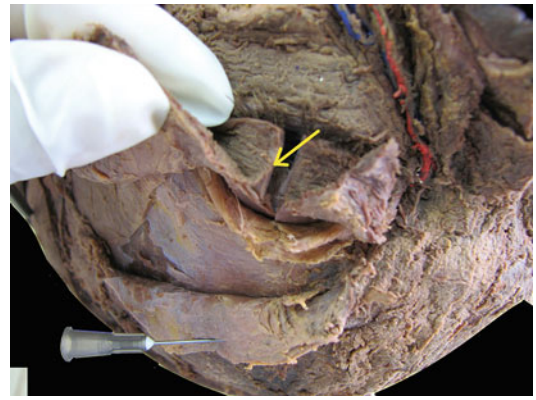

Fig. 3 The corrugator muscles are intimately related to the orbital septum and to the *palpebrae* elevator muscle. The *yellow arrow* shows the *levator palpebrae* muscle

Procerus Muscle

The *procerus* muscle originates (Haddock et al. 2009) from the nasal bone at the glabella and inserts at the forehead skin. This muscle pulls down the medial part of the eyebrow and is responsible for the horizontal wrinkles at the glabellar area (Fig. 1) and when long or hypertrophic is also responsible for the nasal horizontal lines that are a challenge for the cosmetic treatment.

Orbicularis Oculi

The *orbicularis oculi* muscle (Altruda Filho et al. 2005; Gardner et al. 1978; Haddock et al. 2009; Sobotta and Becher 1977) originates from the palpebral and orbital ligament and joins to the horizontal fibers of the *nasalis* muscle (Fig. 4) and inserts at the lateral palpebral *raphe*. It is a circular muscle that acts like a sphincter, and it arises from the nasal part of the frontal bone, from the anterior surface and borders of a short fibrous band, and from the frontal process of the maxilla in front of the lacrimal groove. The lateral portion of the *orbicularis oculi* pulls down the eyelid. It is responsible for the closure of the eyelids and the crow's feet lines.

The *orbicularis oculi pars inferior orbitalis* closes the lids and squeezes them against the eye and originates at the lacrimal bone, frontal process of the maxillae, the skin around the orbit and is also responsible for the lower lid lines.

This muscle can be wide in some individuals; it can reach the eyebrow and cover the malar area being responsible of the very long crow's feet lines

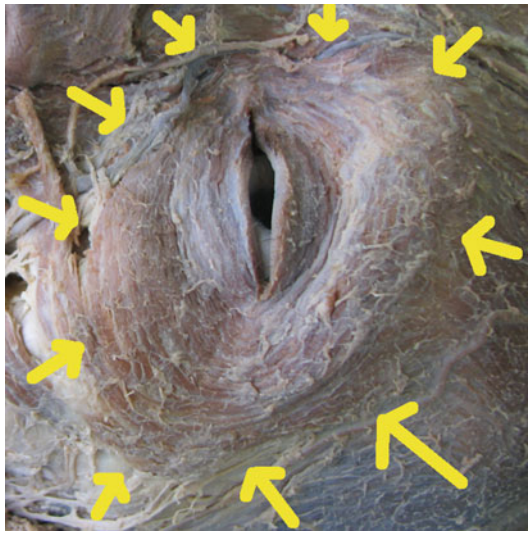

Fig. 4 Orbicularis oculi and its wide distribution around the eyelid

that can go on until the preauricular and also to the inferior temporal area. The perioral and periorbital round muscle acting like a sphincter has a different response to BT; one injection does relax that part of the muscle, not all of it. If we inject botulinum toxin A, for example, it will relax about 1 cm at that location and not the role muscle as a unit.

When we analyze these wrinkles for BT injection, we understand that they need to be treated per area, as at the crow's feet, medial ocular or nasociliary area adding the *procerus* and *nasalis* muscle contraction and lower eyelid lines separately. These lines can also extend inferiorly and laterally until the zygomatic arch and the eyebrow superiorly and medially with a synergetic action of the corrugators.

We need to consider the ocular fad pads (improving or worsening their extrusion), the lymphatic drainage (edema), and the lacrimal gland (dry eyes) as a consequence of an excessive BT injected in too many points or with a high dosage.

Temporalis Muscle

The *temporalis* muscle (Sobotta and Becher 1977) is a mastication muscle, not a mimics muscle. It lies at the temporal fossa, covers the temporal bone, and is superior to the zygomatic arch. Botulinum toxin to relax this muscle is indicated for patients with bruxism who have hypertrophic masseter added to a temple hypertrophy. BT is also indicated to relax the temporalis muscle for migraine treatment. The temporalis muscle arises from the deep part of the temporal fascia and the temporal *fossa* (superficial layer) passing medially to the zygomatic arch and the deep layer arising from the *sphenoidal tuberculae* and inserting onto the margins and medial side of the *coronoid* process and the temporal crest of the mandible. It elevates and retracts the mandible.

Pterygoid Muscle

The lateral *pterygoid* or external *pterygoid* is a muscle of mastication with two bundles. It lies superiorly to the medial pterygoid. At the lower part of the temporal area we consider the medial and lateral *pterygoid* muscle (superior and inferior bundle). The superior bundle of the *pterygoid* lateral muscle originates from the lateral part of the lateral sheet of the *pterygoid* process and the *facies temporalis alaris majoris ossis sphenoidalis* and inserts at the temporomandibular joint. The inferior bundle originates at the lateral facies of the lateral *pterygoid* plate, pyramidal process of the palatine, and the maxillary tuberosity inserting at the *fovea pterygoidea* (Altruda Filho et al. 2005; Haddock et al. 2009; Sobotta and Becher 1977). The muscle protracts, moves laterally, and stabilizes the articular disc and the opening of the mouth. The medial *pterygoid* muscle originates from the facies lateralis of the *pterygoid* process, *fossa pterygoidea*, and the pyramidal process of the palatine and the maxillary tuberosity inserting at the medial side of the mandible angle and elevates the mandible and acts synergistically with the masseter (Tamura 2010a, b).

Nasalis and Depressor *Septi Nasi*

At the nasal region, the *nasalis* muscle has two bundles, one that inserts at the nasal *alae* (dilates the nostrils) and the transversal area of the nasal

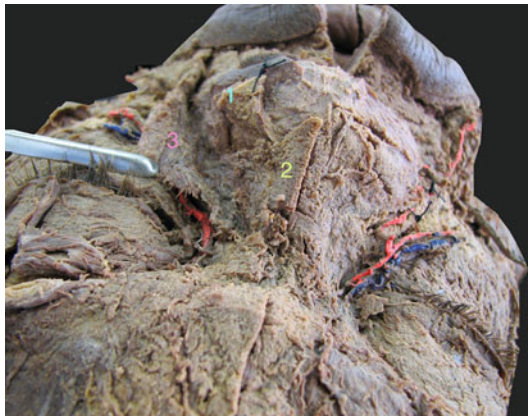

Fig. 5 At the nasal region, the *nasalis* muscle has two bundles, one that inserts at the nasal *alae 1* (dilates the nostrils) and the transversal area of the nasal dorsum – the dilator *naris* muscle (compress the nostrils) *2* and number *3 is the levator labii superioris alaeque nasi muscle*

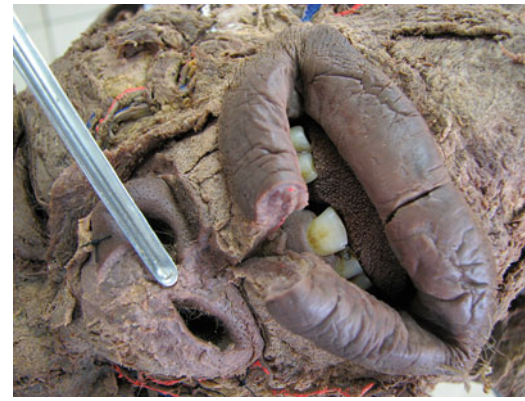

Fig. 6 *The depressor septi nasi* is a vertical *fasciculus* from the maxilla superior to the central incisor tooth, and it passes upward along the median line of the upper lip and inserts into the mobile part of the nasal septum

dorsum – the dilator *naris* muscle (compress the nostrils) (Fig. 5). The *depressor septi nasi* (Fig. 6) is a vertical *fasciculus* from the maxilla superior to the central incisor tooth and it passes upward along the median line of the upper lip and inserts into the mobile part of the nasal septum. It interacts with the movement of the nasal tip and the upper lip, shortening the upper lip and depressing the tip of the nose during the smile. We inject BT in the nasalis muscle (transverse part) to minimize the bunny lines and in the alar part (dilator naris) to control the dilation of the nostrils and the size of the nostrils opening. The injection in the depressor septi nasi muscle softens the wrinkle and retraction of the upper lip, especially concerning the gummy smile with a short vertical length of the upper lip (Tamura 2010a, b).

Musculus Levator Labii Superioris Alaeque Nasi

The levator labii superioris alaeque nasi muscle (Fig. 7) elevates the superior lip and the nasal *alae*, helps to dilate the nostrils, originates from the frontal maxillae process, and inserts at the nostrils and the superior lip. The treatment of this muscle is a key point for the success when we are treating the wide and complete gummy smile that shows the molar teeth. Botulinum toxin injected at this sight smoothens the nasolabial fold. We suggest that the injection site should be at the bundle that inserts at the nostril, medial to an imaginary line between the nasal area and not laterally (Tamura 2010a).

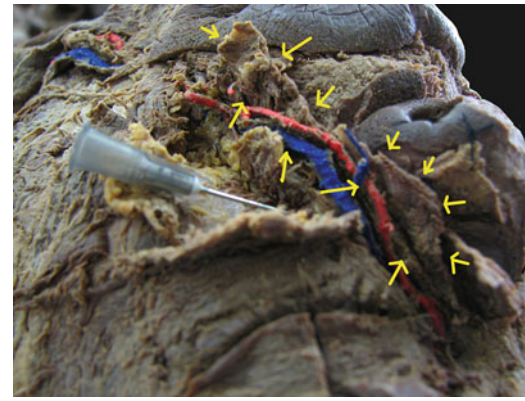

Fig. 7 *The levator labii superioris alaeque nasi muscle* elevates the superior lip and the nasal *alae* and helps to dilate the nostrils

Levator Labii Superioris

The *levator labii superioris* (Sobotta and Becher 1977) elevates the superior lip and originates at the infraorbital margin of the maxilla foramen inserting to the superior lip. Relaxing this muscle

we treat the gummy smile at the medial part of the superior lip; relaxing it too much leads to patient dissatisfaction, so lower BT dosage injection is advisable

Zygomaticus Minor and *Major*

The muscle *zygomaticus minor* pulls the upper lip upward and outward and is innervated by the facial muscle (Fig. 8). It originates at the zygomatic bone posterior to the zygomaticomaxillary suture and inserts at the *orbicularis oris* of the upper lip and with the *zygomaticus major* muscle draws the lips corners upward and outward. The *major* originates from the temporal process of the zygomaticus bone and inserts at the angle of the mouth (Altruda Filho et al. 2005; Sobotta and Becher 1977; Tamura 2010a, b). It is very important to be precise to not inject in these muscles unless the drop and relaxation of the smile is the aim, for instance, when we want to give symmetry to a patient with facial paralysis.

The *risorius* muscle (Albinus muscle, Santorini muscle) pulls outward and laterally the angle of the mouth lengthening the *rima oris. Risorius* muscle originates from the *platysma*, the masseter, and the *fascia parotidea* and inserts at the *orbicularis oris* and the skin at the corner of the mouth. *Zygomaticus major* and minor as well as risorius can be relaxed with BT to soften the nasolabial fold and the wrinkles on the cheek area. When these muscles are treated certainly the smile will change drastically.

Musculus Levator Anguli Oris, Levator Labii, and *Orbicularis Oris*

The muscle that elevates the mouth angle is the *levator anguli oris*, which originates from the canine *fossa*, deeply to the *levator labii*, and inserts at the mouth angle. Around the lips, the *orbicularis oris* (Fig. 9) sits at the mouth *rima*, very superficially and inserts at the skin and the lips mucosa (Altruda Filho et al. 2005; Gardner et al. 1978; Sobotta and Becher 1977). This muscle contracts as a sphincter, and the BT injection does relax only parts of it and not all of it. If we are wondering to treat the upper and the lower lip, injections must be apart and even along the upper lip; mostly injections are made equally one side and the other side. As shown in Fig. 9, we must remember that it is very superficial and thin, though the injections must be also very superficial and near the vermillion of the lip. The superficial injection also avoids relaxing the other muscles of the lower face as the elevators (*zygomaticus major* and *minor*, *levator labii superioris*, *levator labii superioris alaeque nasi* muscle), the *depressors labii* (with *mentalis* muscle), and the mouth angle (*depressor anguli oris* muscle).

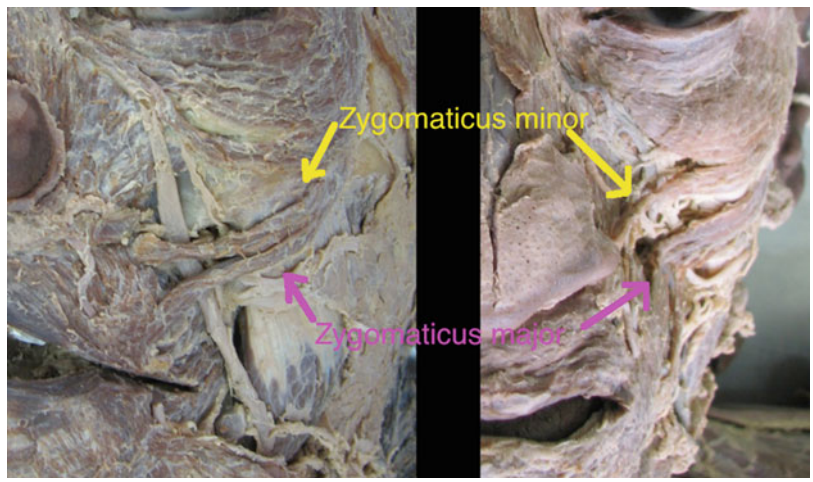

Fig. 8 *Musculus Zygomaticus minor and major*

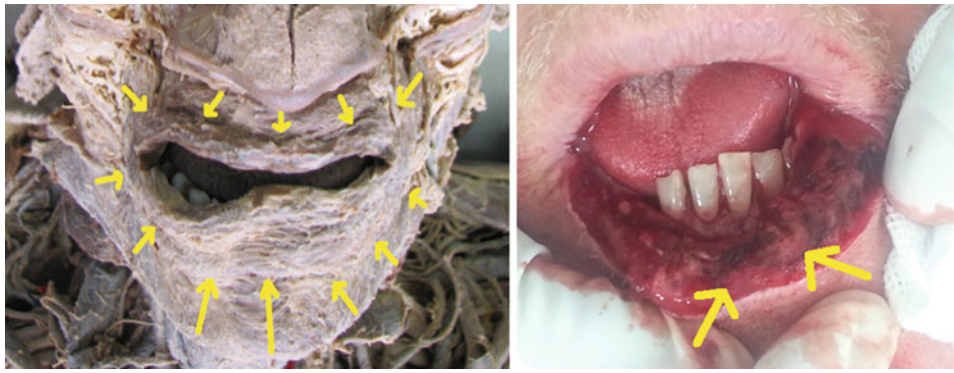

Fig. 9 Around the lips the *orbicularis oris* sits at the mouth *rima*, very superficially and inserts at the skin and the lips mucosa

Buccinator Muscle and Masseter

The cheek muscle, buccinator is located posteriorly to the oral fat and originates from the posterior pterygomandibular *raphe* and the posterior portion of the alveolar portion and inserts at the angle of the mouth, interspersing with portions of the *orbicularis oris* (Altruda Filho et al. 2005; Gardner et al. 1978; Sobotta and Becher 1977). Buccinator flattens the cheek, keeps its tension, retracts the angle of the mouth and is part of the mastication muscle group also helping to suck and whistle. It is intimately related to the tongue and the *orbicularis oris* muscle keeping the food between the teeth and the oral cavity. When BT relaxes this muscle or its paralysis due to a Frey's syndrome, the food accumulates at the oral vestibule. We need to remember this muscle when treating the masseter with BT to not inject too deep at the buccinator muscle.

Masseter (Fig. 10) lies at the parotideomasseteric area and does have a superficial and a deep bundle. The superficial part originates at the inferior margin of the two-thirds anterior zygomatic arc and the deep portion originates at the internal side of the posterior third and the deep bundle inserts along the lateral branch of the mandible; its main action is to elevate the mandible and is considered as the most powerful muscle of the human body. Understanding masseteric hypertrophy with or without bruxism is a key for the new concept of contouring the lower face.

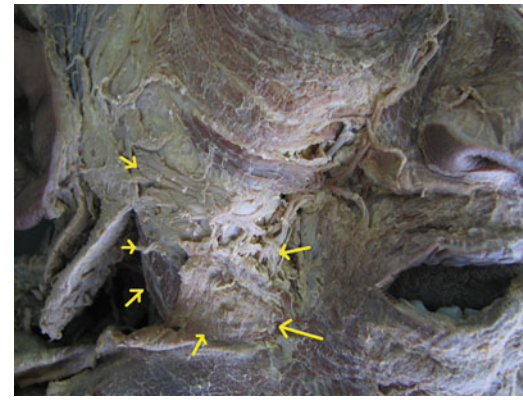

Fig. 10 Masseter muscle lies at the parotideomasseteric area and does have a superficial and a deep bundle

Depressor Anguli Oris (DAO), *Depressor Labii*, and *Mentalis*

The muscular layer of the chin comprehends the *depressor anguli oris*, the *depressor labii*, and the mentalis muscle (Altruda Filho et al. 2005; Gardner et al. 1978; Sobotta and Becher 1977). The origin of the *depressor anguli oris* is the base of the anterior mandible (first molar to the mental tubercle), and it inserts at the mouth angle and other lip muscles. It is the most superficial of the group and the most lateral of the mandible (reference for BT injection) which pulls down the corner of the mouth.

The *depressor labii* originates at the base of the mandible (over to the origin of the *depressor*

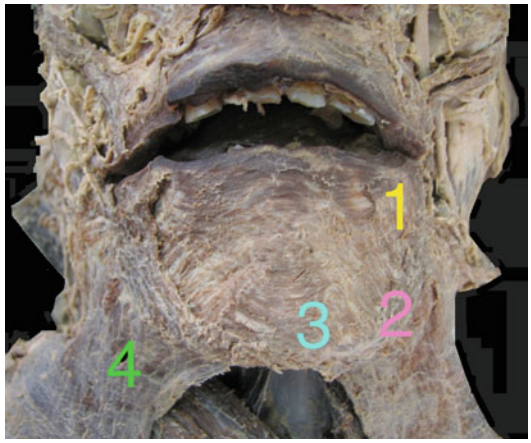

Fig. 11 View of the chin muscular complex: *1* depressor anguli oris; *2* depressor labii; *3* mentalis; and *4* platysma

anguli oris) and inserts at the inferior lip, and the *mentalis* muscle originates at the mental *fossa* (cranial to the mental tubercle) under the central incisive and lateral teeth and inserts at the chin skin, which wrinkles the chin and puckers the lower lip (Fig. 11). The shape of the *mentalis* and its decussation can differ individually. For this reason, sometimes it is necessary to re-treat some area isolated to improve the natural effect of the relaxation.

At the oral commissure the so called marionette lines comes out by the contraction of the DAO, *depressor labii* and the *platysma* muscle and flaccidity of the SMAS (superficial muscle aponeurotic system).

The *platysma* muscle (Altruda Filho et al. 2005; Sobotta and Becher 1977; Tamura 2010a, b) (Fig. 11) does have some action with the facial muscle as it stretches and pulls downward and outward the neck skin with the help of the DAO laterally and downward at the anterior jaw line. It originates at the sternoclavicular joint, clavicle, and scapular acromio and inserts at the base of the mandible and some fibers at the mouth angle. This muscle has a strong portion and runs to the anterior part of the chin toward the lip reaching the so-called modiolus complex. *Platysma* might sometimes spread laterally until the mandible angle and the dynamic evaluation of its extension are essential for the BT injection plan.

Take Home Messages

- The knowledge and deep understanding of the synergism and antagonism of the muscle contraction still generates a lot of doubts and is essential for an excellent outcome after the injection of BT.
- Patients look for a natural look after the injection of botulinum toxin (BT).
- Several authors have published the importance of having an individualized analysis in order to achieve great results at absolutely low risk of asymmetries or other complications.
- There is not a rule or a standard technique for the injection of botulinum toxin (BT). To reach a natural result, it is necessary to understand facial muscles dynamics.

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Botulinum Toxin for Forehead

Beatriz Rosmaninho Caldeira Avé

Contents

Abstract

Today botulinum toxin is considered a gold standard cosmetic procedure for the frontal lines, and although different brands have been introduced to the market, understanding the individual mimics and real muscle extension lead to a differentiated natural outcome. For good and beautiful features, the patient must be evaluated dynamically and other issues must be considered such as the brow level, the facial and rhytids asymmetry as well as muscle hypertrophy and extension. Based on these individuality, the doctor might be comfortable to rapidly classify the lines and predict the distribution of the sites to determine the amount of botulinum toxin to be injected to each one. The physician's aim is a natural look and a long-term treatment, not only to minimize the rhytids, but to prevent the deep forehead lines. Different clinical presentations require an individual analysis and planning.

Keywords

Botulinum Toxin · Forehead · Frontal · Forehead Lines · Rhytids

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_2

Introduction

An increasing number of patients seek minimal invasive procedures. One of the most requested procedures is the treatment with botulinum toxin type A (BoNTA). The treatment of dynamic rhytids and lines with BoNTA is effective and leads to a high rate of improvement with a rapid onset and long duration of action (longer than 4 months for some patients) (Carruthers and Fagien 2004).

The facial movements result from the contraction of the facial muscles creating transient wrinkles and furrows perpendicular to the direction of the muscular contraction. Hyperfunctional lines are common in the forehead on individuals that are highly expressive. The horizontal lines are caused by the contraction of the frontalis muscle, and its contraction might be an important tool to raise a ptotic brow or eyelid to improve the visual field especially concerning elderly patients. Frontalis contraction may also be an emotional response signaling surprise or interest and the forehead lines may give an impression of aging (Cox et al. 2003).

The use of BoNTA to improve the aesthetic appearance of horizontal forehead lines is optimized when clinicians take into account variations in frontalis muscle function, position, and extension as well as considering the anatomy of the brow, its height and shape and then a proper injection technique can be chosen when they devise individualized treatment regimens.

The injection of BoNTA produces durable improvement in the appearance of moderate to severe horizontal forehead lines. It is like an "educational process," leading the patient to lessen the strength of the muscle action through the years. Dose and injection technique must be adjusted and individualized based on the variability of the anatomy and function/volume of the muscles in the forehead and upper face as well as on the patient goals (Cox et al. 2003; Finn and Ellen-Cox 2005). Optimal aesthetic outcomes can be achieved by skillfully balancing the opposing effects of the frontalis muscle and its intricate interactions with the procerus, corrugator supercilii, depressor supercilii, and orbicularis oculi muscles. It must be treated carefully since this is the only one that raises the brow and all other muscles are depressors.

Anatomy and Treatment Plan

The frontalis muscle elevates the brow and is associated with the development of the horizontal forehead rhytids. The goal in treating the forehead is to maintain some movement of the frontalis muscle and avoid complete paralysis, resulting in natural mimics without compromising the height, position, or shape of the brows and the eyelid.

There are significant challenges for the inexperienced practitioners for several reasons as listed below:

(Carruthers and Fagien, 2004) Individual variability in frontalis structural anatomy
(Cox et al. 2003) Individual variability in frontalis functional (habit/expression) anatomy
(Finn and Ellen-Cox 2005) Difficulty in treating it isolatedly because of the potential for the eyebrow ptosis on one hand and failure to efface lines on the other
(Tamura 2002) The potential for over treating and producing a stiff and an artificial appearance

The frontalis is a large, vertically oriented muscle, and there is a considerable individual variation of its structural features. Although usually depicted as two somewhat fan-shaped bands, the midline fibers overlap substantially in some individuals. Forehead shape also differs between individuals in both vertical and horizontal directions. In addition, some individuals have numerous fine forehead lines, whereas others have a single deep horizontal furrow as described by Tamura (2002).

These anatomic features and their variations play an important role in determining the treatment plan for horizontal forehead rhytids. The identification and classification of the patterns (Braz and Sakuma 2010) of the frontalis muscle contraction provide an individualized approach for each patient, which is one of the most important pillars of a successful treatment outcome (Lorenc et al. 2013).

The frontalis interacts with procerus, corrugators, and orbicularis oculi muscles and it is

localized at the forehead, superiorly to the eyebrows and inferiorly to the scalp. It originates at the aponeurotic galea near the coronal suture, inserting on the supraciliary ridge of the frontal bone and onto fibers of the procerus, corrugator, and orbicularis oculi muscles and it is vertically oriented.

Concerning the areas to be treated and the sites of the injections, we need to analyze the functional portion (pars that actually is responsible for the rhytides) of the muscle and then, treat preferably only the upper half of the forehead maintaining the brow mobility but minimizing the wrinkles.

Braz et al. published a review analyzing the muscular contraction pattern, and it was classified according to the predominant hyperkinetic area that was observed at a frontal muscle's maximum contraction. Three major contraction patterns were identified: total, medial/central, and lateral. In 50.6% of cases, the total pattern was observed: the horizontal rhytids observed in the center of the forehead extend laterally beyond the mid-pupillary line, up to the end of the brows (Fig. 1a). The medial pattern was observed in 25.3% of cases: the horizontal rhytids are concentrated in the central region of the forehead, predominantly between the mid-pupillary lines (Fig. 1b). The lateral pattern was observed in 24% of the cases: the horizontal rhytids prevailed on the sides of the forehead, mainly occurring laterally to the mid pupillary line (Fig. 1c).

Technique and Doses

We suggest the techniques and dosages at this chapter based on onabotulinum A. There are differences between ona, inco, and abobotulinum toxins and they are considered unique and not interchangeable. The FDA mandated in 2009 that all BoNTA product labels clarify that the potency units for each product are specific to each preparation. However, in common practice many providers have used a dose equivalent ratio of Botox® (onabotulinum) to Dysport® (abobotulinum) of 1:2, 5, or 1:3, as suggested in the literature to simplify dose comparisons when switching between products. Use of this conversion ratio is most appropriate when considering the safety profile of the products, not its efficacy. Clinical observers also describe a 1:1 between onabotulinum toxin and incobotulinum toxin (Xeomin®). Doctors will develop a familiarity

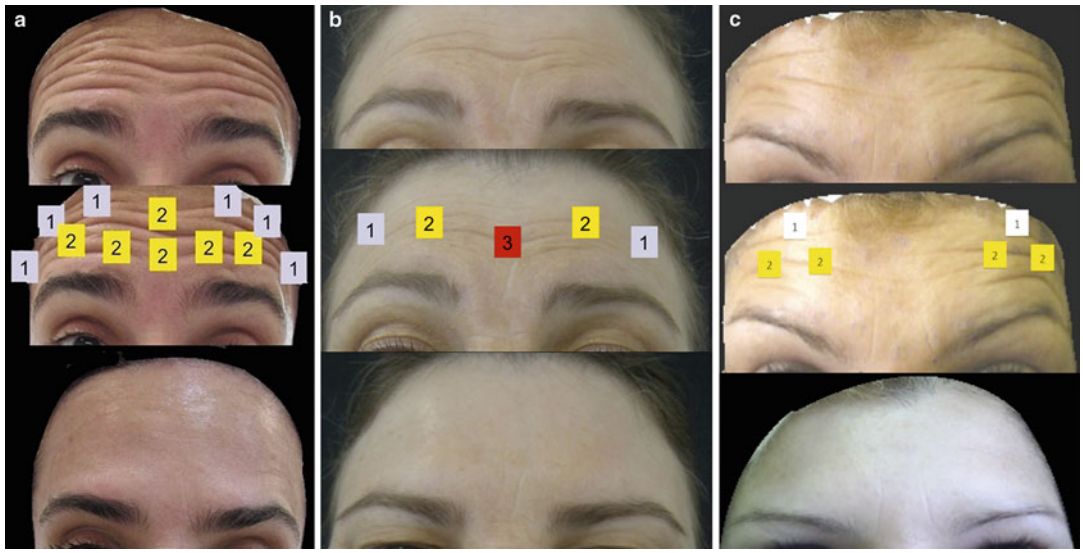

Fig. 1 Different patterns of forehead muscle contraction, sites of botulinum toxin (BT) application, and doses of BT indicated for each site: (**a**) forehead total contraction pattern, (**b**) forehead medial/central contraction pattern, (**c**) forehead lateral contraction pattern

with the efficacy and behavior of each formulation of BoNTA through experience.

Currently, no data from well-controlled studies support the idea that volume of injection contributes significantly to diffusion. In general, physicians should choose a dilution that minimizes the likelihood of diffusion to neighboring muscle groups. We prefer a dilution of 1 ml of saline solution for a bottle of 100 U of onabotulinum toxin.

Topical anesthesia like creams, ice, or vibration anesthesia can help reducing minimal discomfort associated with the injections. Plastic, single-use syringes are recommended; the insulin syringe, with no potential space at the hub, may waste less solution. A 30-gauge needle is standard, but several panel members have reported on their experiences of reduced pain with the use of a 32 gauge needle. The choice of syringes depends primarily on the practitioner preference.

The number of injection sites varies based on the aesthetic goals and the individual characteristics. The number of injection points range from two to 12 or more depending on the technique regarding recently described microdroplets® BoNTA injections. Regardless of the number of injection sites, it is important that all injections remain 1 to 2 cm above the orbital rim to reduce the potential for a brow ptosis especially in individuals who wish to maintain or elevate the brow position. For women, care should be taken to assess the natural position and shape of the eyebrows and whether they are plucked or tattooed. The injections should avoid the first horizontal line above the brows. In addition, filler may be needed to be injected to soften the inferior lines, where botulinum toxin type A injections should be avoided.

The total starting dosage for women varies between 10 and 20 U, preferable the lower dose. For men, we use to start with 20 U to 30 U. Gender differences in muscle mass allow a higher starting dose in men. In addition, men accept and prefer a flatter, less arched brow. Typically, 1 to 5 U are injected in each site, with higher doses used in men. As with other areas, the amount of units depends upon the pretreatment aesthetic analysis. Skin thickness and texture may also contribute to decide the dosage to be injected. Subcutaneous (SC) (Gordin et al. 2014) injection of botulinum toxin A (BoNTA) is equally effective in achieving paralysis of the underlying frontalis muscle as well as intramuscular BoNTA administration. In addition, the SC injection may result in less pain for the rejuvenation of the upper face with botulinum toxin A. For patients with a very thin skin, injections should be made preferably superficially at the subcutaneous plane.

Adverse Effects

Although the majority of side effects are attributed to technique and dosage, there may also be differences between the diffusion of the neurotoxins. Diffusion properties have clinical relevance where precise location of effect is desirable to avoid side effects like asymmetry, eyelid ptosis, blurred vision, and brow ptosis. The most common adverse effect is bruising because of the mechanical skin trauma.

Unsatisfactory results in the frontalis usually are due to:

- Total muscle palsy (mask face), with loss of the brow movement
- Brow ptosis
- Asymmetric muscle relaxation
- Wrinkle persistency

Aesthetics Considerations

Patient evaluation within the framework of facial enhancement will lead to a treatment plan that incorporates the creation of harmony and balance rather than wrinkle removal in isolation.

Aesthetic planning involves understanding and assessing the patient's desires and preferences in the context of an overall treatment plan. These desires and expectations must be discussed with patients before the treatment, since after then, an unattended desire seems like excuses. An extensive discussion before treatment and explanation about the mechanism of action, effects, and duration can increase the likelihood of a successful outcome.

The facial mimics muscles do not act in isolation but have a complex anatomic and physiologic

interaction. The treatment of the glabellar lines, the "crow's feet," or the forehead lines can alter the eyebrow shape and position, which are considered as main parameters to aesthetic evaluations of the upper face.

Gender differences are important for the eyebrow shape: typically, women have a more arched eyebrow, which is considered aesthetically pleasing, and the male brow is flatter. Older patients may use the frontalis to increase their visual field. Therefore, caution is needed in these circumstances.

Patients with severe, deep wrinkles may have unrealistic expectations for the outcome of botulinum toxin type A treatment. BoNTA might have an important prophylactic effect; when indicated at early stages of strong facial mimics and powerful muscle contraction, it is better to treat patients with hyperdynamics lines but do not have static lines yet.

Photographing the patient before treatment and at follow-up is also useful in documenting the effect, the duration, and in planning any touch-ups or new treatments.

The typical interval for retreatment is 3 to 4 months. The duration of the effect might depend on the total unit dosage injected, which is supported by some published data for both men and women.

Planning and Treating

- Assess facial expression at rest and during animation. Distribute the injection sites according to the mimics and muscle contraction of each individual patient.
- Evaluate the range of motion of the frontalis muscle and the rhytides lines.
- Palpate muscles during rest and contraction if possible.
- Assess brow position. In women, be sure to consider whether the brows have been plucked or tattooed. Assess for asymmetries in brow position. As few as one or two injections high up in the forehead can help to bring the eyebrows into symmetry.
- Evaluate any asymmetries and assess potential effects of botulinum toxin type A injection.
- It is not necessary to insert the needle, touch the periosteum and "back off" to inject BoNTA as suggested few years ago; however, the desired effect on brow position will dictate the site, the deepness and the right muscle for the injection.
- Be cautious with patients who have undergone surgery that might have altered the underlying anatomy. Be also cautious about scars on the site of injections.
- Recognize the variables that affect the required dosage in different individuals.
- Begin with the recommended starting doses and add more units or additional sites if necessary at a 2-week evaluation.
- Do not completely paralyze the muscles.
- Consider patient expectations as well as cultural viewpoints in planning the overall effect.
- Assess the need for treatment with other modalities, such as soft-tissue augmentation, lasers, or surgical intervention.
- Less experienced injectors of botulinum toxin type A should stay at least 2 cm above the brow.
- Use caution with lateral brow injections; stay well above the superior orbital rim.
- Centrally focused injections can allow lateral brows to elevate. Ensure that injection sites are located laterally enough to avoid a quizzical eyebrow appearance, but avoid the lower lateral forehead. A high lateral injection can modulate a severe lateral brow elevation. If injections are too centralized, it can lead to a "quizzical" eyebrow shape as a final result.
- A small amount of botulinum toxin type A administered in the procerus muscle can help prevent brow ptosis.
- A midline injection should be considered because many patients have frontalis fibers in that area, even though some schematic drawings fail to depict them but not if there is aponeurosis fascia below the hair line.
- Try not to treat only the frontalis because this is the most important elevator muscle on the upper third of the face.
- Sometimes the frontalis and brow depressors should be treated at the same time for a harmonious result. However, exceptionally we could suggest injecting these areas separately to decrease the amount of botulinum toxin type A.

Diffusion and overlap can result in immobilization. If treatments are undertaken separately, **treat the depressors first**, followed 2 weeks later by the frontalis treatment, but avoiding repeatedly injections in a short time should be avoided.

- Start with a low dose in the frontalis and avoid using a dose of botulinum toxin type A that will cause forehead immobilization. This may also facilitate a uniform dissipation of effects to the upper face and accentuate facial harmony throughout the treatment period.

Comments

Forehead rhytids are treated mostly with neurotoxins, although some practitioners prefer the concurrent use of fillers. It has been suggested that associated procedures may provide a slightly better cumulative benefit (Dubina et al. 2013) and increase the persistence of the rejuvenation treatment. Keep in mind that the majority of ours patients don't want to look done, they want to look better. The natural look is the goal!

Take Home Messages

- The horizontal lines are caused by the contraction of the frontalis muscle, and its contraction might be an important tool to raise a ptotic brow or eyelid to improve the visual field especially concerning elderly patients.
- Optimal aesthetic outcomes can be achieved by skillfully balancing the opposing effects of the frontalis muscle and its intricate interactions with the procerus, corrugator supercilii, depressor supercilii, and orbicularis oculi muscles.
- The goal in treating the forehead is to maintain some movement of the frontalis muscle and avoid complete paralysis, resulting in natural mimics without compromising the height, position, or shape of the brows and the eyelid.
- Concerning the areas to be treated and the sites of the injections, we need to analyze the functional portion (pars that actually is responsible for the rhytids) of the muscle and then, treat preferably only the upper half maintaining the brow mobility but minimizing the wrinkles.
- The total starting dosage for women varies between 10 and 20 U, preferable the lower dose. For men, we use to start with 20 U to 30 U. Typically, 1 to 5 U are injected in each site, with higher doses used in men. As with other areas, the amount of units depends upon the pretreatment aesthetic analysis.

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Botulinum Toxin for Glabella Area and Nose

Bhertha Tamura

Contents

Abstract

Glabella has its great importance as the first cosmetic area to be treated with botulinum toxin A (BTXA) in aesthetic field. Carruthers and Carruthers (J Dermatol Surg Oncol 18 (1):17–21, 1992; Dermatol Surg 33(1 Spec No):S26–S31, 2007) had established a landmark when they realized that a therapeutic treatment for strabismus leads to the relaxation of the glabella area muscles resulting in a relaxed and nice looking patient mimic. The evolution of the aesthetic indications of botulinum toxin allowed us to treat the frontal and the crow's feet lines as well, but residual nasal lines called "bunny lines" occur in some patients after treatment. More than these lines, some patients had not only the "bunny lines" but also lines at the nasociliary area, and Tamura (2005) had published a new approach besides the treatment of the nasalis muscle: the nasociliary area muscles. When we choose a BTXA with a predictable halo of action, each patient has its individual facial mimic, which depends on the muscle characteristics, such as position, strength, length, and size. In order to make the injection technique easier and improve the outcomes, some authors have suggested glabella (De Almeida et al. Dermatol Surg 38 (9):1506–1515, 2012) and nasal area (Tamura 2005) classification. We have compiled literature and our own experience in this chapter.

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_3

Keywords
Glabella · Botulinum toxin A · Bunny lines · Nasalis · Nasociliary · Nasociliary, depressor cilia · Nasal transversal line · Levator anguli oris and alaeque nasi muscle · Bunny lines

Introduction

People with frown lines can be interpreted as being rude, bitter, worried, troubled, and unsuccessful. For this reason, glabella is one of the most important areas of the face to be treated with BTXA in aesthetics undoubtedly. The frown lines should be prevented even in young patients if they have a strong mimic; otherwise, wrinkle correction might be a challenge in the future. Fillers are controversially injected to improve the deep wrinkles with a risk of serious undesirable complications due to the individual anatomic variation and arterial branches around and at this area.

After BTXA has been approved for glabella, frontal line, and crow's feet treatment, other areas, such as the nasal region lines and the nasal transversal line, were brought into focus, due to its importance acting as depressor group muscles of the glabellar area in combination with depressor cilia. At the first years, only the nasalis muscle was treated ("bunny lines"), but some patients had still huge lines at the nasociliary area, especially in oriental origin women, with a flat nasal dorsum. Even though not exclusive for them, the contraction of the depressor cilia and the medial portion of the orbicularis oculi leads after years to a deep horizontal line between the medial ocular canthus where filler injection would not result in a good correction, as it could not be placed for a long time in this hollow, and it frequently move up, down or laterally, worsening the medial facial aesthetic result.

Some anatomic studies had described the glabella, nasociliary and nasal muscles, as well as other structures allowing a better understanding about the action of the depressors and their antagonists. Considering the use of BTXA, we need to understand perfectly these muscles and how they interact between the depressor and elevator vectors and movements to achieve a better result individually.

At the beginning of the following text, we are going to discuss the glabella and then the nasal area, and they all will be analyzed together at the "Take Home Messages" part. The dosage of BTX described will be the same for onabotulinum toxin and incobotulinum toxin. When using abobotulinum toxin A (Speywood units), an equivalent dose should be calculated.

Glabella

The anatomic relationship of the muscles of this area was described at the proper chapter of anatomy for botulinum toxin and fillers. Let's have an insight about their relationship with the frontal muscle. Frontalis muscle fibers are often intimately related to corrugators and procerus muscles on the glabellar area. Although apparently very thin and sometimes short, the corrugators are very powerful, much more than the procerus. Sometimes this group might be widespread and the injection points for BTXA vary. The choice of the right places, adding its effects to the frontal muscle, must be done carefully to avoid an inexpressive feature, called "wax face" or emotionless face.

Starting with the procerus muscle, it is inserted into the nasal dorsum bone directing up to the frontal area and it might be short or long. In the beginning, the technique to find where the BTXA should be placed was the intersection of two imaginary lines marked from the inner eyebrow to the contralateral inner canthus of the eye from both sides. After a while, it was realized that this area is not always located on the procerus muscle, thus leading to a poor result or absence of relaxation in some patients. Nowadays, we check the patient mimic asking them to frown their glabella and identifying the extension of the muscles as well as their location. Hereupon, we localize the insertion of the procerus and test if it moves as a unit or if it moves as two separated bellies (Fig. 1). Procerus muscles might be very short, while others are extended up until the

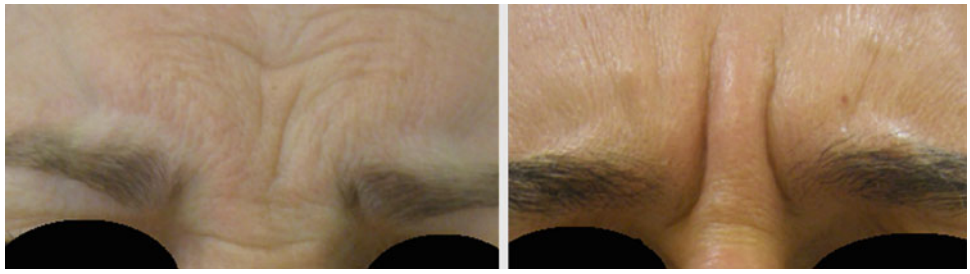

Fig. 1 Procerus muscle might have a bifurcation type contraction or a one-body contraction. The first responds better dividing in 2 points of BTXA injection

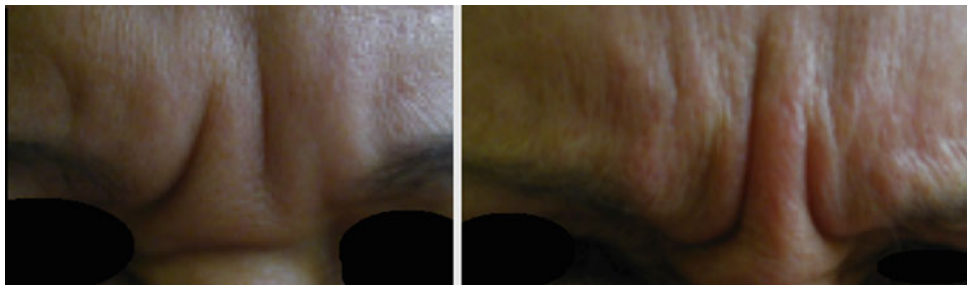

Fig. 2 Procerus muscles might be very short, and others extend up until the middle of the forehead even if the frontal area is wide and high

middle of the forehead even if the frontal area is wide and high (Fig. 2).

The procerus muscles, as well as the corrugators muscles, vary in size, extension, and direction. Pessa (2012, 2014) described that when they contract a corrugator fold separates the medial and lateral corrugator compartment and its direction should be perpendicular to the muscles. Pessa also described the medial frontal fold as their medial limit but we can see patients with double medial folds sometimes (Abramo et al. 2016). Corrugator muscles can be displayed in a linear, triangular, and square shape or even in a complex shape. The corrugator has also a transversal belly and an oblique belly that are positioned, respectively, at the projection of the medial and lateral compartments.

Almost all patients with very strong and huge muscles at the glabella may also have a very strong depressor cilia muscle. Its relaxation turns out to be mandatory for a good and natural result without dropping the area leading to an undesired tired face mimic. The depressor cilia muscles lay at the superior inner orbital rim, and it is almost perpendicular to the transversal belly of the corrugator quite like a continuous downward curve line from the medial end of the eyebrow. Sometimes when this muscle is very strong, we can see or feel it.

Various authors tried to classify or standardize different glabellar muscle contractions to make the injection plan easier for all doctors and achieve good aesthetic results for BTXA applications (Carruthers and Carruthers 2007). One of the most interesting and famous classification was described by De Almeida et al. (2012). The author classified the contraction patterns of the glabellar muscles in mainly five types: the "U" type, the "V" type, the convergent type, the omega type, and the inverted omega type (Fig. 3).

This classification is very useful, but if we do not understand the dynamics of the muscular contraction, we might have unpleasant results especially when there is a mixture of patterns. What

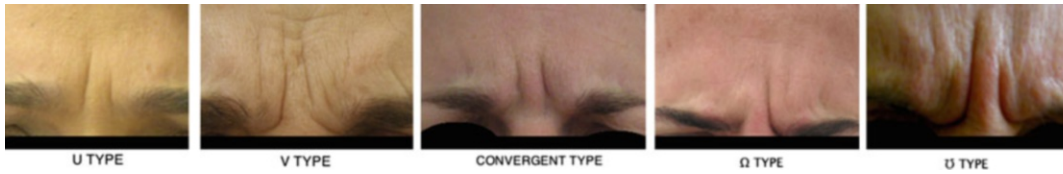

Fig. 3 De Almeida's classification of contraction patterns of the glabellar muscles: the "U" type, the "V" type, the convergent type, the omega type, and the inverted omega type

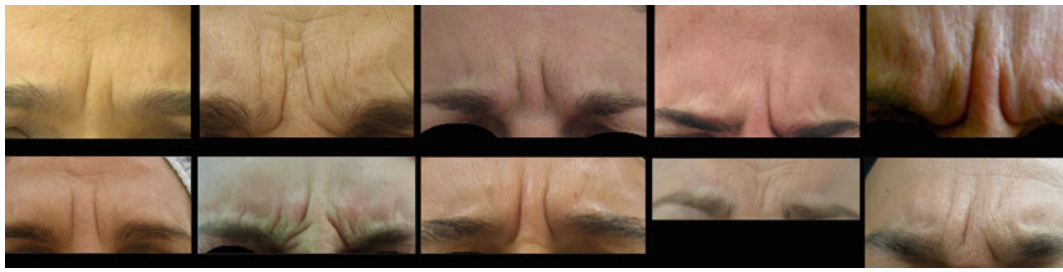

Fig. 4 Various glabella patterns, some with complex features of muscular contraction

we usually do is to delimitate the corrugators and procerus muscles at their maximum contraction with a maker. When the patient relaxes, we mark the injection points. Depending on the strength of the muscle, we calculate the dosage of units of BTXA to be injected in each site (Tamura et al. 2006).

We need to have in mind the extension of all muscles, to quantify the strength of them, to know the direction of the contraction vectors in conjunction to the patient frontal area and eyebrows, and to know the power of the depressor cilia and the nasociliary pars of the orbicularis oculi pulling down all these complex muscles. In Fig. 4, it is possible to see how variable is the contraction of this region (Fig. 4), each one with its personal strength, size, extension, and vectors of opposition force.

Thus, we plan, in general, to inject about 30U of onabotulinum toxin A or incobotulinum toxin A (or Speywood equivalence – abobotulinum toxin A) at this area, sometimes less or more. This amount was calculated based on the experience to treat this area promoting good response, relaxing without freezing. The effectiveness is tested during clinical exams and through before and after pictures.

Figure 5 shows how we manage the glabellar muscles, delimitating their extension and quantifying the strength of each part of the muscle so that we can plan where to inject and how many units to inject in each one. We also suggest that when injecting abobotulinum toxin, as the black dots designed, we should push the needle slightly upward to avoid the drop of the frown area. If the corrugators are different from each side, we should plan the sites of injection as they are presented in each patient and in each side separately. The units should be distributed in one, two, three, or even five points. The same can be considered procerus treatment. If it is short, one point of injection with 5-10U is indicated, or it can be necessary to distribute the units in two or three points of injection, with a total dose compatible to the extension and strength of the muscle.

Procerus Muscle

The procerus muscle originates from the nasal bone at the glabella and inserts into the skin of the forehead pulling down the eyebrow and being responsible for the transversal lines that form at the glabella area. It is important to observe that

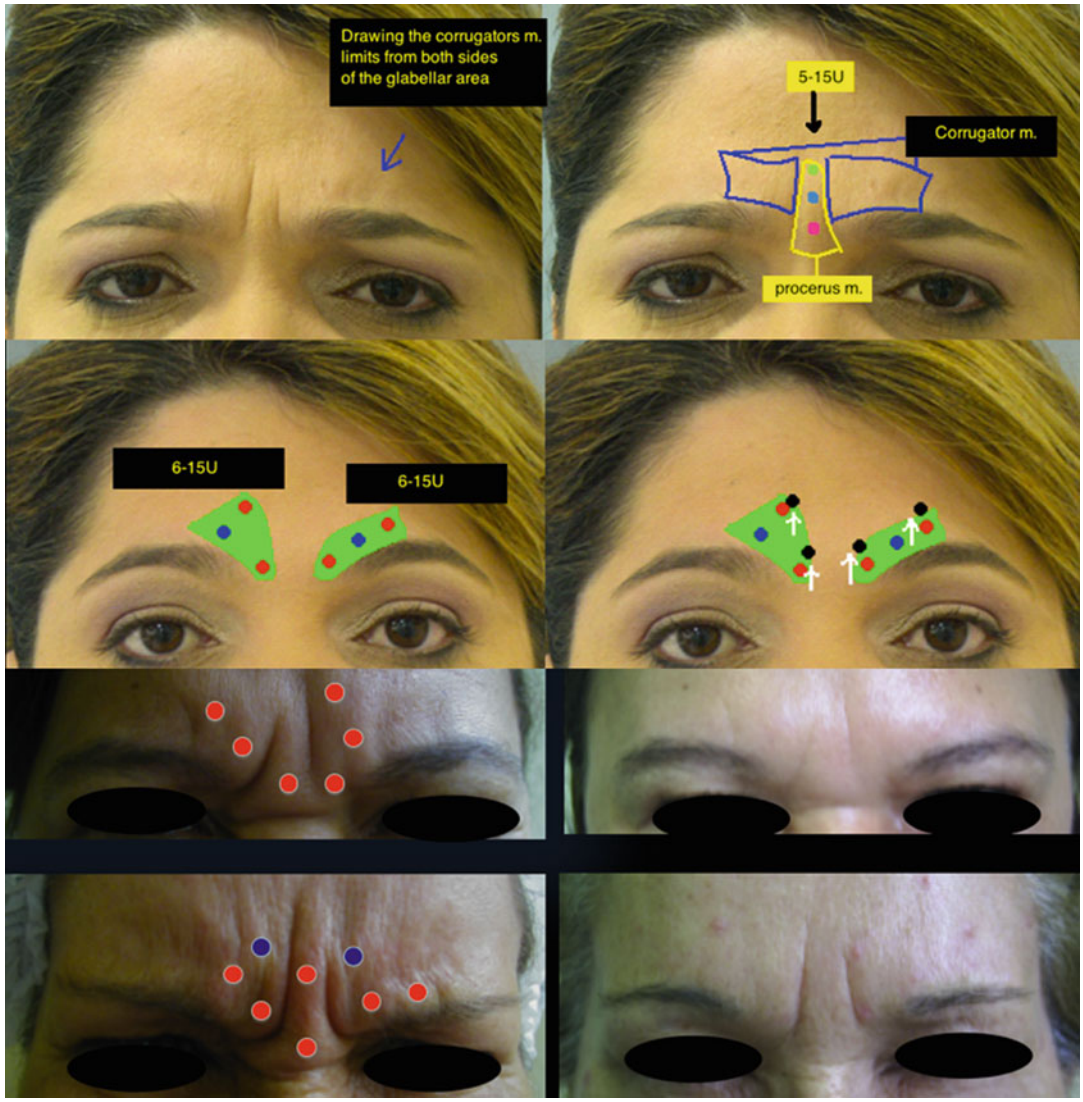

Fig. 5. Delimitating of the corrugator muscles and quantifying the strength of each part of the muscles, we can plan where to inject and how many units to inject in each one. When injecting abobotulinum toxin, as the black dots designed, we should push the needle slightly upward to avoid the drop of the frown area. If the corrugators are different from each side, we should plan the injection site as they present, distributing the units in one, two, three, or even five points of injection. The same is done for procerus treatment; if it is short, one point of injection with 5-10U is enough or the dose can be distributed in two or three points of injection.

frequently this muscle does not contract as a unit, but as two bellies, which might be symmetrical or not. This feature is relevant in order to choose the best option of treatment. The total dose of BTXA can be injected equally in each side or not. There is also another consideration: the length of the muscle (Figs. 1, 2, 5). If it is short, we plan a unique injection at the strongest and biggest part of it, but if it is very long, we can plan to inject in three points, seeking the relaxation of the frontal muscle at the same time at the upper point. When its length is intermediate, more units should be injected at the strongest part of the muscle. As we can notice, it's a completely different assessment

from the early years, when the injection was applied at the intersection of two imaginary lines marked from the inner eyebrow to the contralateral inner canthus of the eye from both sides. During the years, we realized that this point did not always coincide with the strongest part of the procerus.

Corrugator Muscle

The corrugator muscle originates from the inner and anterior portion of the superior and medial orbit margin above the nasal dorsum and inserts to the frontal muscle and the eyebrow skin. Its contraction brings the eyebrow together and pulls down the glabella. In the past we injected BTXA at the hugest part of the corrugator, currently medial to the inner side of the eyebrow, with another injection right up to it. We had changed this technique in 1996 to two injection points, one at the medial part, the strongest, and another at the lateral aspect of the muscle. In some patients another line, parallel to the corrugator's insertion on the eyebrow, can occur due to the strength of the orbicularis muscle contraction. So at this time, we began to inject about 7 units medially and 3 units laterally in the corrugator. Nowadays, we observe that sometimes these injection points are not enough even with this high dose. For this reason, we also analyze each muscle and sometimes inject BTXA in one, two, three, or even five points when injecting onabotulinum toxin or incobotulinum toxin. When using abobotulinum toxin, less points are recommended as this last one has a higher halo of spread. One side might be very different from the other depending upon the individual anatomy.

The direction of each muscle contraction is also very important to preview and prevent the "frozen look," the enlargement of the glabella area, the "heavy eyes," and the puffy eyes. If the vector is lateral and horizontal, their complete relaxation enlarges the glabella. If it is oblique with huge muscle volume, the area might drop medially leading to the impression of heavy eyes medially. If we detect the strength of the depressor cilia, we can relax it, preventing a bad result. Sometimes, there are asymmetries that need to be managed. Evaluating muscle behavior is the key for the best outcome. Figure 4 demonstrates the complexity of the glabella area.

Nasal Area

As we have already explained, the depressor cilia muscle is the key for a better outcome, and we need to include this muscle and the orbicularis as well as the nasalis muscle in the discussion of the treatment of this region. The orbicularis muscle originates from the palpebral and orbital area joining to the transversal nasal muscle. It is a circular-shaped structure.

The power of the depressors should always be observed when the patient has a strong and voluminous glabella and when they need to be relaxed to avoid dropping the area. We inject between 2 to 3 units in each belly (Fig. 6). The orbicularis has a pars medialis, superioris, inferioris, and lateralis. The pars superioris might be treated when it has fibers connected to the corrugators or the frontalis.

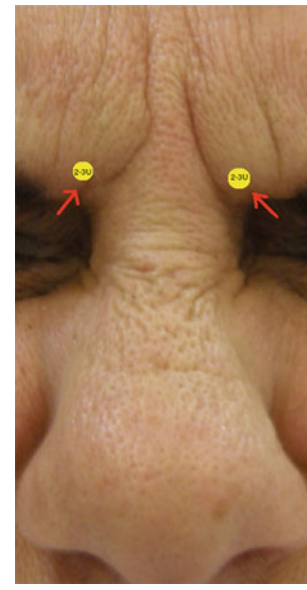

Fig. 6 The power of the depressors should always be observed when the patient has a strong and voluminous glabella as they need to be relaxed to avoid dropping the area. We inject between 2 to 3 units in each belly

The pars medialis might be powerful and associated with the par nasalis; they can wrinkle the nasociliary area, leading to a transversal line or various transversal lines between the eyes.

After glabella, forehead, and crow's feet treatment, as a consequence of those muscle relaxation, some patients complain about the lines on the dorsum of the nose that was named as "bunny lines." These lines are the result of the nasalis muscle contraction and its blockage results in a better outcome. A correlation between the muscles and the lines is shown in Fig. 7.

It is known that at the nasociliary area, the nasalis muscle, the depressor cilia muscle, the orbicularis oculi muscle, and the procerus muscle are synchronized with the pars medialis of the orbicularis muscle. Due to this complex action between them, each patient and each muscular dynamics must be analyzed separately and individually. The procerus contraction solely or with the depressor cilia muscle can lead to a transversal line on the roof of the nose as shown in Fig. 7. In order to understand the different patterns of wrinkles at the nasal area, we can separate lines at the nasal area (modified from Tamura 2007) into (a) inferior dorsum of the nose, due to the contraction of the nasalis muscle without (type I) or with (type II) the action of the levator anguli oris and alaeque nasi muscle (responsible for the elevation of the upper lip and the nasal alae); (b) medium nose (between the inner corner of the eyes) due to the contraction of the nasalis muscle and the medial part of the orbicularis muscle (type III); (c) the upper nose (between the inner corner of the eyes toward the glabella) due to the contraction of the depressor cilia with the superior inner part or the orbicularis with or without the action of the procerus muscle (type IV); and (d) total (type V) including lines at the nasociliary area and the nasal dorsum area (Fig. 8)

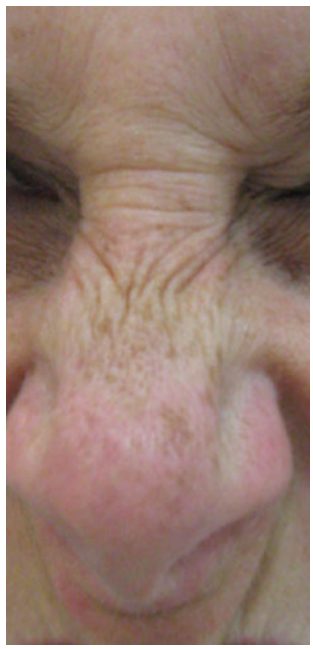

Fig. 7 Lines at the nasal dorsum, "bunny lines"

Type I is being treated as "bunny lines" since Carruthers (Carruthers and Carruthers 1992; Carruthers and Carruthers 2003; Carruthers et al. 2004) had described its muscular dynamics. We use to inject 2 to 4 units; 2 units maximum at each side should be enough to weaken the muscle but not relaxing in total. Little movement is desirable for a natural outcome; excessive and extensive relaxation leads to a paralyzed nose at smile.

The lines type II were described after the treatment of the nasalis muscle solely or combined with the levator anguli oris alaeque nasi muscle (2 units) to soften the nasolabial fold (Tamura 2007). We had checked several outcomes, and some patients contracted the nasalis at the same time of this muscle; therefore, it might be necessary to treat both muscles in some cases.

Type III was observed when the nasalis muscle was treated and transversal lines still remained. These lines were located between the eyes and they were the result of the strong medial area of the orbicularis oculi muscle. We realized that in these cases this part of the muscle should also be treated.

Type IV, when the orbicularis and the depressor cilia muscle are also very strong, with or without the influence of the glabella muscles. There are patients that have all the types together with lines from the glabella to the dorsum of the nose (type V). Each type might be corrected on the spot injecting 2U, or if the patient has the type V, we could diminish the number of points and increase the dose for 3U each site. Figure 9

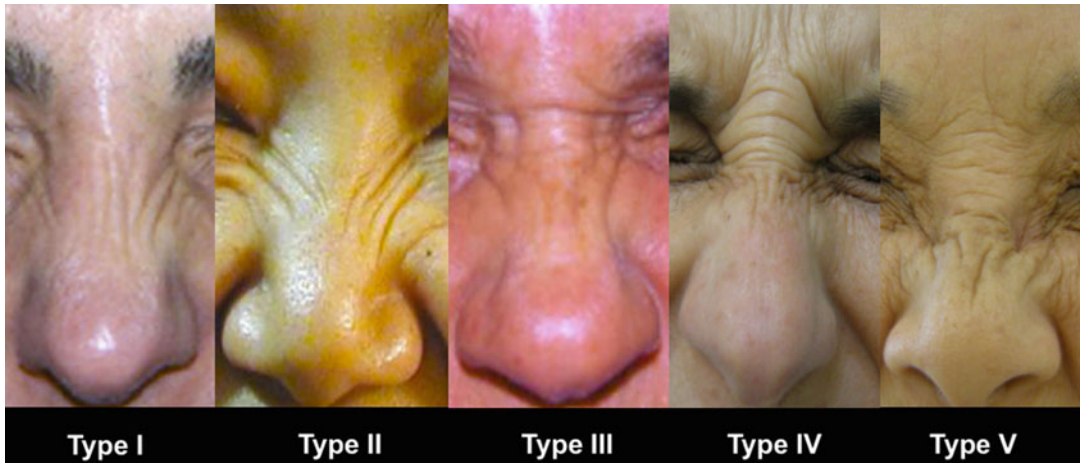

Fig. 8 Nasal area lines' different patterns. Type I is the classical "bunny lines" with the lines at the nasal dorsum. The other types have different muscular interaction.

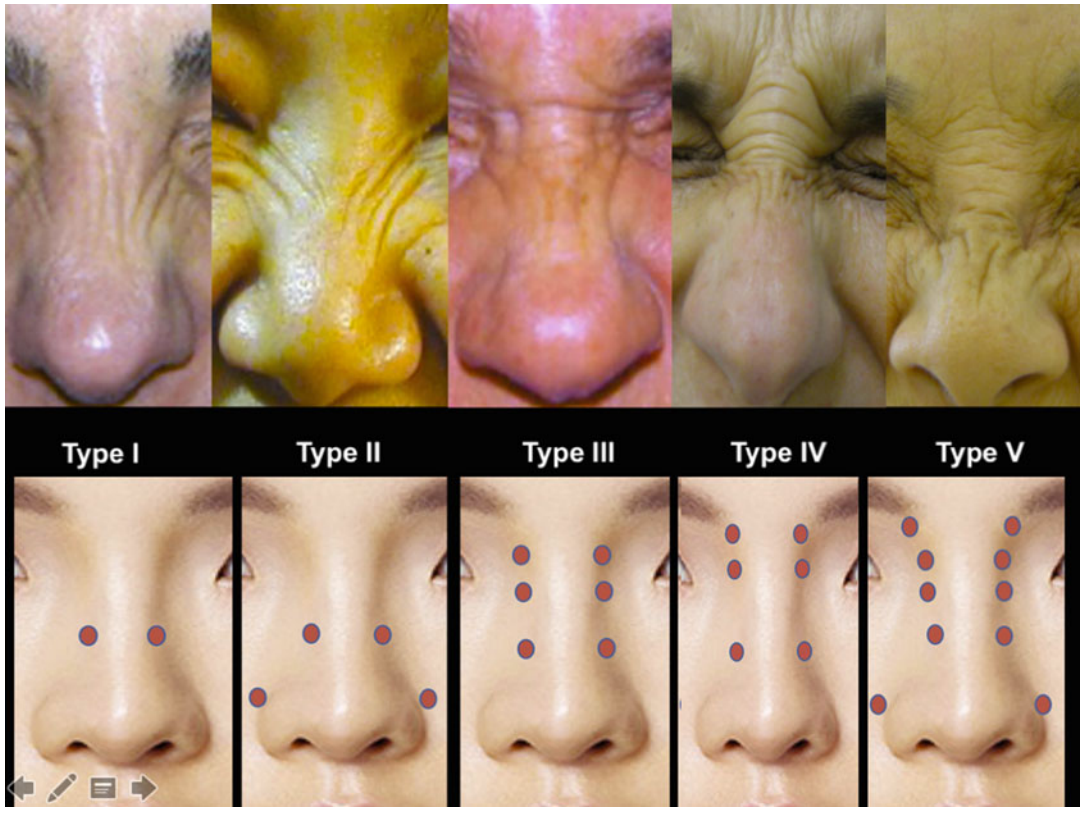

Fig. 9 All the types described with the suggestion of 2U of BTXA to be injected in each point

represents all the types described with the suggestion of the amount of BTXA to be injected in each point.

Take Home Messages

- Check the patient mimic by frowning the glabella area to identify the extension of the muscles and their location.
- We plan in general to inject about 30U (or Speywood equivalence) at this area, sometimes less or more depending on the muscle site, extension, and strength.
- If the corrugators are different from each side, we plan the injection as they present in each patient and each side separately, distributing one, two, three, or even five points.
- What we used to do is to delimitate the corrugators and procerus at their maximum contraction with a maker. When the patient relaxes, we mark the injection points, and depending on the strength of the muscle, we calculate the dosage of units of BTX to be injected in each site.
- About the procerus muscle, if it is short, one point of injection with 5-10U is enough, or we distribute the units in two or three points of injection if it is long. Total dose should be compatible to the side, extension, and strength of the muscle.
- The depressor cilia muscle, the orbicularis oculi muscle, and the procerus muscle are synchronized with the pars medialis of the orbicularis muscle.
- The power of the depressors should always be observed when the patient has a strong and voluminous glabella as they need to be relaxed to avoid dropping the area. We inject between 2 to 3 units in each belly. The orbicularis has a pars medialis, superioris, inferioris, and lateralis. The superioris might be treated when it has fibers connected to the corrugators or the frontalis. The medial area might be strong and participates with the nasalis to wrinkle the nasociliary area, promoting one transversal line or various transversal lines between the eyes.

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Botulinum Toxin for Periorbicular Area

Ana Paula Gomes Meski

Contents

Abstract

One of the most common complaints of aging patients is the appearance of crow's feet lines in the lateral canthal region. Injections of botulinum toxin will smooth out the rhytids and make the skin look younger.

In addition, although published consensus recommendations can guide dosing and injection site placement, expert technical application is critical, as is individualized treatment for each patient, based on an esthetic assessment. This includes an evaluation of the patient's unique functional anatomy and a frank discussion of the patient's desires and goals. Only by addressing these considerations can the best possible outcomes be consistently achieved.

The key to successful treatment with botulinum toxin is to minimize possible complications. The aim of this chapter is to review the application technique and the factors responsible for poor results and provide security measures for its prevention. Emphasis will be placed on technique, prevention, and management of adverse events that are essential for effective treatment.

Keywords

Botulinum toxin · Periorbicular area · Crow's feet treatment · Canthal rhytids · Orbicularis oculi muscle

Introduction

The botulinum toxin is widely used for facial rejuvenation. The periocular region often requires treatment for the correction of wrinkles at the

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_4

outer corners of the eyes, lateral canthal rhytids, called as crow's feet.

Some patients show their emotions through the smile (smile eyes) and thus should not be treated with a great amount of BTXA that results in an unpleasant look.

Classification

Crow's feet patterns change individually, and the treatment needs to fit each one keeping in view a natural improvement of the lines. Kane (2003) described different patterns of animation in this area. In this study, the crow's feet lines for each patient were categorized into four main patterns. The most common pattern was the full fan pattern (47%), where patients have wrinkles in their lateral canthal skin from the lower lateral brow across the upper eyelid, through the lateral canthus, and across the lower eyelid/upper cheek junction. The second most common pattern involved wrinkling of the lower lid/upper cheek area alone (25%). In the third most common pattern (18%), patients exhibited wrinkles only in the upper eyelid skin, down to the lateral canthus. Moreover, in the least common pattern (10%), only the skin immediately surrounding the lateral canthus was wrinkled. The author observed asymmetry for 6% of the patients, and those who have been monitored for several years have not demonstrated conversion to different patterns.

Mechanisms of Action

The treatment of the lateral portion of the orbicularis oculi muscle with botulinum toxin inhibits contraction, reducing crow's feet and elevating the lateral eyebrow. Typically, three injection points are used, but anywhere from one to five injection points may be possible (Ascher et al. 2010) (Fig. 1).

The orbicularis oculi muscle is superficial and thin, encircles the eye, and is divided in three parts: the orbital portion that surrounds the eye, a palpebral portion that covers the eye and is divided into the preseptal fibers, laying in front of the orbital septum, and the pretarsal fibers that form the eyelids. The orbital portion extends superiorly from above the eyebrow to the lateral canthus and inferiorly to the cheek. The orbital portion acts as a sphincter of the eye and is involved in the blink reflex together with the preseptal portion (Fig. 2).

The functions of the palpebral portion of the orbicularis oculi muscle are to close the eyelid both voluntary and as part of the blink reflex and to drain the tear film from the superior lateral gland to the medial lacrimal sac. Crow's feet are the result of orbicularis contraction and pull downward the lateral brow. The "ideal" female eyebrow lies with the highest point of the arch above the lateral canthus, and BTXA can be injected at the lateral brow to lift it.

Indications and Contraindications

Examine the patient from both the front and lateral side. Examine static (at rest) and dynamic (muscle contraction) lines, instruct the patient to perform a big smile, and try to imagine what relaxation of the orbicularis oculi muscle will do to their appearance.

For patients with severe sun damage or poor skin tone during smile, the cheek and orbicularis oculi muscles elevate the facial skin and send it into folds around the lateral orbit, and if the wrinkles are present even at rest, the patient should be warned that complement treatments may be required.

Analysis of facial movement and recognition of any asymmetry or ptosis of eyebrows or

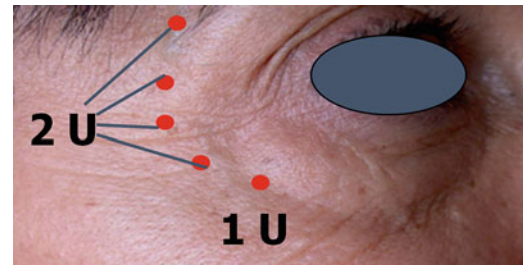

Fig. 1 Botulinum toxin injection points – five points, four superiors with two units each and the lower with one unit

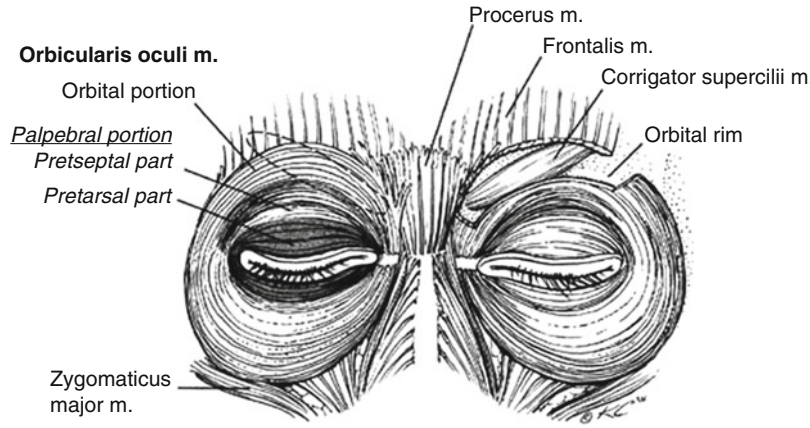

Fig. 2 Muscles of the periocular region

superior lid must be considered when choosing the appropriate placement and dose of toxin to be used.

Blepharoplasty and other facial surgery history are reviewed. The anatomy of the region may have been modified which increases the risk of reaching nontarget muscle treatment. Ophthalmologic history, including keratorefractive surgery (LASIK), is obtained to prevent the risk of dry eyes.

The contraindications for this treatment are severe lower eyelid dermatochalasis, abnormal snap test and eye bags, lagophthalmos, excessive lower eyelid scleral show, and ectropion. The latter two occur more frequently on who has already undergone eyelid surgery or aggressive lower eyelid resurfacing.

Use and Doses

The patient must be prepared, informed, examined, and photographed and must have consented; the anesthesia is done with topical creams. Ice is not recommended as it causes vasoconstriction and can obscure blood vessels.

Each of the three BoNT-A neuromodulator agents must be reconstituted for use with unpreserved 0.9% sodium chloride. In clinical practice, reconstitution volumes can vary based on location and indication. The reconstitution of the 100 U vial of Botox® (onabotulinumtoxinA) and Xeomin® (incobotulinumtoxinA) can be done with 1 ml of saline resulting in 10 U in 0.1 ml; it is advisable to use 0.3 ml syringe for an accuracy application or with 2.5 ml to obtain 4 U in 0.1 ml. The same dilution is used for the Dysport® (abobotulinumtoxinA) vial of 300 U and for the 500 U vial, 1.7 ml to use the 0.3 ml syringe or 3.4 ml for the 1 ml syringe (Table 1).

BoNT-A is typically administered using different syringes and needles. A 0.3 ml 30-gauge insulin syringe is preferentially used to decrease pain.

The recommended dose varies individually. Most cases are treated with 1–5 units per injection point, a total of 8–16 units in each orbicularis oculi muscle.

Two to eight injection points of toxin can be planned in each crow's feet area, depending on the number and length of wrinkles. The injections are generally placed 1 cm outside the orbital rim, above the level of the superior margin of the zygoma, and extend under the eyebrow to the lateral limbus line (Fig. 3). The needle is typically pointed away from the orbit. Injections are superficial, creating intradermal blebs. The injector must visualize superficial veins to avoid bruising and also superficial placement in this area is recommended.

The first injection point is in the middle of the crow's feet area. The second injection point is approximately 0.5 cm superior to the first point. Moreover, the third is approximately 0.5 cm inferior to the first point.

Published literature shows that a wide range of doses (20–75 U) of BoNT-A has been used to treat crow's feet, with injections given at a varying

Table 1 Botulinum toxin reconstitution

BoNT-A product	Units (unit vial)	Reconstitution volume (ml)	Resulting concentration units / 0.1 ml
Dysport®	300	2.5	12 Speywood units
Dysport®	300	1	30 Speywood units
Dysport®	500	3.4	15 Speywood units
Dysport®	500	1.7	30 Speywood units
Botox®	100	2.5	4 units
Botox®	100	1	10 units
Botox®	50	1.25	4 units
Xeomin®	50	0.25–5	Varies
Xeomin®	100	0.25–8	Varies

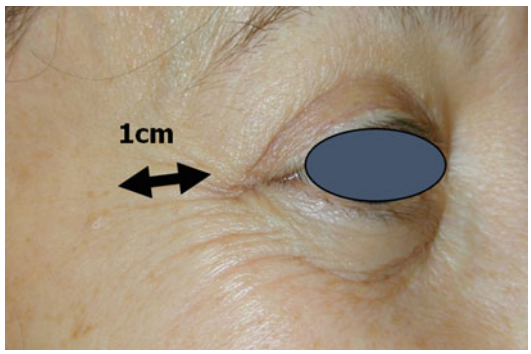

Fig. 3 The injections are placed 1 cm outside the orbital rim

number of sites. Ascher et al., in 2009, compared the efficacy and safety of three doses of BoNT-A with placebo for the treatment of crow's feet (Ascher et al. 2009). This study has established that 15, 30, and 45 U are all highly effective, and most patients will benefit for a period of 12–16 weeks. A dose-response relationship was observed for independent assessment of severity scores at a maximum smile, showing that 30 and 45 U were optimal doses.

The clinical effect of the botulinum toxin type A is first apparent 24–96 hours after injection and peaks in 1–4 weeks. The relaxation of hyperkinetic facial muscle activity begins to reverse at 3–4 months.

The injectors have to examine the height and width of the zygomatic arch. If the orbicularis oculi muscle sags between the cheekbone and the eye, the treatment can create a hollow. In these cases, the injection must be more lateral to avoid diffusion to the hollow area.

Patients with weak orbital septum or protruding orbital fat pads should not be treated under the eyelids as the subsequent loss of tone can lead to sagging of the bags (Fig. 4).

Avoid injecting BTXA into the zygomaticus muscle that results in an asymmetric smile (Carruthers et al. 2004). At 1 cm lateral to the lateral canthus, a widely used landmark for botulinum toxin injections is this area, the zygomaticus major muscle interdigitated with the orbicularis oculi an average of 1.4 cm inferior to the Frankfort horizontal line (Spiegel 2005).

The lip levator muscle is located deeply and below the superior margin of the zygoma; if treated with BTXA by mistake, it may lead to an asymmetric smile and lip ptosis. Diplopia happens when the injection or migration of BTXA affects the oculomotor muscles. The injection row is at least 1 cm lateral from the lateral orbital rim (Small 2012).

Lower lid preseptal fine lines can be improved with BTXA injected intradermally. To avoid ectropion, six units of Dysport® or two units of Botox® or Xeomin® are used for each lower eyelid area (Le Louran 2001).

Side effects and their managements (Matarasso 1998):

1. Bruising (ecchymosis) is the most common complication. Immediate application of ice and pressure can minimize it. The time for resolution depends on the patients' metabolism and the size of the bruise.
2. Photophobia results from reduced squinting. It is uncommon and always mild.
3. Lip and cheek ptosis causing an asymmetric smile can occur with injections placed deeply and inferiorly, below the superior margin of the zygoma, due to inadvertent weakening of the zygomaticus major and levator labii superioris muscle group (Spiegel and Derosa 2005).
4. Diplopia.

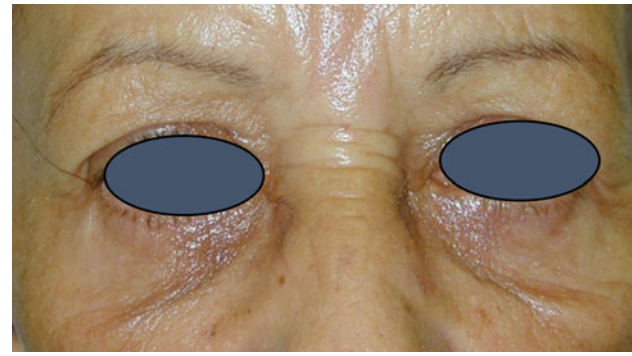

Fig. 4 Contraindication for botulinum toxin treatment – excessive sagging skin

5. Strabismus: botulinum toxin affecting the lateral rectus muscle medially.
6. Incomplete eyelid closure, lagophthalmos.
7. Excessive lower eyelid scleral show.
8. Ectropion, eversion of eyelid margin.
9. Eyelid spasm (twitching).
10. Dry eye and abnormal Schirmer's test. Abnormal tear secretion may have been due to an inaccurate intramuscular injection or an effect on the lacrimal gland. The effect on the gland could be theoretically comparable to the mechanism of action for hyperhidrosis. The gland is located in the lateral third of the upper eyelid and is well protected by the orbital portion of the frontal bone. The pump action of the excretory system of the lacrimal apparatus is a function of the pretarsal orbicularis oculi muscle that contracts to force fluid into the tear sac. Therefore, paresis, partial or total, of the pretarsal portion of the orbicularis oculi muscle alters the Schirmer's test (Matarasso 2002).
11. Infraorbital deformity. Paloma described herniation of the orbital fat in 2001. The deformity was observed 1 week after the procedure on the inferior aspect of the orbital rim and disappeared 5 months after. The author recommended only three or four injection sites into the lateral third of the orbicularis oculi muscle with particular avoidance of the inferior aspect of the orbicularis of the lower eyelid (Paloma 2001). Mitchell described the development of festooning of the infraocular area after injection of botulinum toxin A in a patient with prior transtarsal lower lid blepharoplasty (Mitchel 2003).
12. Epiphora, watery eye due to diffusion of toxin toward lacrimal pump preventing tear drainage. Injectors must avoid the pretarsal area medial to mid-pupillary line.
13. Hooding, wrinkle due to sagging skin and not orbicularis contraction.
14. "Mickey Mouse" sign, large fold of wrinkle below zygoma. It occurs when the patient has good result but poor skin tone, causing wrinkling of the lower face during smiling.

Treatment of the lower portion of the orbicularis oculi muscle reduces wrinkles of the lower eyelids, promotes eyelid widening and eye rounding, and reduces the lower bulge of the eyelid muscle, also called "jelly roll" (Small 2012) (Fig. 5).

Take Home Messages

- Knowledge of the anatomy and physiology of the muscles of facial expression is very important to achieve good results. The physician should always be alert to the individual anatomical variations. Best results are natural, without excessively changing the expression of the patient.

Cross-References

▶ Hyaluronic Acid Filler for Forehead, Temporal, and Periorbicular Regions

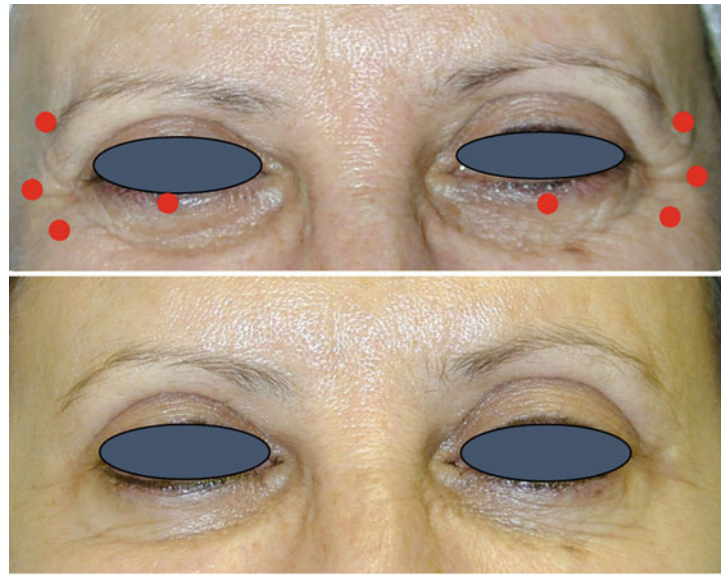

Fig. 5 Treatment of inferior eyelids for reduction of wrinkles

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Botulinum Toxin for Mentum and Perioral Area

Maria Del Pilar Del Rio Navarrete Biot

Contents

Abstract

There is no doubt that the treatment with botulinum toxin is the most popular aesthetic procedure for facial rejuvenation. At the beginning, it was indicated only for the upper face, but now, it is frequently injected for the treatment of the lower face. When treating this area, the goal is to relax the muscles. In the perioral area, the muscle to be treated is the orbicularis oris, important for the execution of simple actions like speaking, drinking, and blowing, and which impairment would be very unpleasant. This is especially important for those who need a total competence of the lips in their jobs, like speakers, musicians, scuba divers, and others. A complete knowledge of the anatomy and the correct injection technique, not exceeding the total number of units recommended, are essential for a safe and successful treatment of the lower face. The anatomy is important not only for the perioral area treatment but also for the mentum, because of the proximity and numerous muscle intersections at this region. For example, when

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_5

treating the mentum, it is possible to accidentally relax the orbicularis oris. We hope that with this chapter, we contribute for a better understanding of the lower face treatment and that after reading it, the injector feels confident to inject this region.

Keywords
Dynamic lines · Botulinum toxin · Paralysis · Lower face · Bar code · Perioral · Upper lip · Lower lip · Vermilion · Columella · Mentum · Orbicularis oris · Levator anguli oris · Depressor anguli oris · Depressor labii inferioris · Dimpled chin

Introduction

Produced by *Clostridium botulinum*, the botulinum toxin (BTX) has been widely used for the last decades in the treatment of facial rejuvenation. This neurotoxin interrupts the releasing of acetylcholine at the neuromuscular junction, blocking the contraction of the muscle that is being treated and consequently smoothing the lines due to the muscle activity, also known as "dynamic lines" (Ascher et al. 2010; Carruthers and Carruthers 2003).

Well-established and widely used treatment for the upper third of the face, the botulinum toxin is being increasingly indicated for the lower third. Although the results in the lower face are not as "noticeable" as in the upper, they are important tool for the global rejuvenation of the face, especially when associated to other treatments, as fillers.

The lips are the most important structure of the lower face and contribute to a more youthful appearance. There has been an increasing search for treatments to rejuvenate the lips and improve the perioral area, especially the perioral lines. Also known as "bar code" lines, they are due to the aging of the skin, in association with constant contraction of the orbicularis oris muscle.

The aging process of the perioral area, as for the rest of the face, is due to intrinsic and extrinsic factors. As extrinsic causes, we can highlight: sun exposure, smoking, alcohol abuse, diet, and air pollution. The intrinsic or genetic aging is due to the loss of subcutaneous fat, collagen, and bone absorption. In the face, the constant contraction of the mimics muscles results in the dynamic lines along the years, that with time turn to be static lines (Carruthers et al. 2010) (Figs. 1 and 2).

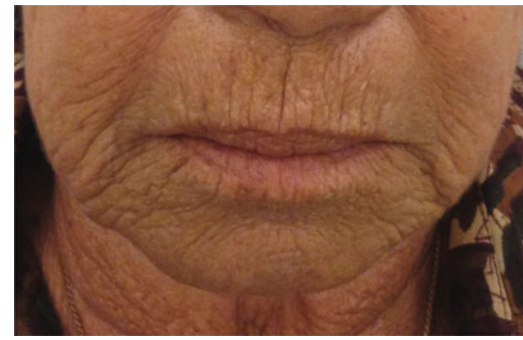

Fig. 1 Aging of the perioral area

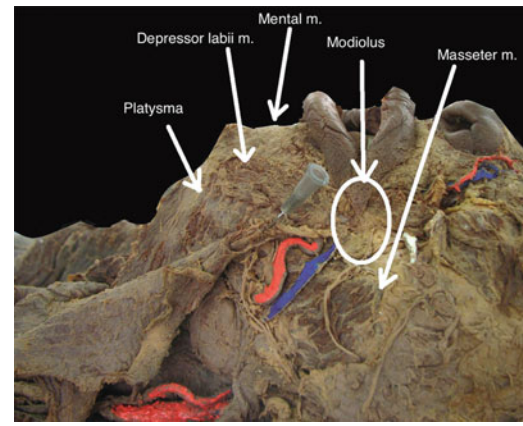

Fig. 2 Mental area muscles (Courtesy by dr. Bhertha Tamura)

Perioral Area

Youthful lips are full and well defined, with an ideal proportion rate of 1:1.6 between the upper and lower lips, meaning that the lower lip has a slightly greater volume than the upper (Mandy 2007). The transition between the oral mucosa and the skin is called the "vermilion," which in the central part of the upper lip, has the shape of an "M", the so-called Cupid's bow. Its two peaks continue upward constituting the "philtral columns." In the youngest,

the limit of the vermilion and the skin is an elevated and well-defined border called the "white roll" (Carruthers et al. 2010).

With aging, there is a thickening of the epidermis, which is noticed in the cutaneous portion of the upper lip. There is also a loss of elasticity and subcutaneous fat as well as thinning of the dermis and bone remodeling, contributing for the aging appearance of the lips. In the upper lip, the transition between the vermilion and the skin becomes flat and there is also a widening in the distance between the vermilion and the columella, leading to an enlargement of the cutaneous portion and thinning of the red lip (vermilion). The lower lip turns inward at the lateral margins and the labial commissures turn downwards. A loss of volume can also happen in the lower lip. All those changes added to the constant contraction, especially of the orbicularis oris, lead to the development of the perioral wrinkles (Raspaldo et al. 2011).

Those with full lips, like in afro descendants, and with an ideal proportion between the lower and upper lips, are less prone to show the visual effects of aging at this area.

When treating the perioral wrinkles multiple etiological factors should be considered. So the use of the botulinum toxin as monotherapy will not be enough for the complete correction, except in young patients, that have only dynamic wrinkles (Cohen et al. 2012). In such cases, BTX works as a prophylactic treatment to avoid the static wrinkles. It is important to remember that the goal is not the total paralysis but just relaxing the muscles in order to improve the wrinkles with no impairment of the lips function. That would be an unacceptable result, especially in those that need the total competence of the mouth and perioral area in their work and everyday tasks. So, this treatment is contraindicated for singers, musicians, divers, speakers, and anyone that uses the muscles of this area for a perfect performance Shetty and Dermatosurgery Task Force (2008).

Anatomy of the Perioral Area

For the correction of the perioral wrinkles, the muscle to be treated is the *orbicularis oris*, but this is a region of complex anatomic structures and muscles correlations that must be well understood by those who are going to inject BTX in this area in order to avoid impairment of the lips function. A brief description of the most important muscles of the region is presented below:

Orbicularis oris – it is so called because once it was believed that the mouth was surrounded by ellipses of striated muscle that worked together like a sphincter. It is known now, that this muscle has four independent parts (upper, lower, right, and left), each of them with a peripheral portion, that is bigger, and a marginal and smaller portion. The junction line between the peripheral and marginal portions corresponds externally to the limit between the vermilion and the skin (Gray 2015). The fibers are divided into superficial and deep layer and it contracts like a sphincter, closing and protruding the lips. The deeper fibers bring the lips together and compress them to the alveolar arch, close to the teeth. The protrusion of the lips occurs by the contraction of the superficial fibers (Raspaldo et al. 2011; Shetty and Dermatosurgery Task Force 2008). Exerting a constant pull on the upper and lower lips, this muscle is responsible for the development of the perioral wrinkles (Raspaldo et al. 2011).

Levator labii superioris and zygomaticus minor – insert onto the skin at the melolabial fold and in the o*rbicularis oris* muscle fibers of the upper lip and together they help to dilate the mouth, retract and evert the upper lip, and deepen the nasolabial sulcus (Gray 2015).

Zygomaticus major – arises from the zygomatic bone, in front of the zygomatic temporal suture, and descending obliquely with a medial inclination; it is inserted into the angle of the mouth where it blends with the fibers of the *levator anguli oris*, *orbicularis oris*, and *depressor anguli oris*. It draws the angle of the mouth backward and upward, as in laughing (Gray 2015).

Levator anguli oris – arises from the canine fossa, immediately below the infraorbital foramen; its fibers are inserted into the angle of the mouth, intermingling with those of the *zygomaticus*,

depressor anguli oris, and *orbicularis oris.* Some superficial fibers insert into the dermis of the melolabial fold's inferior portion. It raises the angle of the mouth, deepens and modifies the melolabial fold (Gray 2015).

Risorius – arises in the fascia over the masseter and passing horizontally forward becomes superficial to the platysma and is inserted into the skin at the angle of the mouth. It is a narrow bundle of fibers, broadest at its origin, but varies a lot in its size and form (Gray 2015). It dilates the mouth and widens the rima oris (Raspaldo et al. 2011).

Depressor anguli oris – arises from the oblique line of the mandible, whence its fibers converge, to be inserted, by a narrow fasciculus, into the angle of the mouth. At its origin it is continuous with the platysma, and at its insertion with the orbicularis oris and risorius; some of its fibers are directly continuous with those of the levator anguli oris, and others are occasionally found crossing from the muscle of one side to that of the other; these latter fibers constitute the transversus mentis. It pulls the angle of the mouth downwards and laterally, during the opening of the mouth and sadness expression (Gray 2015).

Depressor labii inferioris – is a small quadrilateral muscle. It arises from the oblique line of the mandible, between the symphysis and the mental foramen, and passes upward and medial ward, to be inserted into the integument of the lower lip, its fibers blending with the orbicularis oris and with those of its fellow of the opposite side. At its origin, it is continuous with the fibers of the platysma. Much yellow fat is intermingled with the fibers of this muscle. It draws the lower lip directly downward and a little lateral ward, as in the expression of irony, suffering, melancholy, and doubt (Gray 2015).

Buccinator – is a thin quadrilateral muscle, occupying the interval between the maxilla and the mandible at the side of the face. It *arises* from the outer surfaces of the alveolar processes of the maxilla and mandible, corresponding to the three molar teeth; and behind, from the anterior border of the pterygomandibular raphe which separates it from the constrictor pharynges superior. The fibers converge towards the angle of the mouth, where the central fibers intersect each other, those from below being continuous with the upper segment of the *orbicularis oris*, and those from above with the lower segment; the upper and lower fibers continue forward into the corresponding lip without decussation. It compresses the cheeks, so that, during the process of mastication, the food is kept under the immediate pressure of the teeth (Gray 2015).

Modiolus – on each side of the face, a certain number of muscles converge to a point located laterally to the mouth angle, where they interweave, making a dense, compact, and mobile fibromuscular mass called modiolus. At least, nine muscles, depending on the classification used, are attached to each modiolus. The three-dimensional mobility, controlled by the modiolus, makes possible the integration of the cheeks, mouth, lips, and mandible activities. This include chewing, biting, suction, drinking, swallowing, changes in the vestibular content and pressure as well as alterations of the facial expression, and the production of sounds and shouts (Gray 2015).

Patients Selection

As for all the other treatments with botulinum toxin, a careful selection of patients and a correct indication is essential for a successful treatment. As it was said previously, this treatment is completely contraindicated for those who need a total competence of the labial muscles in their jobs. So, singers, divers, speakers, and musicians that play wind instruments should never be treated.

Patients with unreal expectations in relation to these treatment, should not be treated, especially those that have already used botulinum toxin in other areas, for example, the glabella (Shetty and Dermatosurgery Task Force 2008; Semchyshyn and Sengelmann 2003). It is also not recommended for patients with thin/atrophic upper lip or a prolonged columella to vemilion

distance because they might evolve with an even thinner lip thickness (Semchyshyn and Sengelmann 2003).

Procedure

Due to the lips high sensitivity, the use of a local anesthetic cream prior to the treatment is strongly recommended in order to make the procedure more comfortable and less painful. The use of local ice pads directly onto the injection points might also help.

During the treatment, the patient should be seated and the botulinum toxin should be injected in four points in the upper lip and two to four in the lower lip (Raspaldo et al. 2011). It is important to place the points symmetrically, avoiding the corner of the mouth, to prevent the accidental treatment of the elevator muscles that are attached to this point, as this would result in drooping of the lateral lip and drooling. The midline should be avoided, to prevent the Cupid's bow flattening (Carruthers and Carruthers 2003). The lateral points should be at least 1.5 cm from the corner of the mouth and the medial points 1 mm away from the philtrum. The injections are placed at the vermilion border or 2 mm above the upper lip or 2 mm underneath the lower lip (Ascher et al. 2010; Raspaldo et al. 2011).

The injections must be superficial, at the deep dermis or subcutaneous. It is important to avoid injections into the muscle, as the objective is to treat just the superficial fibers (Raspaldo et al. 2011; Semchyshyn and Sengelmann 2003). The total amount of onabotulinum toxin should not exceed 4 U per lip, no more than 2 U per quadrant (Carruthers and Carruthers 2003; Raspaldo et al. 2011; Gassia et al. 2013). When using abobotulinumtoxin, the total dose is of no more than 12 Speywood units, divided in 4–6 points of 1–2 U (Ascher et al. 2010).

It is advisable to be conservative in the first treatment, injecting only the upper lip and using as few units as possible, until the doctor and the patient can evaluate the treatment result (Ascher et al. 2010; Cohen et al. 2012; Semchyshyn and Sengelmann 2003). If it is not necessary, the treatment of the lower lip should be avoided, as it is riskier (Ascher et al. 2010).

Results

When using botulinum toxin for the treatment of perioral wrinkles, spectacular results like those obtained in other areas, the glabella, for example, should not be expected. Improving the perioral lines, avoiding lips dysfunction, is our final goal. These limit the total amount of toxin that can be used and also the final results.

Treating just the superficial fibers of the orbicularis oris, a smoothening of the dynamic lines is achieved, as well as a pseudo augmentation and eversion of the lip with enhancement of the vermilion contour. With the superficial layers relaxed, the contraction of the deeper fibers gives a volumized and everted appearance to the lip, especially in the dynamic mouth movement (Carruthers and Carruthers 2003; Semchyshyn and Sengelmann 2003) (Figs. 3, 4, 5, and 6).

The results obtained in this area, revert quicker than in other areas of the face, like glabella or forehead. Increasing the number of units injected would not increase the duration and would be riskier with a greater chance of adverse events. Comparing a total amount of 7.5 U and 12 U of onabotulinum toxin, Cohen et al. (2012) did not see a longer duration when using the higher dose. The shorter duration is probably due to the constant activity of the orbicularis oris (Semchyshyn and Sengelmann 2003).

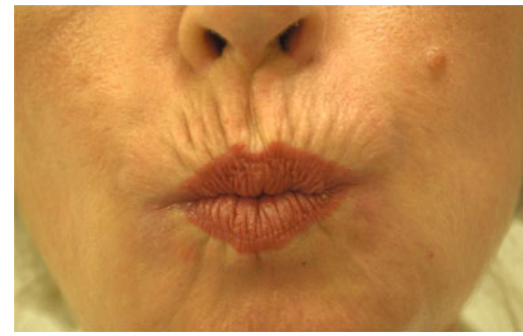

Fig. 3 Contraction of the orbicularis oris – before treatment

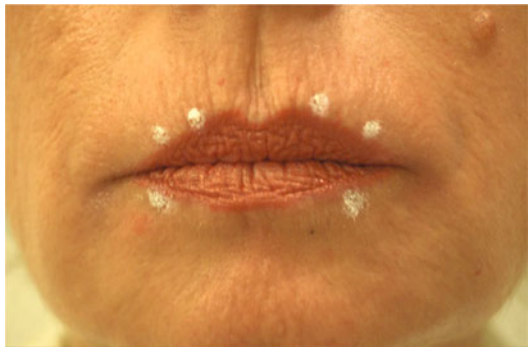

Fig. 4 Sites of injection. Notice that the patient has perioral wrinkles even during rest

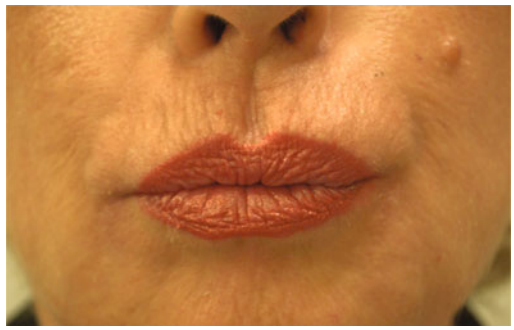

Fig. 5 Contraction of the orbicularis oris. After treatment

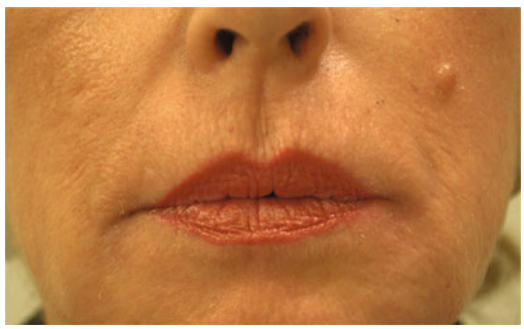

Fig. 6 After treatment – improvement of the perioral rhytids and eversion of the lip

Better results at the perioral area are obtained injecting smaller doses of botulinum toxin in association with other treatments, like ablative or non-ablative resurfacing and fillers (Ascher et al. 2010; Carruthers and Carruthers 2003; Gassia et al. 2013). Small doses of botulinum toxin relax the local muscles and allow the longer permanence of the filler. Using the botulinum toxin as monotherapy and comparing it with BTX associated to a hyaluronic acid (HA) filler and the HA as monotherapy, better and longer lasting results were obtained with the combined regimen. The hyaluronic acid as monotherapy was superior, with better results than the botulinum toxin monotherapy (Carruthers et al. 2010).

Better results can be achieved injecting botulinum toxin preceding treatments (with a safe interval between them) with fractioned lasers in the perioral area, due to the relaxation and less contraction during the healing process (Cohen et al. 2012).

Adverse Effects

Even small doses of botulinum toxin in the perioral area may cause an impairment of the sphincter function of the lip, and simple actions like whistle, pronouncing the “p” and “b”, spit, eat with a spoon, play wind instruments, drink through a straw, and the use of diving equipments may become difficult. For these reasons, this treatment is not recommended for those who need to articulate precisely at speech and need the total competence of the labial sphincter for a good professional performance (Semchyshyn and Sengelmann 2003; Pena et al. 2007). In extreme cases of lip weakening, asymmetry of the mouth and drooling might occur (Pena et al. 2007).

Some patients may feel self-conscious about their lips while speaking, although no functional abnormality exists and no apparent inconvenient cosmetic effect is noted (Semchyshyn and Sengelmann 2003). Even in such cases, actions like eating, drinking, and singing are typically not affected (Carruthers and Carruthers 2003).

The impairment of the lips functions is worse in the first 2 weeks and seems to be dose dependent. Most of the patients who experienced functional alterations and choose to continue treating the lips with botulinum toxin had no symptoms when a reduced number of units was used (Semchyshyn and Sengelmann 2003). Using

abobotulinumtoxin for the treatment of the face, Gassia et al. (2013) realized that the perioral region had the greater incidence of adverse effect thus reduced the total number of units used in this area, from 15 to 10. Doing this, they noticed a reduction of complications rates from 75% to 26.3% (Hexsel et al. 2013).

Some authors believe that the reduction in the total number of units would not be so important, as small reductions are enough to avoid complications. They believe that patients get used to the paresis of the lip and change the way of using it, to regain functionality (Semchyshyn and Sengelmann 2003). To obtain good results and avoid complications, the recommendations of using small doses and inject superficially and symmetrically, must always be respected.

Mentum

In the aging face, there is a decrease in the collagen and the subcutaneous fat of the mentum. The skin is thin and close to the mentalis muscle. These alterations in conjunction with the hyperactivity of the mentalis cause a pebbled appearance, called "peau-d'orange," dimpled chin, or "pseudo cellulitis" (Shetty and Dermatosurgery Task Force 2008; Rapaldo et al. 2011). This irregular aspect of the chin can be better seen when the mentalis is used with the orbicularis oris and the depressor labii inferioris, during speech and chewing (Carruthers and Carruthers 2003). Contraction of the mentalis raises the chin and can also cause a deep crease between the lower lip and the prominence of the mandible (Yutskovskaya et al. 2015).

Some patients are unaware of their dimpled chin, which appears mainly on active mimics. An elegant way to show it is to give them a mirror during consultation (Shetty and Dermatosurgery Task Force 2008).

Anatomy of Mentum

Mentalis – is a small conical fasciculus, located at the side of the frenulum of the lower lip. It arises from the incisive fossa of the mandible and descends to be *inserted* into the integument of the chin (Gray 2015).

The *mentalis* raises and protrudes the lower lip, and at the same time wrinkles the skin of the chin, expressing doubt or disdain (Gray 2015; Shetty and Dermatosurgery Task Force 2008).

Patient Selection

A careful selection of the patients and a good indication are the keys for a successful treatment. As in all the other indications for the use of BTX for the treatment of the facial mimics, the evaluation begins during the consultation, when we observe the patient's natural contractions while he speaks. Once the treatment of the mentum is indicated, if the patient did not notice these alterations, a mirror is given to him, so that he can see his face during animation (Raspaldo et al. 2011).

Botulinum toxin for the treatment of the chin is indicated for all the patients that during facial animation show irregularities of the skin of the mentum and also for those that have a deep crease between the inferior lip and the prominence of the mandible.

It is not recommended for those with a dimpled chin and a hypertrophic mentalis, as this may be a sign of predisposition to oral incompetence (Shetty and Dermatosurgery Task Force 2008).

Procedure

To better identify the points of injection, the patient must be seated and asked to try to reach his nose with the lower lip (Ascher et al. 2010).

The treatment can be done in two or in only one central point. Few authors recommend the application in only one point (Wollina and Konrad 2005), and the majority agrees that better results are achieved when using two points of injection. In our experience, the use of just one point resulted in asymmetry.

The doses for the mentum vary depending on the toxin that is being used. When using the

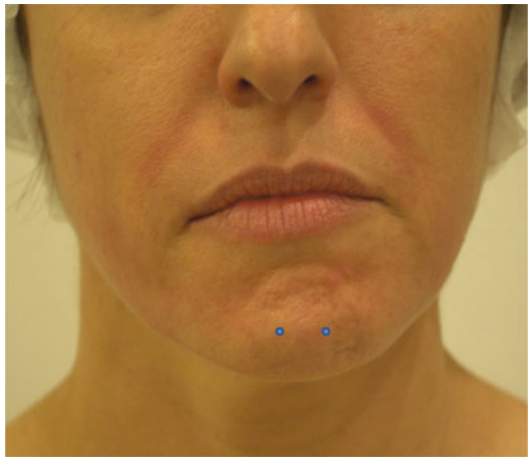

Fig. 7 The mentum during rest. Injection sites

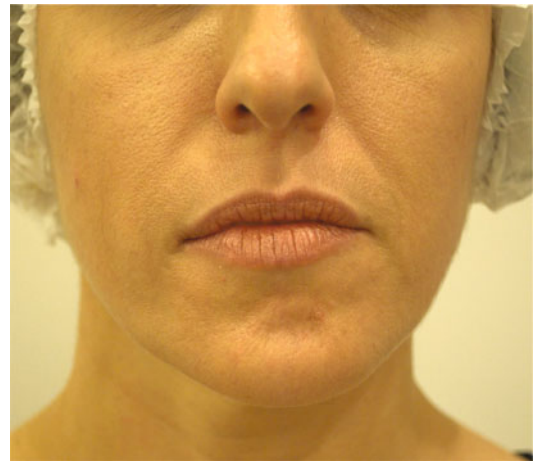

Fig. 9 The mentum during rest. After the treatment

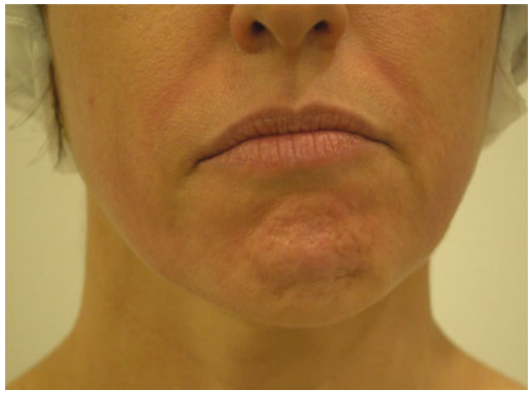

Fig. 8 Contracting the mentalis before the treatment

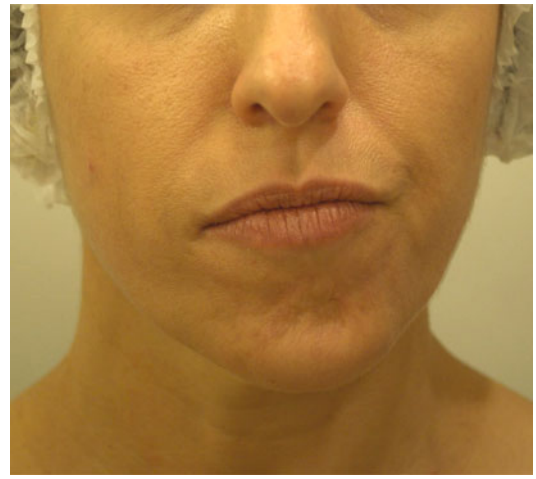

Fig. 10 Trying to contract the mentalis. After the treatment

onabotulinum toxin, the dose should not exceed 5 U per point, with a total dose of no more than 10 U (Raspaldo et al. 2011). Other authors are more conservative and recommend a total dose of no more than 5 U (Wollina and Konrad 2005). The recommended dose of the abobotulinumtoxin is of 5–10 U per point (Ascher et al. 2010) and for the incobotulinumtoxin 6 U is the total dose (Yutskovskaya et al. 2015). The dose can be customized, depending on the muscle mass (Ascher et al. 2010). In our daily practice, we use two points of 2 U of the onabotulinum toxin or two points of 6 U of the abobotulinumtoxin, with excellent results.

The injection points should be placed symmetrically on the chin protuberance, at 5 mm of the medial line (Raspaldo et al. 2011). The needle should be perpendicular to the skin, and injection should be intramuscular, to the middle third of the needle (Ascher et al. 2010) (Figs. 7, 8, 9, and 10).

Results

The treatment of the mentalis with BTX prevents the appearance of skin irregularities during speech and

other facial movements giving a more harmonic and youthful facial aspect. The improvement of the transversal crease between the lower lip and the prominence of the chin, contributes to a better appearance of the perioral region. For the young patient, the use of botulinum toxin in the mentum is prophylactic preventing the development of this defect at the chin. In our daily practice, the patients are very satisfied after the treatment of this region improving a defect that sometimes they did not know until we showed it to them.

Adverse Effects

The use of a total number of units that exceed those recommended might affect the orbicularis oris, as well as the depressor labii inferioris, leading to the incompetence of the mouth as a sphincter and an asymmetric lower lip.

The asymmetry of the lower lip due to the accidental diffusion of the toxin to the depressor labii inferioris is an aesthetic disorder and can be minimized by the injection of 1–2 U of the onabotulinum toxin, or an equivalent dose of other toxin, in the contralateral muscle.

The incompetence of the lower lip, as it was described at the beginning of this chapter, faces unpleasant consequences, such as difficulty to say the "p" and "b", to drink through a straw, to blow, and to whistle. In some cases, the patient is unable to retain the saliva and cannot stop drooling.

We should remember that when treating the asymmetry of the lower lip, the injection point must be away from the orbicularis oris in order to prevent the creation of another adverse event.

When treating at the same time, the mentalis and the depressor anguli oris, the use of smaller number of units is recommended (Ascher et al. 2010), especially in those patients that are doing the treatment for the first time.

The concomitant use of botulinum toxin and fillers, to improve the irregular appearance of the skin and the horizontal crease of the chin, does not have such good results as when they are used in the perioral region (Raspaldo et al. 2011: Carruthers and Carruthers 2003). Even so, some authors recommend the use of this association to achieve better results (Ascher et al. 2010).

Conclusion

The use of the botulinum toxin in the perioral area is an important tool for the treatment of the perioral wrinkles. As monotherapy, its efficacy is limited by the impossibility of using doses that promote the total paralysis of the orbicularis oris that would cause a dysfunction of the lips. Patients should be aware of it, especially those who use the toxin in other areas of the face. However, when used in association with other treatments, like fillers and resurfacing, the BTX contributes for the achievement of better and long-lasting results. As for all the other indications of the botulinum toxin, the correct patient selection and the use of a refined technique are essential for the achievement of good results.

The use of the botulinum toxin, for the treatment of the chin, can greatly contribute to the rejuvenation of the face. Using few units, it is possible to obtain results that usually surprise the patient, who sometimes did not even realize the existence of these defects until we show and correct them.

Take Home Messages

- Botulinum toxin for the perioral region
  - Select patients carefully
  - Use as few units as possible
  - Inject symmetrically
  - Inject at least 1 mm from the philtrum
  - Stay away from the corners of the mouth
  - Inject no more than 2 mm from the vermilion
  - Inject superficially
  - Caution when treating the lower lip
  - Use with fillers and resurfacing treatments
  - Use ice pads and anesthetic cream

- Botulinum toxin for the mentum
  - Inject in two symmetric points
  - Use few units
  - Stay away from the lower lip – to not reach the orbicularis oris
  - Stay medial – to not reach the depressor labii inferioris
  - Inject perpendicular to the skin

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Botulinum Toxin for Mandibular Contour

Rodrigo Moraes Ferraz and Julio Cesar Gomes Silveira

Contents

Abstract

The mandible contour plays a very important role in the beauty and youthfulness of the face. Repeated contraction of the depressor muscles of the lower third of the face and neck is one of the important causes leading to loss of contour in the jawline area. By relaxing these muscles, botulinum toxin A (BoNT-A) injections on the lower face can help postpone plastic surgery to improve the area and also bring a rejuvenated aspect for those patients who are not willing to undergo surgical procedures. It is most likely that repeated treatments starting early in the aging process will avoid muscle shortening and therefore have a very beneficial impact in preventing the changes that lead to loss of

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_6

contour. The masseter muscle defines the posterior jawline, and its hypertrophy is an undesired feature especially for Asian females. BoNT-A has successfully been used to reduce masseter muscle mass and change the contour of the posterior mandible. Physicians have to be educated on the importance and potential benefits of treating the lower face with BoNT-A.

Keywords
Platysma · DAO · Mentalis · Lower face contour · Jawline · Mandibular area · Depressor muscles · Nefertiti Lift · Masseter hypertrophy · Botulinum toxin · BoNT-A

Introduction

A well-defined mandibular line is not only related to beauty, but it is also a key feature of youth in the lower face. This is due to the fact that the jaw loses its definition along the aging process. Although there are different mechanisms that together will cause this change, repeated contraction of mimic muscles in the lower face and neck plays a very important role in the process (Nácul 2005).

Early treatments with botulinum toxin in the lower face and neck targeted the depressor anguli oris (DAO) muscle to improve the Marionette lines and the platysma to reduce lines and skin laxity on the neck. Increased experience has shown that by reducing the action of these depressor muscles, treated subjects obtained a significant improvement in jawline definition. Further understanding of the aging mechanism of the mandibular area has shown that depressor muscle activity will not only pull the skin of the lower face down but also negatively influence fat compartments and ligaments in the area (Le Louarn 2009 May).

Treating the lower face with BoNT requires expertise and anatomy understanding in order to avoid undesired effects, especially around the mouth. Although less obvious and much less common for physicians to treat this area than the upper face, the immediate and especially the long-term results with repeated injections are very rewarding for both patients and doctors.

The masseter muscle is also a very important landmark in the lower face, and its muscle mass is the most important feature of the posterior jawline. Masseter BoNT-A injections can alter the shape of the jawline and has been well documented in Asian populations, with up to 50% reduction in muscle thickness and bulk. More recently, BoNT-A has been shown to be beneficial in improving the aesthetic appearance in non-Asians (Liew and Dart 2008). Western patients require smaller doses but may also have additional improvement in function attributed to bruxism control.

Part 1: BoNT for Recontouring the Jawline

History

In 1998 Brandt and Bellman introduced the idea that the downward pull of the platysma muscle contributes not only to the aged appearance of the neck but also creates jowls with loss of definition of the chin and jawline (Brandt and Bellman 1998). They reported successful elevation of the platysma and the mandibular area by injecting an average of 50–100U of onabotulinumtoxinA (in some cases up to 200U) per treatment session with no serious complications. This dose has been further discussed by different authors who reported serious complications like dysphagia and neck weakness with doses from 75 to 100U of onaBoNT-A, and who also noted the benefits of treating the platysma to improve the lower third of the face with much lower doses (Carruthers 2003).

In 2007, Levy improved the technique of treating the muscles responsible for depressing the lower third of the face and named his technique "The Nefertiti Lift" after the eighteenth-century Egyptian dynasty queen whose beauty and perfect jawline have been depicted in various works of art (Levy 2007). In his original series of

130 patients, patients were treated with an average of 15–20U of onaBoNT-A per side, injected along and below the mandible and also the superior part of the platysmal bands. Le Louarn et al. demonstrated that not only the platysma but the depressor anguli oris (DAO) and the mentalis muscle combined contraction expels their underlying fat posteriorly toward the jowl, thus worsening the mandibular contour (Le Louarn 2007).

Anatomy

The mandible is the longest and strongest bone in the face. It suffers severe and overall bone resorption and in many cases tooth loss as age progresses (Tamura 2010). The inferior edge of the mandible defines the contour of the lower third of the face and its demarcation from the neck. The mandible is anatomically divided into three: ascending branch, horizontal branch (body), and chin. The junction of the posterior edge of the horizontal branch with the lower edge of the ascending branch forms the mandibular angle. The mandibular line is defined by the area between the angle and the chin (Nácul 2005).

The subcutaneous mandibular fat is divided into four fat compartments. Two of them are above the inferior mandibular border, the superior and inferior mandibular fat compartments. A third one is located right below the mandible and the fourth covers the parotid-masseteric fascia. A septum separates the two compartments located above from the one located below the mandible. Some platysmal fibers merge with the mandibular septum and are attached to the anterior mandibular border (Braz and Sakuma 2013).

The muscle anatomy of the lower face is complex because muscles in this area are close together and their fibers merge at different levels and depths to perform heterogeneous functions. The platysma, the depressor anguli oris (DAO), and the mentalis are the three target muscles when recontouring the lower face. It is important to remember their close anatomical relation to the risorius, the orbicularis oris, and the depressor labii inferioris (DLI) in order to avoid unwanted treatment to these muscles and secondary side effects.

The DAO is a triangularly shaped muscle with a large deep base on its mandibular origin and a superficial insertion into the modiolus. Its contraction pulls the oral commissures inferiorly creating the Marionette fold. The mentalis muscle originates deep in the mandible and inserts superficially in the medial chin skin. It raises and protrudes the lower lip when contracted creating a dimpling effect on the skin and flattening the chin (Trévidic et al. 2015). The platysma is a flat, broad, and thin superficial muscle that runs under the thin subcutaneous tissue of the neck. It has its origin in the superficial fascia of the superior chest, from the clavicle and the acromial regions. It runs upward to the mid-cheek, and its fibers merge with those of the risorius, the DAO, the orbicularis oris, the DLI, and finally the superficial musculoaponeurotic system (SMAS) and skin of the cheeks. These connections explain why contraction of the platysma leads not only to descent of tissue in the neck area but also allow the platysma to pull down the cheek skin and the corners of the mouth (Le Louarn 2007; Levy 2015). Contraction of the anterior bands erases the cervico-mental angle and augments its width, whereas lateral bands' contraction erases cervico-mandibular demarcations and increases neck diameter in its lateral part (Le Louarn 2009).

Age-Related Loss of Mandibular Contour

Multiple mechanisms account for the mandible's loss of contour with age. The mandible is the longest and strongest bone in the face, and all its surfaces undergo resorption and thinning, reinforcing the aspect of a drooping face (Tamura 2010). The alveolar parts of the mandible and the maxillae suffer severe bone resorption, frequently leading to tooth loss and reducing the mandible's vertical dimension. As age progresses, the mandible's lateral projection is erased, and the angle of

the mandible appears to merge from the buccal region into the neck.

Loss of fat in the malar and perioral compartments associated with increased skin laxity creates a relative excess of the skin in the lower third of the face, contributing to loss of mandibular contour. Loss of masseteric ligament support allows descent of facial fat to the mandibular border, leading to the formation of jowls (Coleman and Grover 2006). Volume loss and atrophy of the inferior and superior mandibular fat compartments and their ptosis due to laxity of the mandibular septum give the impression of increased volume in the submandibular compartment (Braz and Sakuma 2013). This fat pad may also protrude between the two free margins of the platysma muscle adding to the fullness of this area.

The repeated contraction of depressor muscles on the lower face and neck performs a constant downward pull in the entire mandibular area. Contraction of the platysma's lateral bands directly pulls down the entire mandibular area, aggravating the ptosis of the jowls and submandibular fat, whereas contraction of the anterior bands helps erase the definition between the chin and the neck (Le Louarn 2007) (Fig. 1). The frowning expression created when the DAO is contracted worsens not only the melomental groove but also contributes to increased jowl volume. Mentalis muscles contraction contributes to loss of lower face contour by flattening the chin and indirectly adding to the DAO's inversion of the corners of the mouth (Trévidic et al. 2015) (Fig. 2).

Furthermore, Le Louarn demonstrated that contraction of the depressor muscles around the mandibular line eventually leads to increased resting tone, muscle shortening, and structural aging. This mimic muscle shortening would also cause the deep fat to be expelled superficially and contribute to worsening the jowls (Le Louarn 2007).

Injection Techniques Using Abobotulinum Toxin

The goal when treating the mandibular contour is to regain a defined demarcation between the face and the neck. As previously discussed, weakening the depressor muscles on the lower third of the face reduces the negative effect they have pulling down the structures around the mandibular area, including the skin, fat, and ligaments. It also allows the zygomaticus to elevate the corners of the mouth and consequently the lower face. If we consider the long-term damage caused by the repetitive contraction of the platysma, DAO, and mentalis on the mandibular contour in a patient's life span, we believe that early and

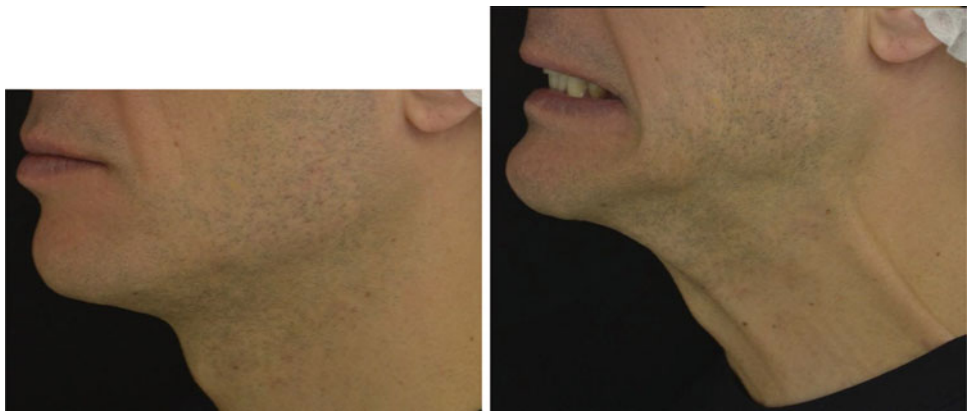

Fig. 1 Mandibular contour at rest in a mid-30s patient (*top*) and depressor action of platysma at contraction (*bottom*). Notice the downward pull the muscle exerts in the jawline area even in a young patient

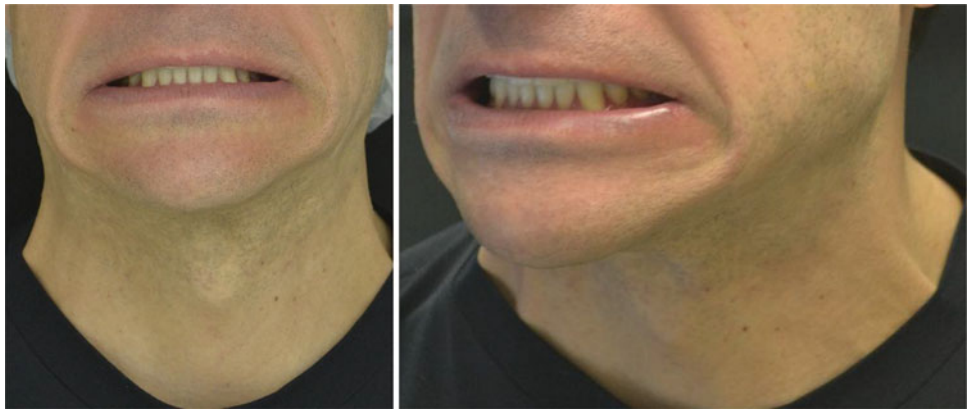

Fig. 2 Contraction of the DAO and mentalis muscles pulling down the anterior jawline

consecutive treatments could not only improve the immediate appearance of the lower third of the face but also help prevent aging and contour loss of the jawline.

Patients with severe skin laxity and/or significant submandibular fat accumulation will not benefit from BoNT-A injections and may be good surgical candidates. Toxin injections are also an important adjunct treatment when fillers are placed in the Marionette and mandibular areas because reduced muscular activity will increase hyaluronic acid filler duration. As previously discussed, bone resorption and loss of fat in the mandibular compartments play an important role in the pathophysiology of lower face aging.

Ideally BoNT-A injections should start early as prevention, even when volume loss is still not an important feature. On the other hand, when loss of contour has been installed, combining fillers to replace volume and rebuild mandibular structure will bring synergistic effects and very rewarding jawline rejuvenation.

Platysmal bands: Patients are asked to contract the platysma, and injection points are marked along the platysmal cords in a total of 2 or 3 points per band depending on muscle length and strength. The posterior bands are always treated when aiming for jawline improvement, and anterior bands are sometimes treated if they have a strong action in the jawline and only if there isn't severe submental skin laxity associated (in those cases toxin injection could worsen the skin ptosis). Injection in 2 or 3 points along the mandibular bone where platysmal insertion can be observed during contraction is also recommended. We inject 5 units of abo-BoNT-A (Speywood units) per point along the bands and try to limit the total to 100 Speywood units (SU) in order to avoid complications. Eventually smaller doses (2.5 SU) are injected between the bands when diffuse muscle contraction is seen in the area. Since the platysma is a very thin muscle, when one cannot be sure the needle is intramuscular, superficial subdermal injections are a good reference depth. Patients are seen after 3 weeks, and if necessary asymmetric contracting bands are corrected by injecting in the active areas (Fig. 3).

DAO: Patients are asked to show their lower teeth in order to help them contract the DAO. It is safer to inject in the lower portion of the muscle, close to where it meets the mandibular line to avoid side effects. If the injection point is not clear when patients contract the muscle, an imaginary line can be drawn following the nasolabial groove to the jawline to determine where to inject. A maximum of 5–7.5 SU are injected deep (intramuscularly) per side into one single point (Fig. 3).

Mentalis: Asking patients to wrinkle their chin or to raise the lower lip will help identify the body

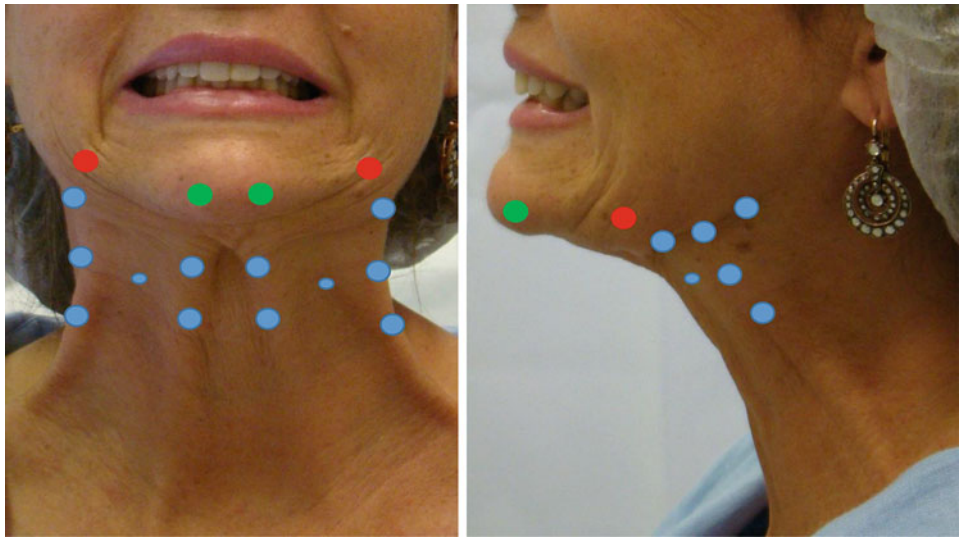

Fig. 3 Injection points for jawline contour treatment. *Blue circles* represent platysma injection points (bigger and smaller doses as described), *red circles* point DAO injection sites, and *green circles* mark where the mentalis should be treated

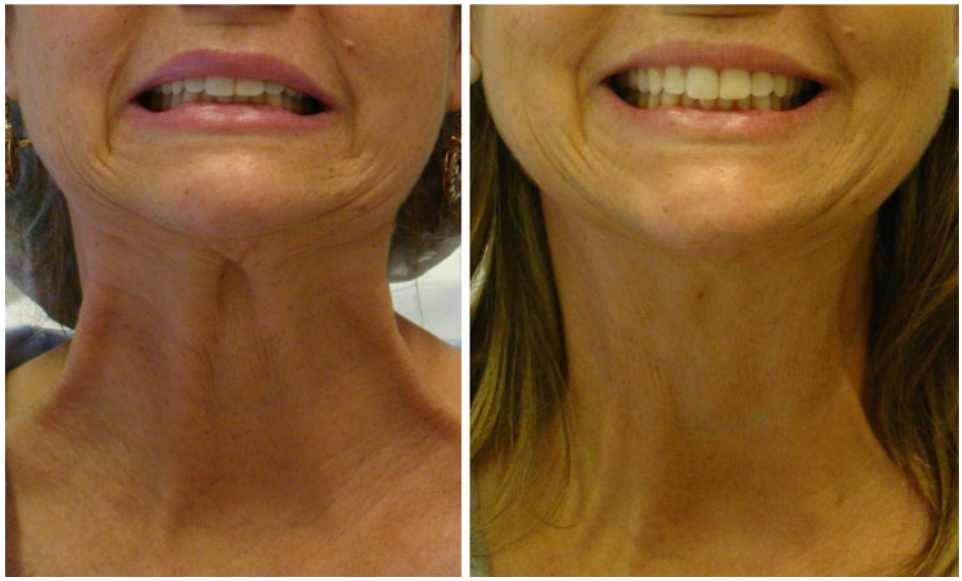

Fig. 4 Patient contracting DAO, mentalis, and platysma before and after BoNT treatment

of the muscle and its strongest central area. Between 5 and 7.5 SU are injected deep into each side of the muscle symmetrically in the mid- to lower chin (Fig. 3).

Figure 4 shows how treating these three muscles will reduce their depressor activity on the entire jawline area by reducing their contraction after BoNT treatment (Fig. 4). Results obtained

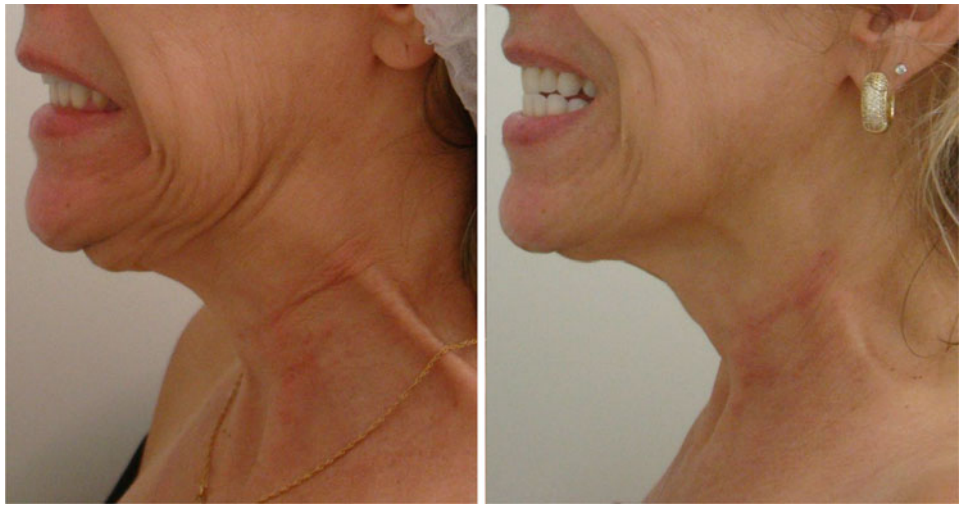

Fig. 5 Mandibular contour at contraction before and after BoNT-A treatment

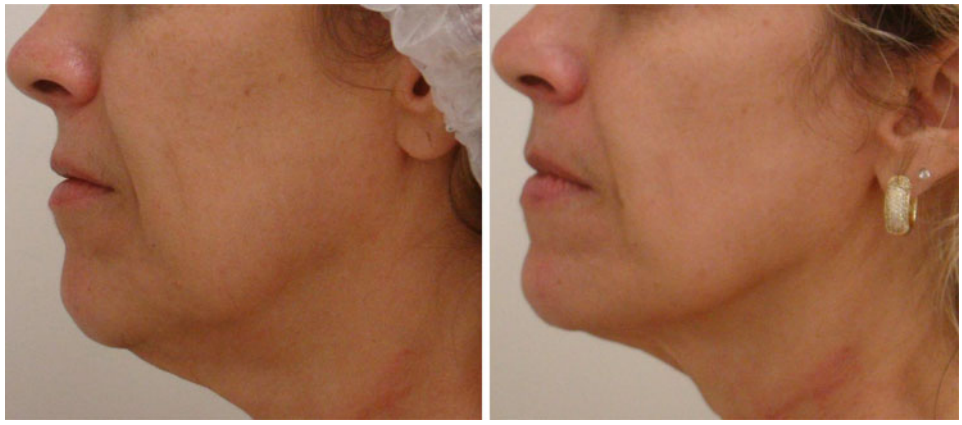

Fig. 6 Mandibular contour at rest before and after BoNT-A treatment

at contraction and at rest are exemplified in Figs. 5 and 6.

Side Effects

In the lower face as a whole, most complications are related to the use of large doses. The use of toxin around the mouth, including the DAO and the mentalis muscles, may lead to an incompetent mouth, asymmetric smile, drooling, flaccid cheek, difficulties in speech, and inability to purse the lips (Carruthers 2009). Caution should be taken to avoid inadvertent injection of the DLI, the most common side effect when treating the DAO and mentalis muscles and causing patients to report asymmetry.

In the neck, large doses of BoNT can lead to swallowing impairment and general local weakness. The use of large doses has led to reports of dysphagia, either due to injection directly into the sternocleidomastoid and omohyoid muscle or

due to diffusion of the toxin into the muscles of deglutition. More commonly patients have reported neck weakness, especially when trying to raise their head from a supine position. This side effect is also due to undesired treatment of the sternocleidomastoid muscle. Precise placement of the toxin in the platysma and avoidance of high doses are important preventive measures since there is no treatment to the complication once it has occurred (Klein 2004).

Part 2: BoNT for Masseter Hypertrophy

History

Masseter muscle hypertrophy is an uncommon condition that can be presented as a widened lower facial contour. It can occur in both genders, usually between the second and third decades of life and can be bilateral or unilateral (Choe et al. 2005). Temporomandibular joint disorders, night bruxism, chewing of gum, and long-term dental treatments are commonly associated with this condition, especially in Western patients, and it is mostly idiopathic in Eastern patients (Park et al. 2003; Liew and Dart 2008). This condition is mostly a clinical diagnosis based on the bulkiness of masseter muscle observed by palpation and by asking the patient to clench the jaw. The differential diagnosis should be made with salivary glands and bone tumors, lymphadenopathy, and lymphomas. Ultrasound and computerized tomography can be helpful for a diagnosis.

The shape of the mandible bone and the bulkiness of the masseter muscles will be very important to define the posterior contour of the lower face. Masseter muscle hypertrophy will produce an increased width of the lower face or a square face. Historically, this is aesthetically viewed as unfeminine especially among Asian women (Chang et al. 2011).

Treatments of masseter muscle hypertrophy involve conservative therapy, surgery, and, most recently, the use of botulinum toxin. The use of muscle relaxants and occlusal splints are conservative modalities. Surgical treatment consists of partial resection of the hypertrophic masseter muscle using an intraoral or extraoral approach. However, the muscle removal is risky as it may injure the mandibular branch of the facial nerve and can be complicated by bleeding, pain, scars, and trismus (Yu et al. 2007). In 1994 BoNT-A was described as a potential treatment of masseter hypertrophy, offering a simple and breakthrough alternative to surgery for contouring the lower face.

Anatomy

The masseter is one of the muscles of mastication and is located on each side of the face. The superficial portion originates from the anterior two-thirds of the inferior border of the zygomatic arch up to the zygomatic process of the maxilla. The deep portion originates from the deep and medial surface of the zygomatic arch. The superficial and deep portion insertions are the angle and ramus of the mandible. The parotid gland is intimately related to the masseter muscle. The parotid duct serves as a conduit for saliva between the parotid gland and the oral cavity. A virtual line drawn from the tragus connecting to the midportion of the upper lip estimates the most common location of the parotid duct, which lies along the middle third of this line.

Injection Technique Using Abobotulinum Toxin

Differently from treating hyperkinetic facial wrinkles with botulinum toxin, the treatment of masseter muscle hypertrophy will be based on the temporary muscle atrophy induced by the acetylcholine blockade at the neuromuscular junction by BoNT-A. Therefore, the results will be observed later than we usually see when treating facial wrinkles. Animal experiments show muscle atrophy histologically as soon as 10–14 days after injection and continuing over a 4–6-week period.

Fig. 7 *Left* Before injection of BoNT-A. *Right* 3 months after injection of BoNT-A (Source: Chang et al. 2011)

The fiber atrophy is a reversible phenomenon, and recovery usually occurs over 4–6 months (Park et al. 2003).

When treating masseter muscle hypertrophy, most patients show significant muscle mass reduction in around 3 months after injection, and patients usually report an improvement in facial contour between 3 and 6 months after the injection (Fig. 7). Most patients report the return of masseter hypertrophy at about 9 months after the treatment (Yu et al. 2007). In addition to the aesthetic benefits, many patients have functional relief from teeth clenching and bruxism (Liew and Dart 2008).

The effective dosage of botulinum toxin A for treating masseter hypertrophy is usually 100–200 SU per muscle (Choe et al. 2005; Park et al. 2003). The lower posterior portion of the muscle is a safer injection site and can prevent a paralysis of the risorius and zygomaticus muscles and injury to the parotid duct. When marking the injections site we should ask the patient to clench their teeth and outline the anterior and the posterior borders of the masseter muscles (Fig. 8). A line connecting the tragus to the midportion of the upper lip estimates the general location of the parotid duct, which lies along the middle third of this line. Injection points must be below this line, placed on the main bulk of the muscle. We use 5–6 points separated by 1 cm intervals and inject 30–40 SU per point, deep and intramuscular

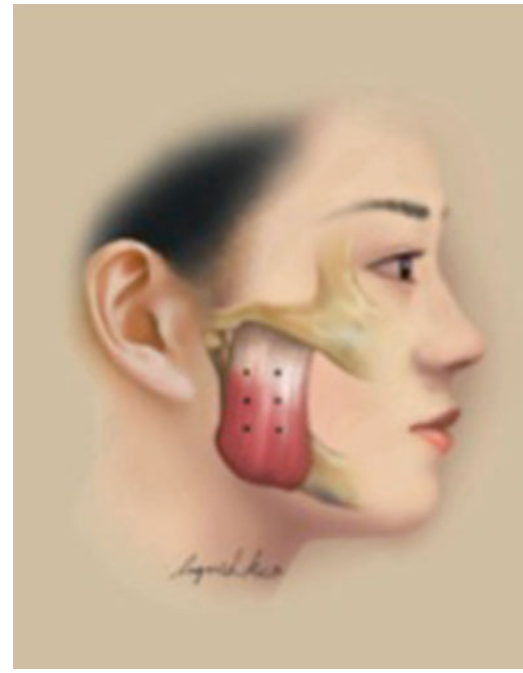

Fig. 8 The masseter muscle and injection sites (Source: Chang et al. 2011)

(Liew and Dart 2008). Single injection point should be avoided as patients can have irregular muscular bulging during mastication in the remaining parts of the muscle that were not treated and may need additional injections later (Choe et al. 2005).

Side Effects

Pain at injection site is the most common side effect. Many patients experience a decrease in the biting force during the first weeks, but this will most often improve after 3 weeks by compensation of other masticating muscles. Patients should be warned about masticatory difficulty when eating hard food in the first few weeks. Speech disturbance can also occur but it is also transient, lasting from 1 to 4 weeks after injection. Reduction in the width of the mouth aperture on smiling is probably related to the diffusion of botulinum toxin to the neighboring buccinators or risorius muscles, and therefore we should keep the injection point at least 1 cm from the anterior border of the masseter muscle (Liew and Dart 2008). Facial asymmetry should be monitored when the results become evident 3 months later and can be corrected with additional treatment to correct the bigger bulge. Care should be taken when treating patients with prominent cheeks, as they may be accentuated by the later atrophic changes of the masseter muscle (Choe et al. 2005). On the other hand, if the placement of the injection site is too high or too close to the anterior border of the masseter, the patient can have a sunken cheek as a complication (Yu et al. 2007). This can be avoided by placing the injections on the lower posterior portion of the masseter. The most serious side effects are the traumatic punction of the parotid duct or injection of botulinum toxin in the interior of the parotid gland. The first can produce leaking of saliva and even fistulae formation into the skin and may need surgical correction. The later can block saliva secretion by the gland until the botulinum toxin effect ends. To avoid these complications, treatment must be done below the imaginary line connecting the tragus to the midportion of the upper lip (Tamura 2007).

Take Home Messages

- Early treatment of depressor muscles in the lower face can prevent loss of jawline contour.
- Muscle activity is one of the important factors causing loss of mandibular contour.
- Lower doses are required when treating the lower face when compared to the upper face.
- Fibers of the DAO, mentalis, and platysma muscles intermingle in the mandibular area where they have synergistic effects.
- Multiple injection sites are preferable to single injection site when treating the masseter.
- Injection must be on the lower posterior portion of masseter, at least 1 cm from the anterior border of the masseter muscles and below an imaginary line connecting the tragus to the midportion of the upper lip.
- Results for masseter hypertrophy appear 3 months after injection and usually last for 9 months.
- Avoid treating the masseter in patients with prominent cheeks.

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Botulinum Toxin on the Neck

Rodrigo Biagioni Ribeiro de Abreu Maia and
Adriana Biagioni de Almeida Magalhães Carneiro

Contents

Abstract

The use of toxin botulinum A (BTXA) for aesthetic indications continues to grow in popularity due to its safety, quick effects, and short recovery time. Its use on the neck to improve vertical and horizontal lines is becoming more common, due to the better understanding by physicians of the role of the contraction of the platysma muscle during the senescent changes seen in the neck. The downward pull of the platysma over time leads to a loss of the definition of the chin and the jawline, the jowls, the vertical bands, and the horizontal rhytides. The cervical treatment can also soften the melomental fold and improve the lateral cheek lines by weakening the

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_7

downward force exerted by the platysma on the structures of the lower face. Knowledge of the anatomy of this region, familiarity with toxin botulinum injection, and technical experience are crucial for the best results. This chapter discourse about the treatment of the vertical bands and the horizontal lines of the neck using botulinum toxin.

Keywords

Botulinum toxin · Neck · Platysmal bands · Necklace lines · Jow · Jawline · Jowls · Vertical bands · Lower face · Platysma · Horizontal lines

Introduction

Botulinum toxin has been widely used to improve facial aesthetics. However, its cosmetic use is not restricted to the face, and application techniques in other places, such as the neck, has been expanded and improved in some countries.

The increase of the treatment at the middle and lower thirds of the face and the neck with botulinum toxin is due, in part, to the safety and efficacy of botulinum toxin in these regions but also to the better understanding by the physicians of the influence of the muscle contraction and volume depletion in the aging process (Carruthers and Carruthers 2003).

Anatomy

The platysma, the mimic muscle with the largest surface, is a broad sheet of muscle that originates from the superficial fascia of the upper chest, clavicular and parasternal regions, although it can vary in extension (Fig. 1), sometimes originating higher at the clavicular level or as a V shape upside down with the lateral parts covering the lateral pectoralis and at the center originating at the furcula level. It envelops the anterior and lateral neck except for a thin strip devoid of fibers at the midline in some patients. When the platysma have no fibers at the midline, they can be seeing as separated bands or partially crosslinked bands, and some patients lose the strip devoid of fibers at the midline with the aging process. The platysma crosses the mandible and then blends into the superficial muscular aponeurotic system involving the muscles of facial expression of the lower face, including the depressor anguli oris, mentalis, risorius, and orbicularis oris.

Fig. 1 Playtisma muscle, its extension, and few correlated neck muscles (Courtesy by dr. Bhertha Tamura)

The larynx and the muscles of deglutition are located deep to the platysma in the neck but the platysma is very thin at the medial area where they are located. Injections in a deeper layer at the medial line above or below the hyoid bone in a greater number of units or with a BTXA that has a larger halo of action may lead to serious complications (Carruthers and Carruthers 2003; Becker-Wegerich et al. 2002; Cartee and Monheit 2011; Spósito 2002). Suprahyoid muscles are the digastric, the stylohyoid, the mylohyoid, and sternocleidomastoid and infrahyoid the sternohyoid, tireohyoid and the omohyoid. The muscles from the jaw to the clavicle participate with the sternocleidomastoid and platysma for the movement of the neck, especially to move the head upward and downward as well as act as part of the deglutition. Impairment of these muscles might lead to dysphagia, weakness of the neck for movements as pulling the head, and also respiratory complications.

There are three primary anatomic variants of the platysma with even more different anatomic varieties described in the literature. Frequently this muscle extends beyond the typical insertion points (Fig. 1) (Becker-Wegerich et al. 2002).

Aging Process

The contraction of the platysma muscle results in horizontal and vertical wrinkles at the cervical region and at parts of the middle and lower décolleté. In association with the posture of the neck, the platysma is also responsible for the semicircular lines around the neck – necklace lines. The cervical treatment can also soften the melomental fold and improve the lateral cheek lines by weakening the downward force exerted by the platysma on the structures, especially the depressor anguli oris m., to which it inserts in the lower face (Carruthers and Carruthers 2003; Becker-Wegerich et al. 2002; Cartee and Monheit 2011; Spósito 2002; Stephan and Wang 2011).

There is an invariable loss of soft-tissue support and elasticity of the neck, resulting in a more prominent contraction of the platysma muscle. That, combined with an age-related separation and clumping of anterior fibers of the platysma generates apparent, tense muscular cords vertically in the neck – the platysmal bands (Cartee and Monheit 2011).

The aging changes of the muscle of the neck may be accompanied by a jowl descending, a submandibular gland ptosis and bone resorption. In patients having such characteristics, added to a fat accumulation, the botulinum toxin can emphasize the muscle strands, rather than soften them but might improve the necklace lines if the patient does not have a short cervical length. It is therefore required careful selection of patients for the treatment of neck, and those with obvious platysmal bands, good local skin elasticity and minimal fat descent are good candidates for best results (Carruthers and Carruthers 2003; Matarasso et al. 1999; Kane 1999; Stephan and Wang 2011).

Botulinum Toxin A

There are at least four botulinum toxin A products available: Botox (Onabotulinum toxin A), Dysport (Abobotulinum toxin A), Xeomin (incobotulinum toxin A), and Prosigne. The most important difference between them is the effectiveness of the units that depends on the biological preparations by each manufacturer. Numerous in vitro and in vivo studies have attempted to define the equivalence between Botox units for OnaBontA (bU) and Speywood units for AboBontA (sU), the most used toxins. The authors use and recommend a conversion of 1:2.5, which has become the most commonly quoted unit ratio among experienced injectors and has been demonstrated comparable efficacy with the two botulinum toxin A products (Cartee and Monheit 2011; Spósito 2002; Stephan and Wang 2011).

Vertical Platysmal Bands Treatment

Abobotulinum Toxin A (AboBontA) Technique

Vertical platysmal bands are treated with a series of 2–5 injections of 2–4 U in each band superficially, beginning near the jawline and progressing caudally at 1.5–2 cm intervals. The injection is placed intradermally. Asking the patient to contract the platysma and pinching the band before injection can be helpful (Fig. 2).

The total dose per band should be kept less than 25 U. To limit the total dose, no more than three or four bands should be treated in one session. Care must be taken to avoid deep injections in the neck or overdosing (greater than 100 U).

Onabotulinum Toxin A (OnaBontA) Technique

We are facing the neck treatment as a unique structure with different platysma behavior or extension and contraction pattern as the global

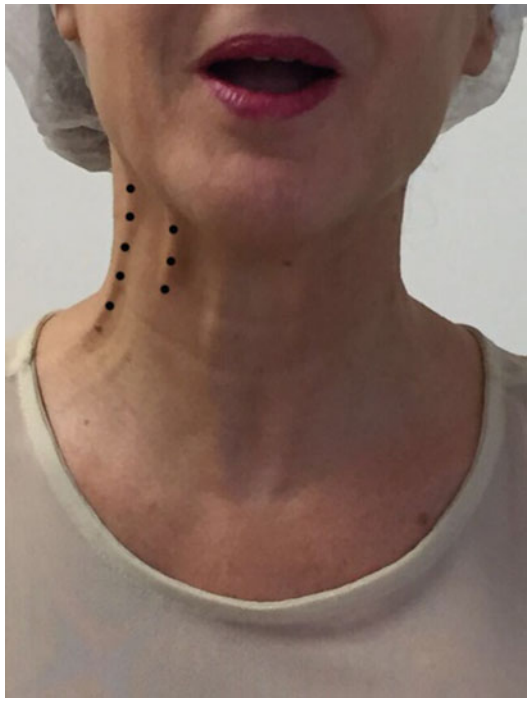

Fig. 2 Contracting the platysmal bands

results for the facial contour, the bands, the necklace lines can be improved analyzing each patient and their personal anatomy (Tamura 2012). But if considering only the bands, we use to inject 1–2 U very superficially pinching them between the fingers. Two botulinum toxin units near the jaw and 1 U near the clavicle and depending on the muscle strength every 1.5–2 cm apart. In general, we also try to identify the posterior band and treat them as they become strong after the medial bands weakens. Maximum 30 U for all bands.

Horizontal Lines Treatment

Abobotulinum Toxin Technique

The horizontal necklace lines are caused by the superficial musculoaponeurotic system attachments in the neck and can be treated by injecting small doses of botulinum toxin distributed along lines over multiple sites (Fig. 2). Doses of 1–2 U are injected in the deep intradermal layer, along the horizontal neck lines at approximately 1 cm intervals. Subcutaneous injections should be avoided because there are deeper venous perforators that can bleed, and the underlying muscles of deglutition, of the larynx or the sternocleidomastoid, could be affected. No more than 15–20 U of botulinum toxin should be used for horizontal lines per treatment session.

Onabotulinum Toxin Technique

In early times we used to inject 0.5–1 U every 1–1.5 cm on the sides of the horizontal neck lines and not at the lines, 1 cm apart from the lines (0.5 cm above and under the lines) but the results were not predicable; some patients had good results, others almost no results. After the improvement of the technique, facing the platysma as the most important muscle of the neck for the treatment of lines, bands, and facial contour we have changed the technique. Asking the patient to contract the platysma, detecting the strongest band and extension of the muscle, we usually inject 3–6 U in the jawline, then reducing to 3–4 U until the most distant (lower) point, in which we inject 1 unit. Minor impairment of the head movements might happen even with 25–30 U and 50 U should be avoided (Tamura 2012). Figure 3 shows a before and after with this technique.

Adverse Effects and Complications

The cosmetic use of botulinum toxin in general has been safe and well tolerated. The adverse effects have been ephemeral. Potential complications of the application of botulinum toxin A in the neck are mild pain, erythema, discrete edema, and bruising at the site of injection, local infection, sensation of loss of strength, transient numbness, and allergy (Carruthers and Carruthers 2003; Becker-Wegerich et al. 2002; Cartee and Monheit 2011; Spósito 2002; Stephan and Wang 2011; Tamura 2012; Klein 2003; Sorensen and Urman 2015; Sarrabayrose 2002).

Excessive doses of botulinum toxin in the neck over 50 U(onaBontA)–100 U(aboBontA) can

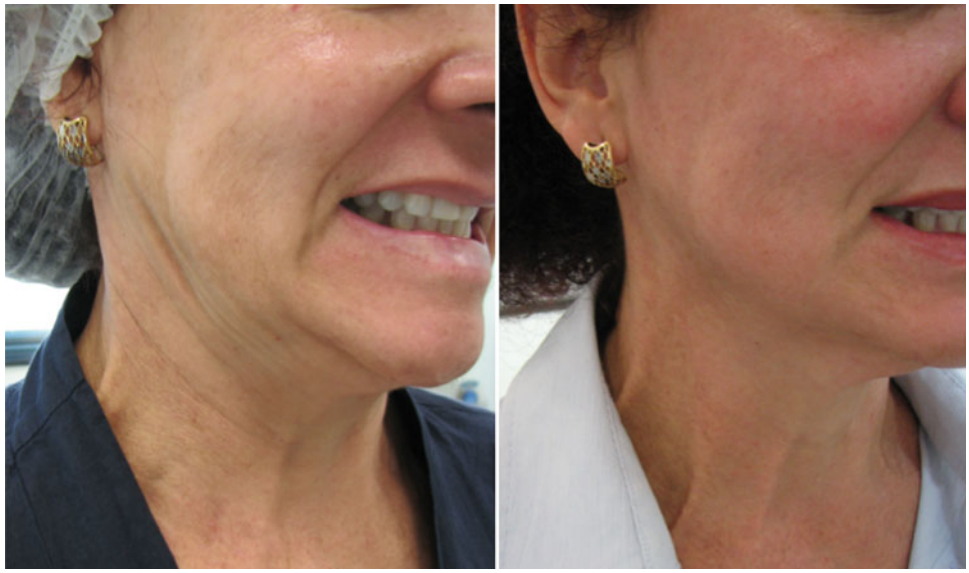

Fig. 3 Pre and post treatment of platysma muscle

produce dysphagia, hoarseness, and weakness when bending the head due to either local diffusion or direct injection of the toxin into the sternocleidomastoid, laryngeal muscles, omohyoid, or muscles of deglutition. If dysphagia occurs, the patient should be encouraged to change his usual diet to a soft liquid diet. Metoclopramide stimulates motility of the upper gastrointestinal tract and could improve swallowing in some cases (Cartee and Monheit 2011; Stephan and Wang 2011; Tamura 2012; Klein 2003; Sorensen and Urman 2015).

Contraindications

Absolute contraindications include allergy to the drug or its components, such as albumin, infection at the site of injection, during pregnancy or breast feeding, and patient's unrealistic expectation. Relative contraindications are associated neuromuscular disease, use of synergic drugs (such as aminoglycosides and calcium channel blockers), aspirin or nonsteroidal anti-inflammatory drugs within 4 weeks prior to the procedure, and associated and/or decompensated coagulopathy (Cartee and Monheit 2011; Spósito 2002; Stephan and Wang 2011; Klein 2003; Sarrabayrose 2002).

Take Home Messages

- The platysma originates from the superficial fascia of the upper chest, clavicular, and parasternal regions. It envelops the anterior and lateral neck except for a thin strip devoid of fibers at the midline. It also crosses the mandible and then blends into the superficial muscular aponeurotic system (SMAS), involving the muscles of facial expression of the lower face. The larynx and the muscles of deglutition are located deep to the platysma.
- The contraction of the platysma muscle, in association with the posture of the neck, results in horizontal and vertical wrinkle formation at the cervical region and at parts of the décolleté. Separation and clumping of anterior fibers of the platysma generates the tense vertical bands.
- Cervical treatment of the neck using botulinum toxin can also soften the melomental fold and improve the lateral cheek lines by weakening the downward force exerted by the platysma on the structures to which it inserts in the lower face.
- In patients with jowl, submandibular gland ptosis and bone resorption, the application of botulinum toxin can emphasize the muscle

strands, rather than soften them. Careful selection of patients for the treatment of neck is required, and those with obvious platysmal bands, good local skin elasticity, and minimal fat descent are good candidates.

- The authors use and recommend a conversion factor of 1:2.5 between Botox units for OnaBontA (bU) and Speywood units for AboBontA (sU), which has become the most commonly quoted unit ratio among experienced injectors and has been demonstrated comparable efficacy with the two botulinum toxin A products.
- Vertical platysmal bands are treated with a series of 2–5 intradermal injections of 2–4 U in each band (abobotulinumtoxin A), beginning near the jawline and progressing caudally at 1.5–2 cm intervals. Asking the patient to contract the platysma and pinching the band before injection can be helpful (Fig. 2).
- The total dose per band should be kept less than 25 U. No more than three or four bands should be treated in one session. Caremust be taking to avoid deep injections in the neck or overdosing (greater than 100 U of aboBontA).
- Horizontal lines can be treated by injecting doses of 1–2 U in the deep intradermal plane, along the horizontal neck lines at approximately 1 cm intervals.
- Subcutaneous injections should be avoided to prevent bleeding and involvement of the underlying muscles of deglutition of the larynx or the sternocleidomastoid.
- No more than 15–20 U of abobotulinum toxin A should be used for horizontal lines per treatment session (Fig. 2).
- The adverse effects are ephemeral, and potential complications are mild pain, erythema, discrete edema, and bruising at the site of injection, local infection, sensation of loss of strength, transient numbness, and allergy.
- Doses over 100 U of botulinum toxin in the neck can produce dysphagia, hoarseness, and neck flexor weakness by either local diffusion or direct injection of the toxin into the sternocleidomastoid, laryngeal muscles, omohyoid, or muscles of deglutition.
- Absolute contraindications include allergy to the drug or its components, such as albumin, infection at the site of injection, during pregnancy or breastfeeding, and patient's unrealistic expectation.
- Relative contraindications are associated neuromuscular disease, use of aspirin, nonsteroidal anti-inflammatory or potentiating drugs within 4 weeks prior to the procedure, and associated and/or decompensated coagulopathy.

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Botulinum Toxin for the Décolletage

Bhertha Tamura

Contents

Abstract

The décolletage should be explored when a discussion about toxin for the neck lines and bands is performed. The platysma muscle is the most important muscle that should be treated for the necklace lines, bands, and facial contour. To obtain the best outcomes, we need to understand the main features of the platysma's anatomy and define if the muscle contraction is the main cause or if it has a coadjuvant role in the etiology of V-shaped lines on décolletage area. Nowadays, there are a plenty of techniques used to treat this region, before or after botulinum toxin injection, such as LASERs, IPL, collagen stimulation products or fillers, ultrasound equipment, and others.

Keywords

Décolletage · Platysma · V shape · Botulinum toxin · Neck

Introduction

With the improvement of the aesthetic facial and neck treatments, patients started complaining of other aging signs on the body as the décolletage (Becker-Wegerich et al. 2002), arms, hands, belly button, thighs, and legs, as a natural evolution of the art of rejuvenation (Carruthers and Carruthers 2003). However, as for all new indications, it is

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necessary to understand the anatomy and to know the right techniques to obtain best results. In the beginning, we used to treat the neck separately from the chest/décolletage and did not realize that they contract as a unique structure. Patient asking for an exclusive décolletage (Spósito 2002) line treatment is rare. In most cases, they come to the office at their middle age with some signs of aging, such as poikiloderma, melanosis, keratosis, and elastosis. This clinical presentation needs a rejuvenation program, because BTXA injection performed isolated will probably give a very light improvement.

Anatomy

Platysma is a muscle that covers partially the lower face, the neck, the chest, the pectoralis major, and the deltoid and overlaps the sternocleidomastoid, and its fibers cross the clavicle and proceed obliquely upward and medially along the side of the neck (Fig. 1a, b). The term platys is a Greek etymology of "wide" and originates at the subcutaneous layer and fascia covering the pectoralis major and the deltoid at the level of the first or second rib and inserts at the lower border of the mandible at the symphysis, the risorius, and the skin of the lower face, including the zygomaticus and the orbicularis oris area. Platysma depresses the angle of the lower lip, forming lines at the neck skin and the upper chest when the jaws are "clenched," and is innervated by the VII facial cervical branch (Tamura and Anatomia 2010a, b; Matarasso et al. 1999; Tamura 2012; Gray 2008).

The fibers of each side of the platysma intermingle together below and behind the symphysis mentis (not a real symphysis), where they can be fused at an early period of life. It is not a true symphysis as there is no cartilage between the two sides of the mandible. Beneath the platysma, the external jugular vein descends from the angle of the mandible to the clavicle.

Fig. 1 (**a**) A widespread platysma with both bands separated in the middle from the symphysis mentis (**b**) Lateral view of the platysma

Variations occur in the extension over the face and over the clavicle and shoulder; it may be absent or interdigitate with the muscle of the opposite side in front of the neck; attachment to clavicle, mastoid process, or occipital bone occurs. Neck bands become most noticeable with age, aggravated by weight lifting or facelift.

The larynx and the muscles of deglutition are located deep to the platysma in the neck, but the platysma is very thin at the medial area; thus, we need to remember the main muscles at this area, the suprahyoid muscles, the digastric, the stylohyoid, the mylohyoid, and the sternocleidomastoid, and the infrahyoid muscles, the sternohyoid, thyrohyoid, and the omohyoid. The muscles from the jaw to the clavicle participate with the sternocleidomastoid and platysma for the movement of the neck, especially to move the head upward and downward but also to participate on the deglutition. Impairment of these muscles might lead to dysphagia, weakness of the neck for movements as pulling the head, and also respiratory complications (Tamura and Anatomia 2010a, b; Matarasso et al. 1999; Tamura 2012; Gray 2008).

Technique

Besides the regional anatomy knowledge, it is crucial to diagnose correctly which patient has lines at the décolletage that can be improved with BTXA injections (Kane 1999; De Almeida et al. 2017; Labbé et al. 2017). There are at least three main clinical aspects: type I lines, which become visible or worsened with platysma contraction associated or not with moderate aging signs; type II skin lines, which become visible or worsened with platysma contraction with severe aging signs; and type III static lines without any movement on platysma contraction with mild, moderate, or severe aging process. The difficulty consists of diagnosing the types, extension, and strength of the platysma. BTXA will not improve static lines.

Clenching the teeth firmly, forcing downward the angle of the mouth, and contracting the platysma at the facial contour, the neck, and the chest will give us a slight clue of its extension, its contraction, and its role as one of the causes of the décolletage lines. If the area of the wrinkles corresponds to the area of the platysma, we delineate the area and mark the injections points every 1.5–2 cm, injecting 1–2U/point. Depending on the muscle strength, the distance can be shorter. The injection should be in the deep dermis as suggested in Fig. 2. Figure 3 shows the platysma contraction along the neck and chest.

Best results might be achieved when all the extent of the platysma is treated. When injecting BTXA at the décolletage, best results are achieved when the neck area is also relaxed.

Discussion

Few points must be considered when analyzing the right indication and techniques to achieve a successful result. It is very important to control patient's expectations. Considering the different

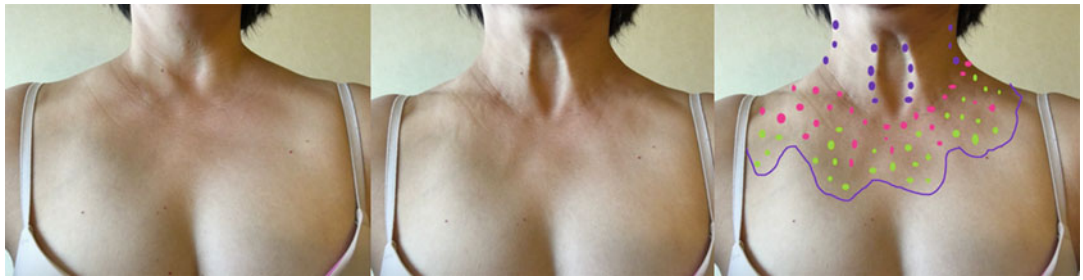

Fig. 2 Extension of the platysma, its neck and chest contraction. The violet dots represent the injection plan at the neck's area. The pink and green dots represent the chest area. The plan is to inject 2U in the violet dots and 1U in the pink and green dots

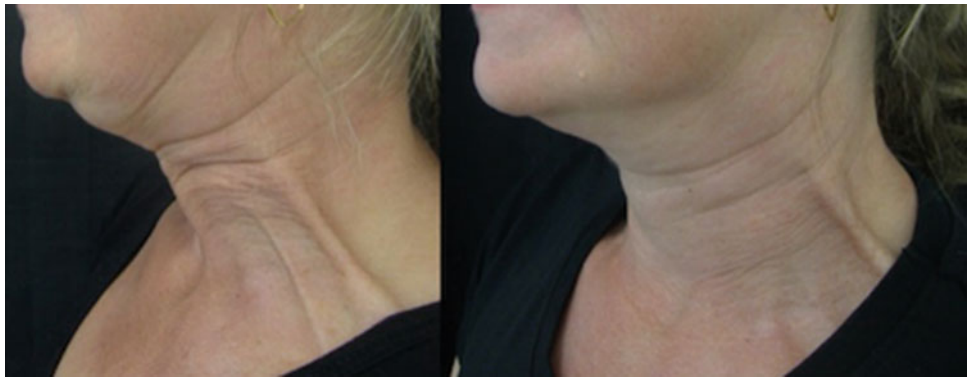

Fig. 3 shows the platysma contraction along the neck and chest

types of décolletage, we could predict the best treatment and the best result:

Type I: Lines that become visible or worsened with platysma contraction associated or not with moderate aging signs. Botulinum toxin A is helpful with the right injection technique associated with other superficial aging skin treatments.

Type II: Skin lines that become visible or worsened with platysma contraction with severe aging signs. First stage of treatment is to treat the skin. Options include topical creams, light-based devices, radiofrequency, peelings, collagen stimulators, fillers, and injectable hydration. If the lines are subtle, the treatment of the skin might improve, but if the lines are deep, due to the platysma muscle, BTXA might soften them.

Type III: Static lines without any movement on platysma contraction with mild, moderate, or severe aging process. Options for skin treatment include light-based devices, radiofrequency, peelings, collagen stimulators, fillers, and injectable hydration. Additional topical creams can also be prescribed. BTXA might not be indicated.

Complications

The most common undesirable side effect is ecchymosis that happens quite frequently.

The muscles from the jaw to the clavicle participate with the sternocleidomastoid and platysma for the movement of the neck, especially to move the head upward and downward and to act as part of the deglutition. Impairment of these muscles might lead to dysphagia, weakness of the neck for movements as pulling the head, as well as respiratory complications (Tamura 2012; Klein 2003). These complications are mainly a consequence of the neck treatment, but not the chest treatment.

Take Home Messages

- To treat the décolletage, a rejuvenation program associating techniques is necessary, because BTXA performed isolated can promote a very light improvement.
- Platysma muscle originates at the subcutaneous layer and fascia covering the pectoralis major and the deltoid at the level of the first or second rib and inserts at the lower border of the mandible at the symphysis, the risorius, and the skin of the lower face, including the zygomaticus and the orbicularis oris area. Platysma depresses the angle of the lower lip, forming lines at the neck skin and the upper chest when the jaws are "clenched."
- Variations occur in the extension over the face and over the clavicle and shoulder; it may be absent or interdigitate with the muscle of the opposite side in front of the neck; attachment to

clavicle, mastoid process, or occipital bone occurs.

- Besides the regional anatomy knowledge, it is crucial to diagnose correctly which patient has lines at the décolletage that can be improved with BTXA injections.
- If the area of the wrinkles corresponds to the area of the platysma, we delineate the area and mark the injection points every 1.5–2cm to inject 1–2U/point, depending upon the muscle strength.
- Few points must be considered when analyzing the right indication and techniques to reach a successful result. It is very important to understand and to control patient's expectations. Considering the different types of décolletage, we could predict the best treatment and the best result.

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Botulinum Toxin for Hyperhidrosis in the Axillary Area

Ada Regina Trindade de Almeida and Suelen Montagner

Contents

Abstract

Axillary hyperhidrosis (AH) impacts social and occupational lives of lots of people in all continents, and its real incidence probably is underestimated. Botulinum toxin is a safe and effective treatment option for axillary hyperhidrosis. Although its pathophysiology is not very clear, with some controversial topics, so far the beneficial effect of neuromodulators in inhibiting localized sweating temporarily is well known.

Before the procedure, the correct identification of the affected area is mandatory. The objective is to enhance efficacy avoiding drug waste or leaving areas without treatment, because the hyperhidrotic location does not always match the hairy axillary region.

Handling this medication, including dilution and injection techniques, depends on medical experience and may have some variations,

Conflict of Interest: Dr. Ada *has been a consultant in Allergan, Inc. and participated in clinical trials for Allergan and Galderma.*

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_9

including methods to make the procedure as painless as possible. Evidence supports a Level A recommendation for BoNT-A for axillary hyperhidrosis.

Keywords
Axillary hyperhidrosis · Excessive underarm sweating · Botox · Botulinum toxin · Neuromodulators

Introduction

Axillary hyperhidrosis (AH) is a disease that impacts social and occupational lives of lots of people all over the world (Doft et al. 2011; Glaser et al. 2007). It begins at adolescence and affects men and women similarly (Hornberger et al. 2004). When associated with axillary malodor, it is called bromhidrosis.

The pathophysiology of primary focal hyperhidrosis is not well understood. It can be a result of hyperstimulation of eccrine glands, but some authors also believe that apoeccrine sweat glands may be involved (Hamm et al. 2006).

Eccrine glands are distributed over almost the entire body surface (Sato et al. 1989a) and are most numerous on the palms, soles, forehead, axillae, and cheeks (Kreyden and Scheidegger 2004). They are innervated by cholinergic postganglionic sympathetic nerve fibers, excrete sweat, and also contribute for the body temperature regulation (Mota and Sotto 2004). When patients with excessive sweating were compared to normal controls, histological studies have not shown morphological alterations nor increase in the number or size of the sweating glands (Bovell et al. 2001). However, preliminary findings of an interesting study suggest that the eccrine gland's secretory clear cell exerts a main role at the fluid transport. Only this cell is equipped with a co-transporter and aquaporin channels, and for this reason, it is probably the source of excessive sweating in this form of hyperhidrosis (Bovell et al. 2011).

For the other hand, apocrine glands are selectively located at the urogenital regions and the axillae and are stimulated by epinephrine and norepinephrine (Bovell et al. 2011; Lindsay et al. 2008). They produce a viscid secretion that can become malodorous due to bacterial breakdown (Atkins and Butler 2002).

Apoeccrine glands as described by Sato et al. in 1989 share morphological characteristics from its eccrine and apocrine counterparts corresponding to 10–45% of all axillary glands. It was also suggested that they would respond to cholinergic stimuli and, intensely, to epinephrine and isoproterenol infusion (Sato et al. 1989; Mota and Sotto 2004; Atkins and Butler 2002). However, subsequent histological studies were not able to demonstrate evidence of apoeccrine glands at the axillary sample tissues (Bovell et al. 2001, 2011). The occurrence of these glands remains controversial (Bechara 2008; Bovell et al. 2011, 2007).

History of Botulinum Toxin and Classification

Botulinum toxin (BoNT) injections have been safely and effectively used as a treatment option for focal hyperhidrosis since 1996, with high levels of patient satisfaction (Glaser et al. 2007; Kalner 2011). Two types of botulinum toxins – BoNT type A (BoNT-A) and BoNT type B (BoNT-B) – were studied in axillary HH, and both demonstrated effectiveness in temporarily inhibiting sweating, although acting at different target sites. BoNT-A binds to and cleaves the 25-kDa synaptosomal-associated protein (SNAP-25), while BoNT-B acts on the vesicle-associated membrane protein (VAMP or synaptobrevin) (Rosell et al. 2013; Trindade De Almeida et al. 2011), both blocking the acetylcholine release from cholinergic neurons innervating sweat glands (Lowe et al. 2007; Trindade De Almeida et al. 2011).

The use of BoNT type A (BoNT-A) for the treatment of axillary hyperhidrosis was approved in 2004 by the US FDA (Grunfeld et al. 2009), and since then, a plenty of studies have confirmed its efficacy, beneficial effects, and paucity of side effects (Heckmann et al. 2001; Naumann and Lowe 2001; Scamoni et al. 2012; Lakraj et al. 2013; Lecouflet et al. 2013).

Many commercial BoNT-A products are available around the world. The formulations are not identical, presenting individual potencies, and caution is necessary to ensure proper use. To reinforce these differences, the FDA established specific drug names to those products approved for use in the US medical market. A summary of them is presented in Table 1.

There is no exact ratio globally accepted among different formulations. Reviewing the related published literature, the most commonly accepted dose correlation among products are 1U OnaA = 1U IncoA = 1U BoNT-A (Lanzhou)- = 1U Medy-Tox = 2.5–3u AboA.

The available BoNT-B (rimabotulinumtoxinB) products are NeuroBloc® in the EU and Myobloc® in the USA. Unlike BoNT-A, it is not commercially available worldwide, and probably for this reason, a limited number of studies of axillary hyperhidrosis being treated with this toxin type were published. Few articles describe a long distance side effects of the toxin, such as dry eyes and dry mouth, which are not commonly observed after the use of BoNT-A. Dose correlation found between BoNT-A and BoNT-B varied from 20 to 100u RimaB/1U OnaA (Baumann et al. 2005; Dressler et al. 2002; Frasson et al. 2011; Nelson et al. 2005).

Naumann et al. in a evidence-based review of hypersecretory disorders and botulinum toxins found two Class I (*prospective, randomized, controlled, and with masked outcome assessment clinical trial with strict requirements*) studies – one with OnaA (Naumann et al. 2001) and one with AboA (Heckmann et al. 2001) – and five Class II (similar *to Class I trials but lacking one or some of the required criteria*) studies of BoNT-A as a treatment for axillary hyperhidrosis (Naumann et al. 2013). They concluded that the evidence supports a Level A recommendation for BoNT-A in general and Level B recommendation for OnaA and AboA individually, for axillary hyperhidrosis. RimaB and IncoA received Level U recommendation (insufficient data).

Some BoNT comparative trials for axillary hyperhidrosis will be discussed in detail in the following paragraphs.

Studies comparing BoNT-A products:

> Kalner performed a prospective same-patient comparison between OnaA in one axilla and AboA in the other, using a conversion factor of 1OnaAu:3AboAu. She observed that OnaA resulted in a faster onset of action, within 1 week, against 2 weeks for AboA and had a longer duration of benefits (9 months), while the axilla treated with AboA maintained the results for 6 months.(Kalner 2011) In another comparative trial performed in 2007 with 10 patients, Talarico-Filho et al. did not find statistically significant differences in the onset of sweating reduction or in the duration of the benefits, using the same conversion factor. (Talarico-Filho et al. 2007)

Dressler, in a double-blind comparative study of 46 patients, used 50U of OnaA in one axilla and 50U of IncoA in the contralateral one and found no difference in efficacy, onset of action, duration, or side effects between the two formulations. Both 100U/vial products were reconstituted in 10 mL of saline (10U/mL) (Dressler 2010).

Table 1 Commercially available BoNT-A

Botulinum toxin	Trade name	Origin
OnabotulinumtoxinA (OnaA)	Botox®	(Allergan, USA)
AbobotulinumtoxinA (AboA)	Dysport®	(Ipsen Biopharm, UK) in the USA, Europe, and Latin America
BoNT-A	Prosigne®	(Lanzhou, China) in Asia and Latin America
BoNT-A	Neuronox®	(Medy-Tox, South Korea) Asia, Botulift in Latin America
IncobotulinumtoxinA (IncoA)	Xeomin®	(Merz Pharma, Germany) Canada, Germany, the USA, Latin America
BoNT-A	PureTox	(Mentor Corporation, Santa Barbara, CA) uncomplexed BoNT- A. Phase III studies

Studies comparing BoNT-A and BoNT-B products:

In 2011, Frasson et al. treated ten patients using 2500U of RimaB in one axilla and 50U of OnaA in the contralateral one (50UB:1UA). They considered BoNT-B more effective than BoNT-A in reducing sweating production, with faster onset, longer duration of benefit, and higher treatment satisfaction scores. No systemic adverse effects were described. According to the authors, their findings differed from those found in the literature because other studies used lower toxin ratios (40:1 or 20:1) and higher dilutions (Frasson et al. 2011).

In another recent study (2015), An et al. treated 24 patients using 1500U of RimaB in one axilla and 50U of OnaA contralaterally. At a conversion ratio of 1:30, they considered that both neuromodulators had equally effective anhidrotic effects through 20 weeks after a single injection. There was no difference in onset or duration of action between them, nor any significant motor or autonomic side effects were observed. Patient satisfaction was equivalently high to both toxins (An et al. 2015).

In order to reduce side effects and to improve benefits, further studies are still required to treatment standardization. The toxin product will be selected at the physician's discretion and experience according to its safety and availability.

Toxin Solution

A review about handling botulinum toxins found no standardized dilution for the use of neuromodulators in the treatment of focal hyperhidrosis (Trindade De Almeida et al. 2011). Reported dilutions found in the literature vary from 1 to 10 mL of saline for onabotulinumtoxinA (with the majority of physicians using between 2 and 5 mL), while for abobotulinumtoxinA the reconstitution volumes vary from 1.25 to 10 mL (with the use of 2.5–5 mL being the most frequent). In the only study with incobotulinumtoxinA for hyperhidrosis, the dilution used was 10U/mL. Table 2 summarizes the dilution volumes described in the literature.

Table 2 Reported dilutions for hyperhidrosis

Toxin	Dilution Range	Most Commonly Used Dilution
OnabotulinumtoxinA	1–10 mL of saline	2–5 mL
AbobotulinumtoxinA	1,25–10 mL	2,5–5 mL
IncobotulinumtoxinA	1–10 mL of saline	10 mlL(one paper)

The present authors prefer to reconstitute the 100U vial of onabotulinumtoxinA (Botox) in 2 mlL of saline, achieving a dose of 50U per mL.

It was also reviewed that several different substances can be added to the toxin solution, with no harm to the toxin, such as hyaluronidase, lidocaine, epinephrine, etc.

Among these substances, the most interesting one for axillary hyperhidrosis treatment is lidocaine. A recent double-blind, randomized, comparative study treated eight patients with 50U of OnaA diluted in 0.5 mL of saline plus 1 mL of 2% lidocaine into one axilla and 50U of OnaA diluted in 1.5 mL of saline into the other axilla (Gülec 2012). Vadoud-Seyedi also treated 29 patients in a similar manner in 2007 – with a dilution of 5 mL (Vadoud-Seyedi and Simonart 2007). Both studies showed equal effectiveness of BoNT-A reconstituted in saline or lidocaine. However, the toxin diluted in lidocaine caused less pain and may be preferable for treating axillary hyperhidrosis.

When reconstituted with saline admixed with hyaluronidase, onabotulinumtoxinA has its efficacy maintained after 2 weeks and shows enhanced diffusion, as observed by Goodman, in 2003 (Goodman 2003).

Evaluation Methods

After the selection of the toxin, it is important to identify the area to be treated. Minor's iodine-starch test is a useful method to map the extension of the affected area (Cohen et al. 2007), as well as the posttreatment residual sweating, but it does not provide accurate information on the amount of sweat produced.

The test is not expensive, is very easy to apply, and is usually performed before any topical or regional anesthesia (Glogau 2004). The first step is to remove any wetness of the affected area with an absorbent paper. Then, a 3–5% iodine solution is applied to the underarm and neighboring region and allowed to dry for a little while. In some patients, the continuous sweat must be wiped again just before the starch application to avoid false reactions (Fig. 1). In contact with starch plus iodine, the sweat acquires a dark purple color, being clearly visible. It is important to note that the commercialized PVPI topical solution with 10% iodopovidone contains only 1% of free iodine. Therefore, when using this substance, Minor's test results could not be satisfactory (Burks 1998).

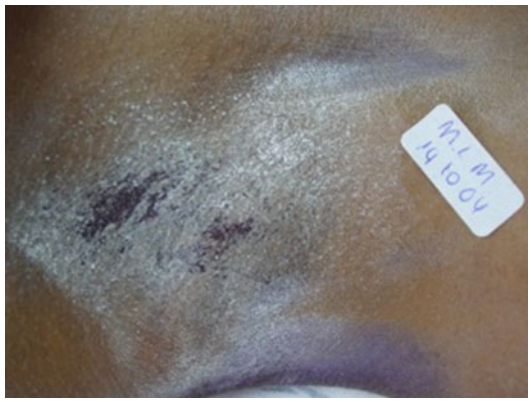

Fig. 1 In contact with starch plus iodine, the sweat acquires a dark *purple* color, which is clearly visible at the *center*. Normal areas need to be kept dry in order to avoid false positive, visible at lower region

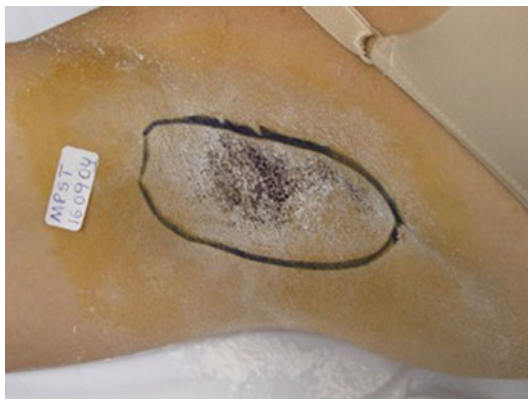

Fig. 2 In this individual, the iodine-starch test shows that the hyperhidrotic region is smaller than the hairy area

Another important detail to take into account is that the axillary hyperhidrotic area does not always coincide with the hairy underarm region. For example, if the excessive sweating location is confined to small sites contained in the hairy region (Figs. 2 and 3), the treatment of the whole hair-bearing location will require the use of excessive and unnecessary amount of botulinum toxin units. For the other hand, in some individuals the hyperhidrotic region exceeds or is located outside the hairy area, as observed in Fig. 4. In such cases, if the botulinum toxin treatment is confined to the terminal follicular area, the response will be unsatisfactory, as some regions will be left untreated. It is also not uncommon that the distribution of the affected areas may assume bizarre shapes, like "M," "S," "8," etc., but even these cases will be easily highlighted by the iodine-starch test. For this reason, Minor's test is mandatory to precisely identify the real affected area in order to optimize the injection of the toxin and ensure effective treatment response.

For iodine-sensitive patients, Ponceau's red tincture is an alternative described in the literature (Bushara and Park 1994). This tincture when mixed with starch and in contact with sweat develops a pinkish color. For both techniques, the distribution and maximal perspiration sites must be recorded in photographs for future comparison.

Another useful method for research trials is the gravimetric testing. In daily practice, it is not often applied, because it is time-consuming and requires a precision scale. Under controlled temperature conditions, the produced sweat volume is measured over a fixed period of time. Initially, the affected area is dried using absorbent tissue, and then, a previous weighed filter paper is applied and left on place for a certain period of time. The volume of produced sweat during this time interval is quantified by measuring the weight of the paper before and after contact to the sweating area. There are variations in the evaluation period among authors. Heckmann et al. (2001) prefer one-minute contact with the

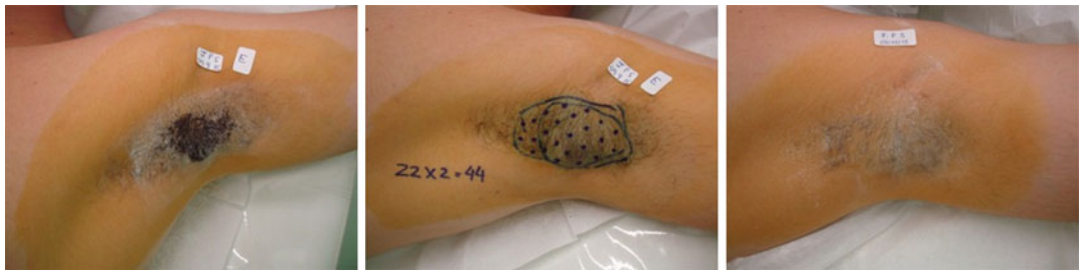

Fig. 3 A patient with the hyperhidrotic area smaller than the hairy area. At the center, the marked area treated with 44U of onabotulinumtoxinA (22 points of 2U each) and after the treatment

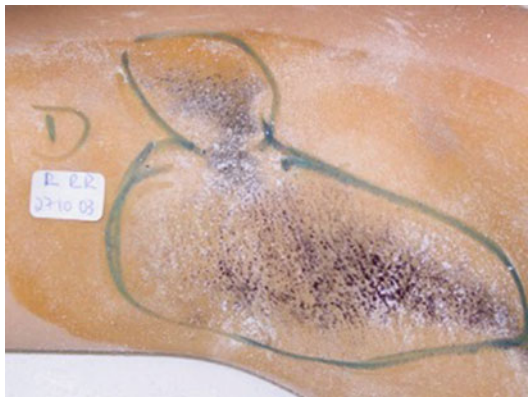

Fig. 4 In this patient, the excessive sweating areas are not limited to the hair-bearing regions. The delimitation of the area being treated ensures the effectiveness of the treatment

affected area, while Naumann and Lowe and Hund et al. consider 5 (Hund et al. 2002; Naumann and Lowe 2001); Bahmer and Sachser, 10 (Bahmer and Sachse 2008); and Odderson, 15 min (Odderson 2002).

The Hyperhidrosis Area and Severity Index (HASI) is the association of the two previous methods, gravimetry and Minor's test, and was proposed by Bahmer et al. It uses a transparent square-lattice grid and a counting system where one centimeter (cm) represents one point. After estimation of the sweating area, the volume of secretion weighed through gravimetry after 10 min is divided by the number of sites in the affected area. The HASI score is given in mg of sweat by cm^2 per minute. They consider hyperhidrosis when HASI reaches values above 1 mg/cm^2 per minute.

Evaluation of Impact on Quality of Life

Hyperhidrosis impacts routine life in several aspects like interpersonal relationships, work, leisure activities, and self-esteem and is considered by many as a stigmatizing condition. Feelings of shame, intrusiveness, and depression are frequent among sufferers.

The quality of life (QoL) of focal idiopathic hyperhidrosis affected individuals may be measured through several tests. The most frequently used is the Hyperhidrosis Disease Severity Scale (HDSS), in which a score of 3 or 4 indicates severe hyperhidrosis; of 2, moderate; and of 1, absence of it. The HDSS evaluates the impact of the disease in daily life using a single question: "How would you rate the severity of your hyperhidrosis?" with four possible answers as the following: my sweating is *never* noticeable and *never* interferes with my daily activities (score 1), my sweating is *tolerable* but *sometimes* interferes with my daily activities (score 2), my sweating is *barely tolerable* and *frequently* interferes with my daily activities (score 3), and my sweating *is intolerable* and *always* interferes with my daily activities (score 4) (Strutton et al. 2004).

Another instrument described by Campos and colleagues was termed the clinical protocol for quality of life. This questionnaire includes one general question asking for overall QoL reduction and 20 questions belonging to four domains covering compromising effects on function and social activities, personal limitations with partners, emotional impairment, and restrictions under special circumstances. The answers are

scored, and the result is ranked to one of the five QoL levels (De Campos et al. 2003; Wolosker et al. 2010).

The most frequent questionnaire used to measure the effects of dermatologic diseases on QoL is the Dermatologic Life Quality Index (DLQI). It is general and consists of ten items covering symptoms and feelings, daily leisure, work and school activities, personal relationships, and treatment. Each item has four assortments, between 0 and 3, and the total score ranges from 0 to 30 (Finlay and Khan 1994).

Some other tools to measure the HH impact on QoL had been described, but so far, there is no consensus among different medical specialties in the use of one specific instrument whose final score would facilitate comparison between different populations and/or therapeutic modalities.

Injection Technique

When the affected area was identified and recorded by photographs, its contour is then delimited, and the distribution of injection points is chosen using a marker pen or gentian violet. At this moment, it is possible to apply a local topical anesthetic, which will improve patient's comfort during the procedure. If applied before, the anesthetic cream might impair the test.

Skiveren et al. investigated whether the use of a 30G versus a 27G needle influenced pain intensity in 38 patients treated with BoNT-A for axillary hyperhidrosis. The pain scores recorded after the first five injections were significantly lower for the 30G needle than for the 27G needle. For this reason, smaller needles are preferable to improve patient comfort (Skiveren et al. 2011).

The injection should be intradermal using a 30G needle attached to the syringe (0.3- or 0.5-mL syringes, Ultrafine II 30U or 50U insulin syringes; Becton Dickinson Co, New Jersey, USA), which eliminates the dead space between the needle and the syringe, as well as the risk of expelling the needle during injection. The number of injections and the total dose will depend on the involved surface area.

Table 3 Reported mean dose per axilla for each BoNT

Toxin	Mean Dose
OnabotulinumtoxinA	50–100U
AbobotulinumtoxinA	100–300U
IncobotulinumtoxinA	50U
RimabotulinumtoxinB	2,500–5,000U

Once injected, it is noted that the toxin concentration will be higher at the central point, with a decreasing gradient along the peripheral areas (Glogau 2004). The aim of the treatment is to create overlapping and confluent anhidrotic halos in order to achieve maximum outcome (Klein 2003).

Table 3 summarizes the usual BoNT doses for axillary hyperhidrosis as described in the literature.

Approximately 10–20 intradermal injections in 0.1–0.2-mL aliquots (total dose: 50–100U onabotulinumtoxinA) are used for each axilla, spaced 1–2 cm apart. Injections may also be performed in the superficial fat without adverse events or significant reduction in efficacy.

The vast majority of patients have excellent treatment results. The effects begin 2–4 days after injection and last approximately 6–9 months; however, in some cases, it may last more than 1 year. In our experience, the longest duration outcomes are obtained when the excessive sweating location could be precisely delimitated. Only when the patient could not sweat during iodine-starch test, the hair-bearing area is injected, and in some of these cases, longer duration could not be warranted.

A recent publication by Brehmer et al. recently describes what some authors were perceiving in daily practice: that repetitive botulinum toxin treatments led to a significant increase in the anhidrotic effects in axillary hyperhidrosis. In a retrospective analysis in 101 patients with axillary hyperhidrosis confirmed and quantified by gravimetric analysis and Minor tests, injected with 50U of onabotulinumtoxin type A/per axilla that received at least three sessions of treatment, the efficacy duration was evaluated after the first, second, and last treatment. The median duration of efficacy was 4.0 months, 4.5 months, and

5.0 months after the first, second, and last injection, respectively. However, the amount of axillary hyperhidrosis by gravimetric analysis was not quantified prior to every botulinum toxin retreatment session (Brehmer et al. 2015).

Alternative Techniques

Other techniques have been used as a variation of the traditional needles punctures.

A multi-injection round plate with five or seven 27G device used for intralesional steroid therapy of alopecia areata was described. According to the authors, a rapid application in uniform and homogeneous manner was obtained, avoiding repeated punctures (Grimalt et al. 2001).

A multiple-site marking grid made of flexible silicon sheet with holes punched out at a 1-cm distance was also described (Exmoor Plastics Ltd –Taunton, UK). After the location of the excessive sweating, the grid is positioned on the affected area, and the site is marked through the holes in the grid with a skin marker pen (Jain 2006).

Singh et al. suggest the use of microneedling as an emerging technique for delivering botulinum toxin in a safe and pain-free way (Singh et al. 2015).

However the use of these alternative techniques implies in availability of the devices, while traditional injections only depend on easily available materials, in addition to well-trained professionals.

Table 4 provides a summary of all practical information needed for a good performance of BoNT treatment of excessive underarm sweating.

Table 4 Practical information for BoNT treatment of axillary hyperhidrosis

Always perform Minor's test before applying BoNT-A
The test must be performed before any topical anesthesia
Highlight the area to be treated
Take photographs for future comparison
Distance between injection sites: 1–2 cm
Onset of action: 2–4 days
Duration of effect: 6–9 months

Transcutaneous Botulinum Toxin

The botulinum toxin A molecule directly applied to the skin is not absorbed due to its large molecular size. For this reason, the development of a noninvasive, effective, and safe method to deliver botulinum toxin through the skin has been objective of recent research (Glogau 2007).

A biopharmaceutical company (Revance Therapeutics, Inc.) developed a mechanism that allows a transepidermal absorption of large molecules. It is composed of a peptide derived from residues of the transactivator of transcription protein that allowed the creation of the first topical formulation of BoNT-A (RT001) to date (Carruthers and Alastair 2015). The use of this transport peptide vehicle allowed successful transcutaneous penetration of BoNT-A (Chow and Wilder 2009; Glogau et al. 2012).

In a small controlled clinical trial, Chow and Wilder found statistically significant reduction of sweat production in 12 cases of axillary hyperhidrosis using 200U of onabotulinumtoxinA reconstituted with saline admixed with the transport peptide. The duration of effect was not mentioned (Chow and Wilder 2009).

This innovative method promises a revolution in the treatment of hyperhidrotic affected areas and may be useful in the future for other indications as well.

Conclusion

Botulinum toxin proved to be safe and effective for hyperhidrosis treatment, although its pathophysiology remains controversial. Nevertheless, according to evidence-based review, the beneficial effect of type A neuromodulators in inhibiting localized sweating temporarily supports a Level A recommendation, for axillary hyperhidrosis.

Take Home Messages

- Axillary hyperhidrosis impacts social and occupational lives of lots of people in all continents, and its real incidence is probably

underestimated. Botulinum toxin is a safe and effective treatment option for axillary hyperhidrosis.

- The BoNT-A formulations are not identical, presenting individual potencies, and caution is necessary to ensure proper use.
- Reported dilutions found in the literature vary from 1 to 10 mL of saline for onabotulinumtoxinA (with the majority of physicians using between 2 and 5 mL), while for abobotulinumtoxinA, the reconstitution volumes vary from 1.25 to 10 mL (with the use of 2.5–5 mL being the most frequent). In the only study with incobotulinumtoxinA for hyperhidrosis, the dilution used was 10U/mL.
- Hyperhidrosis causes impact at the everyday life in several aspects like interpersonal relationships, work and leisure activities, and self-esteem and is considered by many as a stigmatizing condition. Feelings of shame, intrusiveness, and depression are frequent among sufferers.
- Botulinum toxin proved to be safe and effective for hyperhidrosis treatment, although its pathophysiology remains showing some controversial topics.

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Botulinum Toxin for Hyperhidrosis in Palmoplantar Area

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Abstract

Hyperhidrosis is a skin condition that leads to excessive production of sweat more than required for normal thermoregulation, affecting both men and women from childhood or adolescence. It is estimated that hyperhidrosis affects 3% of the US population. Areas such as the palms and soles are frequently affected, and it may exert deep negative impact on patient's

M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_11

personal and professional life. Treatment is difficult, and various therapeutic methods are available with limited effectiveness. Botulinum toxin has been used for 20 years safely and effectively. We will discuss the literature and bring clinical experience with this treatment.

Keywords
Sweat · Hyperhidrosis · Botulinum toxin

Introduction

Sweat is secreted by eccrine sweat glands that are stimulated by cholinergic fibers of the sympathetic nervous system. Its main function is to regulate body temperature, and it is produced in heat situations and emotional disorders such as anxiety. Excessive production of sweat, which goes beyond the physiological stimuli, is called hyperhidrosis (Fig. 1). It affects nearly 3% of the population and may represent a significant negative impact on quality of life, both social and professional (Campanati et al. 2003).

The sites of greatest concentration of these glands are the palms of the hands, soles of the feet, and underarms that are also the most commonly involved areas.

Peculiar forms of hyperhidrosis are described as gustatory sweating (Frey syndrome), front focal hyperhidrosis, inguinal, and perianal, among others.

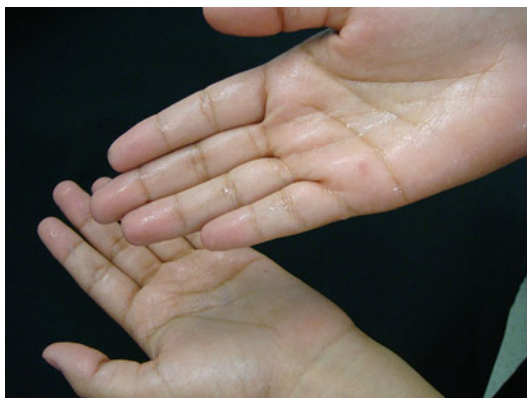

Fig. 1 Excessive sweat in palms (palmar hyperhidrosis)

In addition to the social impact and significant impairment in quality of life, hyperhidrosis has been linked to diseases such as bromidrose, eczema, chronic infections, and pitted keratolysis (Ayres 2015).

There are reports of botulinum toxin treatment in hyperhidrosis since 1996, but it was approved by the FDA for the treatment of axillary hyperhidrosis in 2004 and, since then, is routinely used off label for hyperhidrosis in other areas.

Classification

Hyperhidrosis can be classified as primary or secondary and also as focal or generalized types. Focal hyperhidrosis is restricted to parts of the body and can be caused by local heat or food or represent a primary idiopathic type. Generalized hyperidrosis affects all skin, and its etiology is usually secondary, varying from exposure to heat, use of drugs, and metabolic and febrile diseases, among others.

- Primary or idiopathic: does not have a well-established cause, although studies have shown that family history is positive in 30–50% of cases, (Chia et al. 2012) suggesting genetic involvement. There is also much evidence for abnormalities in autonomic nervous system function. It is usually induced by emotional stress and affects underarm (51%), plants (30%), palm (24%), and face (10%) (Chia et al. 2012). It affects both sexes (Ayres and Sandoval 2016) and usually appears in childhood and adolescence. The diagnostic criteria include hyperhidrosis at least in the past 6 months without secondary cause, and it has at least two of the following: impairment of daily activities, bilateral and relatively symmetric sweating, episodes at least once a week, beginning before age 25, ceases during sleep, and family history (International Hyperidrosis Society 2016).
- Secondary: can be localized or generalized and may be due to underlying conditions such as menopause, infections, malignancy, drugs, genetic syndromes, and neurologic, endocrine and vasomotor disorders, among others.

Diagnosis

The diagnosis is essentially clinical, with complete personal history to exclude the possibility of secondary causes for the frame. It is based on the level of impact on the patient's quality of life, which can be measured by the Quality of Life Questionnaire in Dermatology (DLQI) and Severity Scale Hyperhidrosis Disease (HDSS), and also in the amount of sweat that may be reviewed by gravimetric testing and Minor's test.

To perform gravimetry, a filter paper is placed in contact with the area to be evaluated, where it stays for 1–5 min. In palmar hyperhidrosis, the weight difference of the paper before and after contact with the skin should be more than 100 mg of sweating in 5 min for both sexes, according to a retrospective analysis published by Thorlacius et al. (2015).

The starch iodine test or Minor's test is the most practical and used in everyday clinic. It helps to quantify the sweating, to limit the affected area, and also helps the evaluation of response to treatments performed. At first 3–5% iodine in alcoholic solution is applied in the area, and then cornstarch is applied above it. The sweat becomes purple after the interaction with iodine and starch, delimiting the area of increased production of sweat (Fig. 2).

Fig. 2 Iodine-starch test or Minor's test showing area of palmar hyperhidrosis

Treatment

There are several ways of treating hyperhidrosis, since clinical therapies to surgical approaches, but all have limitations and possible complications. The dermatologist's challenge is to find the optimal therapeutic intervention for each patient, based on the location and intensity, also considering the DLQI and the HDSS (Brown et al. 2014). We will discuss the options in primary hyperhidrosis, with emphasis on toxins for palmoplantar hyperhidrosis.

Topical

Topical medications are the first choice in the treatment of palmoplantar hyperhidrosis because they are easy to access and handling, for having low cost and relatively satisfactory results. However, it requires continuous application by its short half-life and often requires high concentrations of products for a better response, which can cause dryness, itching, and eczematization. The mechanism of action of antiperspirants is a mechanical obstruction of the sweat glands, with decreased sweat production.

The aluminum chlorohydrate at a concentration of 20–50% in ethanol or salicylic acid gel is the most effective and most used drug. It should be applied to dry palms and soles at night to increase the absorption and can be removed only in the morning, about 6–8 h later. This process should be repeated every night until there is a reduction in sweating, when the frequency of applications will be decreased to 1 time every 1–3 weeks. It can also be associated with other procedure such as iontophoresis and botulinum toxin, especially in more severe cases or in case of partial response of these treatments.

Iontophoresis

It is a second-line therapy for the control of moderate hyperhidrosis and first line in severe cases, with or without topical agents. It is a simple, well tolerated, safe, and effective in some cases, but

required serial treatments to reduce perspiration and maintenance therapy, which lowers the adherence. The mechanism of action is still not well established.

The technique is the introduction of ionized substances through intact skin by electric current. It can be made with water, solutions containing anticholinergics in more severe cases, and botulinum toxin has also been described. Glycopyrrolate has been reported in some papers with superior response to water iontophoresis, in spite of the higher risk of possible side effects by systemic absorption of the drug. The use of iontophoresis and botulinum toxin is not routine, but the most recently published work on this approach supports the idea of a longer anhidrosis than in relation to water iontophoresis (Davarian et al. 2008).

Solish et al. (2007) recommend 20–30-minute sessions, 3–4 times a week, using a device that sends a current of 15–20 mA. The sweat control usually occurs between the sixth and 15th day after the session begins when the maintenance every 1–4 weeks may be started. The duration of the treatment varies from 2 to 14 months after the last session.

Kacar et al. (2014) present iontophoresis as an effective therapeutic modality in children with palmar hyperhidrosis in a retrospective study published in 2014, but protocols must be better established as the ideal interval between sessions.

Adverse events are infrequent and well tolerated as xerosis, scaling, and erythema; however, there may be systemic absorption of anticholinergic drugs when they are used, which can cause dry mouth, visual disturbances, and urinary retention, among others.

Contraindications to the procedure are pregnancy, arrhythmia, pacemaker, intrauterine contraceptive devices, or metal prostheses.

Systemic

Anticholinergic drugs are systemic drugs commonly used to treat hyperhidrosis, since the eccrine sweat glands are cholinergic fibers stimulated by the sympathetic nervous system. They act as competitive inhibitors of acetylcholine in the synapse junction. Therapeutic options are considered isolated or adjuvants in the treatment of severe palmar hyperhidrosis when there is failure in response to aluminum chlorohydrate and/or iontophoresis or botulinum toxin, according to Solish et al. because of the potential risk of adverse events such as dry mouth, constipation, urinary retention, palpitations, mydriasis, hyperthermia, and convulsions. Even so many studies have shown the effectiveness of some drugs of this class and with relative safety, taking this treatment modality to the second choice in the control of palmar and axillary hyperhidrosis.

Oxybutynin has been increasingly used and has shown a promising drug including in children, according to Wolosker et al. (2014), with clinical improvement of symptoms and DLQI in more than 80% of patients. Dry mouth was the main side effect and only one child had drowsiness. In the experience of the authors, this drug is a new and cost-effective therapeutic option, with safety and effectiveness. They suggest starting with 2.5 mg once a day, and the dose is gradually increased up to 5 mg two times a day within a 12-week interval.

Glycopyrrolate is another potential emerging drug as second-line treatment. There is an improvement in about 70% of patients at a dose of 2–6 mg. In a retrospective analysis of 2012, Paller et al. (2012) showed a cost-effective use of medication in the pediatric population, effectively in more than 70% of cases and dose-dependent side effects, particularly dry mouth and dry eye. In Kumar et al. (2014) reinforce the same findings and the importance of glycopyrrolate as a therapeutic option in children.

Surgical Treatment

Endoscopic thoracic sympathectomy should be considered when there is refractory to all medical therapies because it is an invasive procedure with considerable risks of complication. Compensatory hyperhidrosis is the main one and can occur in over 60% of cases.

The results are effective and permanent, and the technique is safe. The most recent studies have

shown satisfactory results in palmar hyperhidrosis with significantly reduced rates of compensatory hyperhidrosis, by using the technique of unilateral endoscopic thoracic sympathectomy, instead of the usual bilateral mode.

Devices

Energy-based devices, such as radiofrequency, have recently been described for the treatment of primary axillary hyperhidrosis, suggesting they are effective in reducing the amount of sweating. However, very limited published data of successful treatment is available, and studies in palmoplantar hyperhidrosis are lacking.

Botulinum Toxin

Botulinum toxin inhibits the release of acetylcholine from the presynaptic nerve terminal, obtaining a temporary and reversible chemodenervation in eccrine sweat glands, reducing the production of sweat (Grunfeld et al. 2009).

It is a therapy of first choice in the treatment of severe hyperhidrosis and second line in moderate cases. It is considered a revolutionary therapeutic modality to control sweating for its efficiency and high levels of satisfaction in improving the DLQI and HDSS in most cases, even in children as shown by Santos et al. (2009), Kouris et al. (2015) and Gordon and Hill (2013). However, its limited effect a few months, the high cost, and the pain caused by various application points, especially on the palms and plants that are richly innervated, make an additional challenge procedure in the treatment of these areas (Benohanian 2009; DÉpiro et al. 2014; Doft et al. 2012).

Managing Pain

Although considered to be a safe treatment technique, it is considered to be very painful for some patients. Pain can be a limiting factor to the performance of the procedure, and therefore analgesia is essential. Several methods are available; however, there is not an ideal gold standard method. Each case should be assessed individually, respecting the experience of the professional. The techniques described are the use of topical anesthetics, dipping the hands into ice water, vibratory anesthesia, crioanalgesia, dichlorotetrafluoroethane spray, ice packs immediately before punctures, needleless injection systems such as Med-Jet®, medial nerve blockade and ulnar Bier block anesthesia or modified by Solomon method, and more recently the use of nitrous oxide as inhalational analgesia (Almeida et al. 2001).

The authors recommend the use of topical anesthetic under occlusion for 30 min followed by applying ice directly to the skin immediately before each puncture (Fig. 3).

For palmoplantar hyperhidrosis, when the patient does not tolerate the pain with the described analgesia and does not present contraindications, anesthetic block can be performed. The palmar sensory innervation is mainly due to the median nerve, responsible for much of the palmar innervation, the ulnar nerve, and the radial nerve responsible for innervating the side of the palm and thumb (Fig. 4). The median nerve is located between the tendons of the palmar and radial flexor carpi that can be viewed in the central part of the wrist in flexion. The median nerve can be blocked injecting 3–5 ml of lidocaine or anesthetic solution between tendons 1 cm apart the wrist line. The ulnar nerve can be blocked by

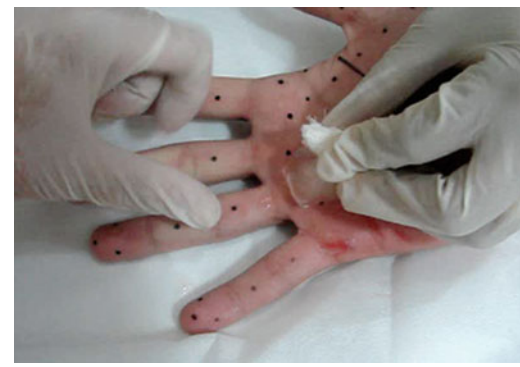

Fig. 3 Ice application immediately before each puncture to minimize pain during botulinum toxin injection for palmar hyperhidrosis

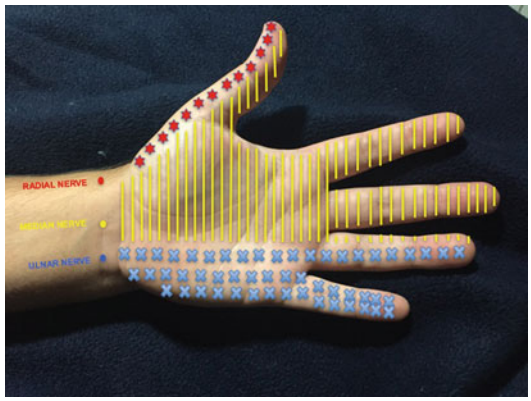

Fig. 4 Areas of sensitive innervation in palms

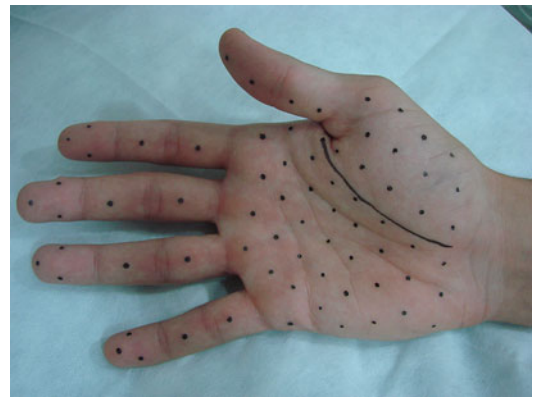

Fig. 5 Applications points for botulinum toxin injections

injecting the same amount of anesthetic between the ulnar artery and the tendon of the flexor carpi ulnaris, guiding the needle into the ulnar styloid process, 1 cm apart the wrist line. When the radial nerve blockade is required, it can be done by injecting the anesthetic in the lateral surface of the wrist line with reference to the radial artery, as they are side by side, always with care to avoid intravascular injection.

Application Technique

Before application, the area to be treated should be limited to Minor's test and photographed for later comparison. Generally the whole palm and sole are affected including the region of the fingertips. Although usually there is an extensive area affected, often some parts have a higher intensity of sweating and can be prioritized.

The dilution of botulinum toxin may be in 2–4 ml of 0.9% saline with or without preservative, for each vial of 100 U of onabotulinumtoxinA or the equivalent of other toxins (El Kahky et al. 2013). The application must be in intradermal level injecting 1–3 U of onabotulinumtoxinA per point with 1–2 cm distance between them (Fig. 5).

In the treatment of palmoplantar hyperhidrosis, the recommended total dose is between 100 and 200 U of onabotulinumtoxinA. Hypohydrosis starts 2 days after injection, and a new Minor's test should be performed after 2 weeks, when results can be seen (Fig. 6) and a new application can be carried out if excessive sweat is remaining.

According to Tamura et al. (2004) experience for treating plantar hyperidrosis, diluting 100 U vial of onabotulinumtoxinA in 4 or 5 ml of saline is suggested. A foot shoeing a shoe size 35 can benefit from 50 U by foot if hyperhidrosis is mild to moderate.

The treatment lasts lower than in axillary hyperhidrosis, about 6 months, ranging from 4 to 12 months.

Contraindications

Contraindications to botulinum toxin are pregnancy; lactation; allergy to albumin; patients with neuromuscular disorders, such as myasthenia gravis and Lambert-Eaton disease; and peripheral motor neuropathy (amyotrophic lateral sclerosis).

Side Effects

Side effects of the procedure include local pain, bruising, and formation of antibodies after repeated treatments, which appears to be related to high doses and short breaks between sessions. The temporary muscle weakness especially of hands and fingers occurs in 5–77% of patients. It is self-limiting in 10–42 days, dose related and application in the subcutaneous tissue. The authors suggest superficial intradermal injections

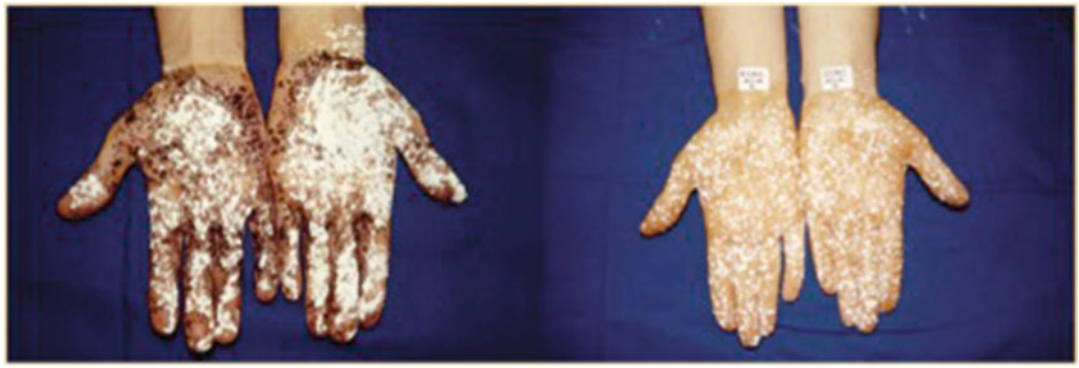

Fig. 6 Iodine-starch test before and 2 weeks after botulinum toxin injections for palmar hyperhidrosis

and small doses, no higher than 1 U onabotulinumtoxinA per square centimeter, in thenar and hypothenar areas.

Although botulinum toxin is a safe and effective treatment for palmoplantar hyperhidrosis, some patients do not tolerate needle injections, and pain is a limiting factor for others. Therefore, new methods of application have been described such as iontophoresis and more recently topical botulinum toxin, whose studies are in phase 3 of research and expected to be in the near future commercially available. Recent studies from Issa et al. have shown the fractional laser-assisted botulinum toxin delivery as a new possibility for hyperhidrosis treatment.

Fractional Laser-Assisted Botulinum Toxin Delivery for Hyperidrosis

The skin is almost impermeable for most hydrophilic and charged molecules, and a molecular weight (MW) of 500 Da is generally accepted as the upper limit for passive diffusion of lipophilic molecule. Therefore, there is strong interest in developing dermal penetration enhancement techniques (Haak et al. 2012).

Recently, the use of ablative fractional RF or CO_2 laser associated with high-pressure ultrasound (US) has been described as a successful method for drug delivery in alba-type stretch marks (Issa et al. 2012), hyperthrophic scar treatment (Issa et al. 2013), and areata alopecia (Issa et al. 2015).

BTXA injections are highly effective in treating hyperhidrosis; however, pain associated with injection is the major limitation (Benohanian 2009). Fractional laser-assisted drug delivery for palmar hyperhidrosis treatment was suggested by Letada et al. (2010) in a study using aminolevulinic acid on the palmar area. The authors had evaluated this new modality of treatment (fractional laser-assisted BTXA) for hyperidrosis in some cases.

Protocol Used by Authors

Before each session, the area to be treated was cleaned with alcoholic clorexedine and then with physiologic solution. Any anesthesia was necessary, but an air cooling device was applied during the procedure.

The treatment procedure comprised three steps: (1) ablative fractional CO_2 laser for skin perforation, (2) topical application of BTXA, and (3) acoustic pressure wave US to enhance BTXA penetration into the skin (Fig. 7).

The fractional CO_2 laser device used in this protocol has a roller tip which slides on the skin surface, producing micro-channels (pixels). It triggers a short-duration pulse of fractioned light via special beam splitter lens with fixed gaps between each 7×1 pixels. Laser parameters: CO_2 roller tip with 60 W, 50 mJ/pixel, spacing 1 mm. It produces microscopic holes having depth of 150–300 μm and diameter of 125–150 μm. The acoustic pressure module (US) is composed of a

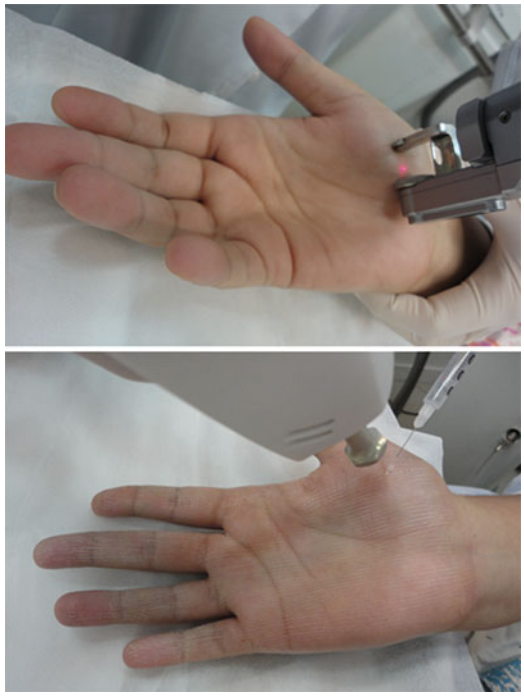

Fig. 7 TED procedure with fractional ablative CO_2. First step, applying the CO_2 roller tip; second step, botulinum toxin (BTXA) on the perforated skin; third step, applying the acoustic pressure US on the palmar area

transducer, a sonotrode, and a distal hollow. The mode of operation is based on mechanical pressure and torques by propagation of US wave (27 kHZ), creating a hammering-like effect on the thin layer between the topical BTXA, the skin, and the sonotrode. US parameters: 50 Hz (frequency of shocks) with 50% of impact intensity for 5 s in each 2 × 2 cm grid.

The 100 units of 900 kD botulinum toxin (Botox®) was diluted in 2 ml of physiologic solution 0.9% and dropped (2 U/2 cm^2) on the skin pretreated with laser.

With aim to compare this new modality of treatment to the standard protocol of botulinum injections, we used only 50 U of BTXA after the laser, and the other 50 U was injected on the contralateral hand.

After the procedure patients were advised to wear latex gloves for 4 h before cleaning the hands.

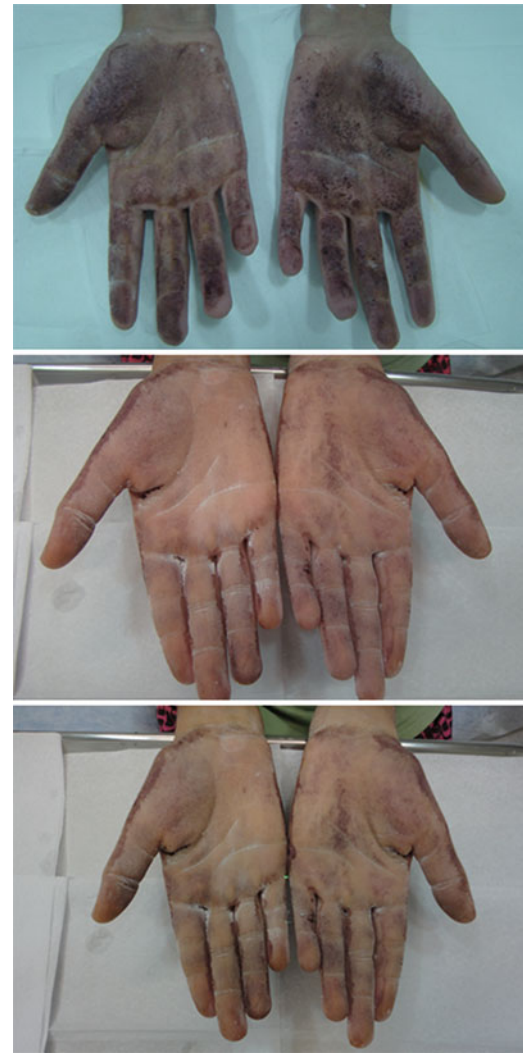

Fig. 8 Iodine-starch test before, 30 days and 3 months after TED procedure (CO_2 laser + BTXA + US) on palmar area

Clinical Effects

A 2-point improvement in hyperhidrosis disease severity scale (HDSS) score (80% reduction in sweat production) could be observed after 1 and 3 months in most cases, and it was sustained for 6 months (some cases) in both hands (injected and laser assisted) (Fig. 8). Curiously, iodine-starch test showed a homogenous reduction of sweat on the side treated with TED comparing to the side

treated with injection where a halo of BTX diffusion was noticed.

Side Effects

Side efffects included discrete erythema and a low intensity pain (burning sensation) during the procedure and for the following 4 h.

Discussion

This new method can be a good option for patients who cannot sustain the pain or tolerate needle injections. More studies are necessary to determine the best parameters and to define the protocol.

Take Home Messages

- Although the exact pathophysiology of primary hyperhidrosis is not completely known, there is much evidence for abnormalities in autonomic nervous system function and may be genetically determined.
- Treatment options available to patients with primary hyperhidrosis can be categorized as nonsurgical (topical antiperspirants, iontophoresis, systemic medication) or surgical (endoscopic thoracic sympathectomy, excision of axillary tissue).
- The use of botulinum toxin A has become an important option in the treatment of palmoplantar hyperhidrosis especially in patients who do not respond to conservative therapies.
- To avoid muscle weakness, be careful to inject intradermally and superficially and small doses, no higher than 1 U onabotulinum toxin A per square centimeter, especially in thenar and hypothenar areas.
- Patients with fear of needle and sensitive to pain can benefit from other methods of application of botulinum toxin such as iontophoresis or fractional laser-assisted botulinum toxin delivery.
- Fractional laser-assisted BTXA for hyperhidrosis is a very new possibility, and more studies are necessary to establish the protocol.

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Botulinum Toxin for Hyperhidrosis of Uncommon Areas

Érica O. de Monteiro

Contents

Abstract

Hyperhidrosis of other facial areas is less common, but a considerable problem for affected subjects. There are few reports of BTX treatment of single parts of the face, e.g., the forehead, the nasal, and cranial region. Patients with hyperhidrosis of the face and scalp would be sufficiently treated by intradermal injections of botulinum toxin (BTX) type A.

Keywords

Sweat glands · Sudoriparous glands · Sweat · Hyperhidrosis · Excessive sweating · Hyperhidrosis craniofacial areas

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Introduction

Sweat glands, also known as sudoriparous glands, are small tubular structures of the skin that produce sweat. Hyperhidrosis disorder is a condition that results in excessive sweating. Localized variants of hyperhidrosis are mostly primary and affect typically the axillae, palms, soles, and forehead. Hyperhidrosis of other facial areas is less common, but a considerable problem for affected subjects (Benson et al. 2013; Lauchli and Burg 2003; Wolosker et al. 2014).

Hyperhidrosis is seen in almost all ethnic groups. The patient can have serious physiological effects such as damp, cold hands; dehydration; and skin infections secondary to maceration of the skin. Hyperhidrosis can also have devastating negative emotional impact on individual lives, interfering with routine work and social interactions (Benson et al. 2013; Lauchli and Burg 2003;

M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_12

Wolosker et al. 2014; Solish et al. 2007; *Modified Protocol for the Application of Botulinum Toxin Type A for Hyperhidrosis of the Nose* 2016).

Fortunately, recent advances in medicine provide many forms of treatment for hyperhidrosis. Systemic medications, antiperspirant topics, iontophoresis, botulinum toxin, and surgery may be indicated for many cases (Benson et al. 2013; Lauchli and Burg 2003; Wolosker et al. 2014; Solish et al. 2007; *Modified Protocol for the Application of Botulinum Toxin Type A for Hyperhidrosis of the Nose* 2016). Patients with hyperhidrosis of the face and scalp would be sufficiently treated by intradermal injections of botulinum toxin (BTX) type A.

Pathophysiology and Clinics

Primary hyperhidrosis commonly affects the hands (palmar hyperhidrosis), the feet (plantar hyperhidrosis), and the underarm (armpit), but can also affect other areas such as the face, scalp, back, neck, submammary region, groin, thighs, and buttocks. It affects both sides of the body of the same shape and often starts in adolescence or even in childhood. Normally it is not present when sleeping and may affect other members of the same family. The cause is not known, although anxiety may worsen it. Although it is not temporary, it can sometimes improve with age (Benson et al. 2013; Lauchli and Burg 2003; Wolosker et al. 2014; Solish et al. 2007; *Modified Protocol for the Application of Botulinum Toxin Type A for Hyperhidrosis of the Nose* 2016).

Secondary hyperhidrosis can affect the whole body (generalized hyperhidrosis) or specific areas, or it may affect only one side of the body. People with secondary hyperhidrosis often sweat during sleep. Possible etiologies of secondary hyperhidrosis include systemic disease or infection, obesity, hormonal conditions (such as hyperthyroidism), menopause, or diabetes. It can also be secondary to the use of medications, including antidepressants (such as fluoxetine). These causes should be excluded before considering hyperhidrosis as primary (Benson et al. 2013; Lauchli and Burg 2003; Wolosker et al. 2014; Solish et al. 2007; *Modified Protocol for the Application of Botulinum Toxin Type A for Hyperhidrosis of the Nose* 2016).

Deep in the dermis, sweat glands are most abundant in the armpits, palms, and soles. Innervation is made by postganglionic sympathetic fibers, with the neurotransmitter acetylcholine (Benson et al. 2013; Lauchli and Burg 2003; Wolosker et al. 2014; Solish et al. 2007; *Modified Protocol for the Application of Botulinum Toxin Type A for Hyperhidrosis of the Nose* 2016) (Fig. 1).

When the cause is not clear, it is believed that primary hyperhidrosis starts with excessive activity of the sympathetic nervous system, specifically, in the sympathetic ganglia of the thoracic chain, located next to the spine. This chain controls the glands responsible for body perspiration. Depending on which part of the chain becomes

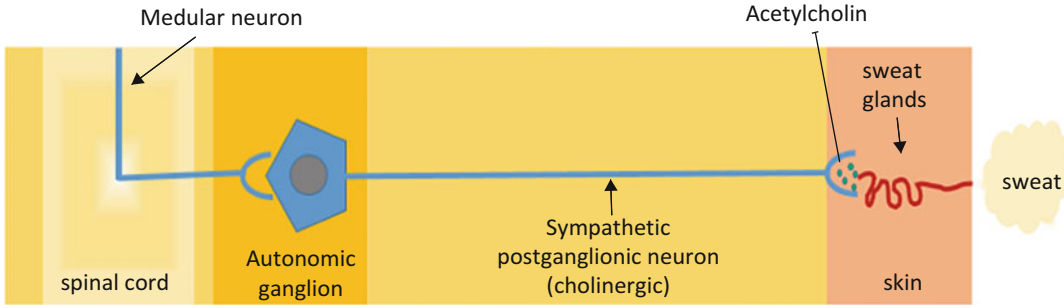


Fig. 1 Schematic representation of the sympathetic innervation of sweat gland. The representation inspired from: http://sweating.ie/normal-sweating/; http://www.hyperhidrosisuk.org/treatment-options/affected-areas.html

hyperactive, different parts of the body become affected.

Facial hyperhidrosis, and/or head, often also involves the neck. The condition resulting from overactivity of the sympathetic nervous system can leave the skin greasy and with shiny appearance.

Diagnosis

The distribution of the affected area can be determined by iodine-starch test (Minor's test) which is also used to identify areas of residual sweating after treatment. It consists of applying iodine in 3–5% alcohol solution, followed by cornstarch powder in the affected area, previously dried with absorbent paper. By reacting with the two substances, sweat turns violet, marking the affected site (Benson et al. 2013; Lauchli and Burg 2003; Wolosker et al. 2014; Solish et al. 2007) (Fig. 2).

Prior topical anesthesia can be applied and allows greater comfort for patients. The injection is secure without significant adverse events and, however, is usually very painful in the facial area. The effect begins between 24 and 72 h lasting 4–9 months. Reapplication can be made according to medical evaluation (Benson et al. 2013; Lauchli and Burg 2003; Wolosker et al. 2014; Solish et al. 2007; *Modified Protocol for the Application of Botulinum Toxin Type A for Hyperhidrosis of the Nose* 2016; Monteiro 2008).

Treatment

The treatment of hyperhidrosis depends on the etiology, location, patient tolerance, and other conditions. We can summarize the main choices for the treatment of hyperhidrosis in Tables 1 and 2 (Benson et al. 2013; Lauchli and Burg 2003; Wolosker et al. 2014; Solish et al. 2007; *Modified Protocol for the Application of Botulinum Toxin Type A for Hyperhidrosis of the Nose* 2016).

Unusual Area: Craniofacial Hyperhidrosis

Craniofacial hyperhidrosis has profound negative impact on the patient's social life. It is more common in male; the emotional and food stimulus can be more common than in other forms of hyperhidrosis. It is usually idiopathic or primary.

Anticholinergic topical glycopyrrolate in 1–2% occlusive cream could be attempted; it may be possible systemic adverse events such as dry mouth, blurred vision, and mydriasis.

Oxybutynin 10 mg per day may control the symptoms of facial sweating. Pay attention to

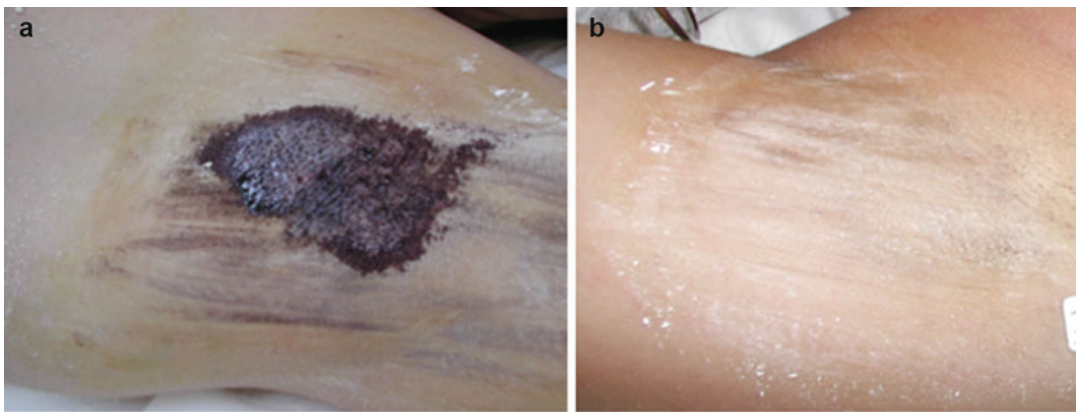


Fig. 2 Minor's test. Before (a), and after (b) botulinum toxin type-A injections

Table 1 Hyperhidrosis's treatment options

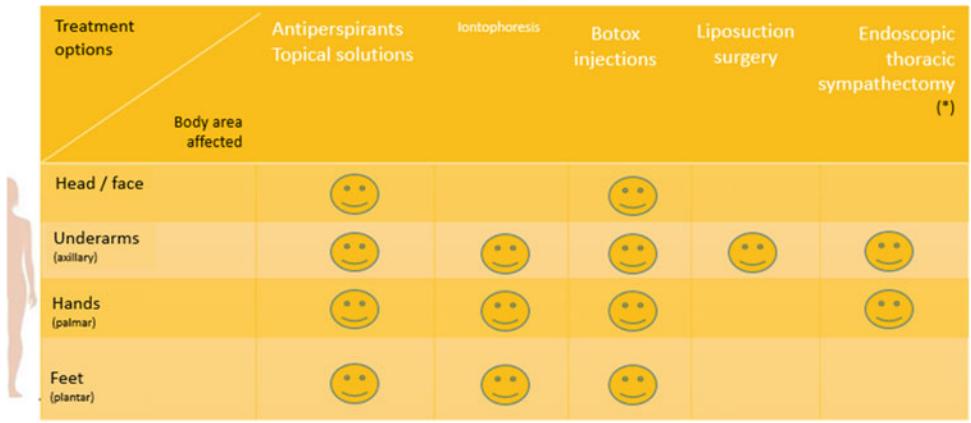


Table based on "International Hyperhidrosis Society", from www.sweathelp.org july 2016, except for the author's option to indicate axillary iontophoresis to selected patients.
(*) Only after all other treatments have been tried and failed.

Table 2 Generalized hyperhidrosis: differential diagnosis

The causes	
Infections	Acute viral or bacterial infections, chronic infections, such as tuberculosis, malaria, brucellosis
Drugs	Alcohol, cocaine, heroin (including withdrawal), ciprofloxacin, acyclovir, esomeprazole, sertraline, and other antidepressants
Endocrinology	Diabetes, hyperthyroidism, menopause, pregnancy, carcinoid syndrome, hypopituitarism, pheochromocytoma, acromegaly
Neurological problems	Stroke, spinal cord injuries, post-parotidectomy sweating, Parkinson's disease
Others	Lymphoma and other myeloproliferative disorders, congestive heart failure, anxiety, obesity

adverse events such as dry mouth, erectile dysfunction, headache, and urinary retention.

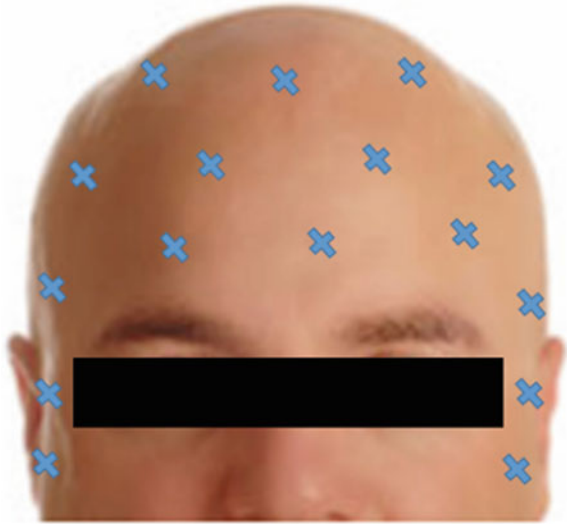
There are cases of successful treatment with botulinum toxin type A injection. Following evaluation of the facial area to be treated with Minor's test (Fig. 2), apply 1–2 units per point of botulinum toxin type A Botox, Prosigne, Xeomin, or Botulift or 3–6 units per point of Dysport; each injection can be pointed 1.5–2.0 cm in distance. Special care in the face with evolutionary often transient adverse events, such as facial asymmetry, abnormal smile, orbicularis weakness of the mouth, and others, should assess the risk-benefit and be discussed with the patient.

In the scalp, the dose ranges from 2 to 4 units per point of botulinum toxin type A Botox, Prosigne, Xeomin, or Botulift or 6–18 units per point of Dysport; each point spaced 2,0–2.5 cm (Figs. 3, 4, and 5). (Benson et al. 2013; Lauchli and Burg 2003; Wolosker et al. 2014; Solish et al. 2007; *Modified Protocol for the Application of Botulinum Toxin Type A for Hyperhidrosis of the Nose* 2016; Monteiro 2009; Talarico Filho et al. 2008; Costa et al. n.d.).

Minimizing the area of BTX diffusion is important to minimize the potential for adverse effects. This is particularly important when the injection sites are close to the muscles, like the centrofacial area. The degree of diffusion can be influenced by the dose and site of injection, the injection volume, and the injection technique.

Transcutaneous Botulinum Toxin

A new peptide carrier system (transdermal transport) delivers the botulinum toxin through the skin layers, and they are future prospects for the treatment of facial sweating.

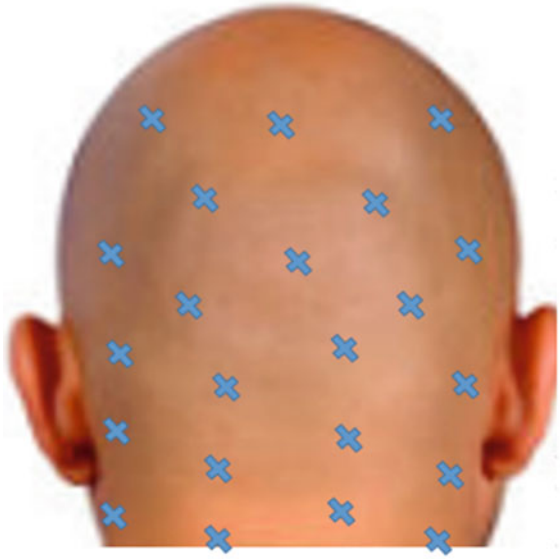


Posology

Botox®, Prosigne®, Xeomin® or Botulift® 100U vial. Reconstituition with 1.0 mL saline without preservative, final dilution 1U/0.1 mL. After Minor´s test, inject 1-2 U per point ( ). Distancy betwen points 1-1.5 cm.

Dysport® 500U vial. Reconstituition with 1.66 mL saline without preservative, considering Dysport®: Botox® relationship 3:1. After Minor´s test, inject 1-2 U per point ( ). Distancy betwen points 1-1.5 cm.

Fig. 3 Botulinum toxin forehead sites



Posology

Botox®, Prosigne®, Xeomin® or Botulift® 100U vial. Reconstituition with 1.0 mL saline without preservative, final dilution 1U/0.1 mL. After Minor´s test, inject 1-2 U per point ( ). Distancy betwen points 1-1.5 cm.

Dysport® 500U vial. Reconstituition with 1.66 mL saline without preservative, considering Dysport®: Botox® relationship 3:1. After Minor´s test, inject 1-2 U per point ( ). Distancy betwen points 1-1.5 cm.

Fig. 4 Botulinum toxin cranial sites

Final Considerations

Hyperhidrosis is characterized by excessive production of sweat. It manifests itself in various forms, affecting areas such as the armpits, hands, feet, and craniofacial region. Facial hyperhidrosis may lead to social embarrassment and psychological disorders. The therapeutic approach should use all arsenal available to minimize the social and psychological discomfort.

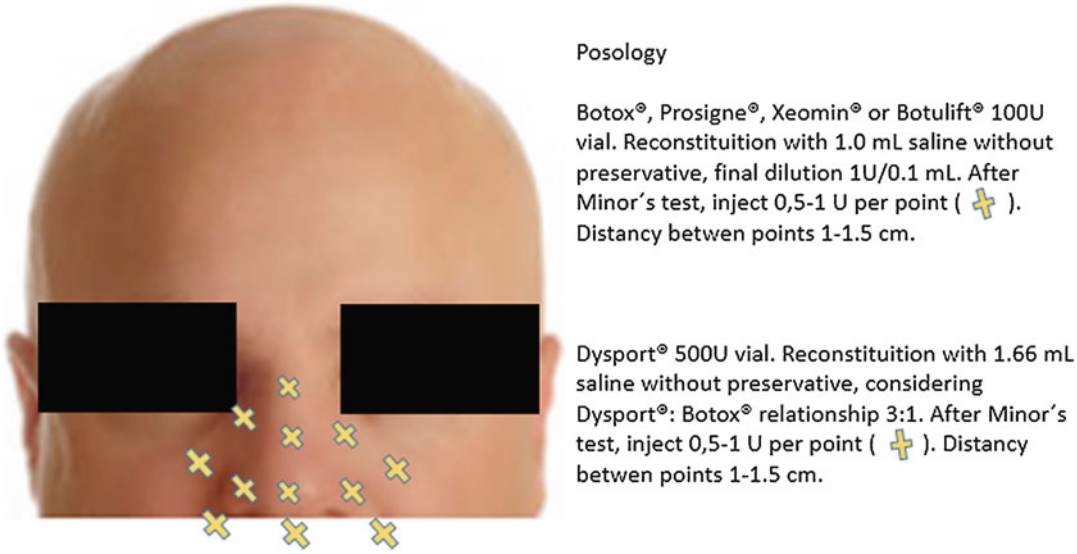


Fig. 5 Botulinum toxin nasal sites

Take Home Message

- Hyperhidrosis of other facial areas is less common.
- There are few reports of BTX treatment of single parts of the face, e.g., the forehead, the nasal, and cranial region.
- Facial hyperhidrosis can be successfully treated with botulinum toxin type-A.

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Microbotox, Mesobotox, Botulinum Toxin Microdroplets

Bhertha Tamura

Contents

Abstract

Microdroplets of botulinum toxin, also called microbotox or mesobotox, is the injection of multiple microdroplets or microinjection of a diluted botulinum toxin (BTX) solution into the dermis or the interface between the dermis and the superficial layer of the facial muscles, glands, and skin structures. This technique can be considered a new approach for botulinum toxin treatment; therefore, new studies to define the protocols are necessary. The indications for this method are quite similar to those common aesthetics indications for BTX, but in some cases it might be a good choice for a better outcome without excessive muscle relaxation. Topical anesthetics can be applied before this treatment, as it involves multiple punctures and some patients might complain about pain. This chapter will describe the suggestions and techniques reported in the literature and our personal experience. We have been using this technique since our publication in 2004, in which we described the results of BTX injection for the treatment of cutis laxa and explained the intimate relationship of the muscle fibers and the SMAS (Superficial Musculoaponeurotic System).

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_35

Keywords
Mesobotox · Microbotox · Botulinum toxin microdroplets · Botulinum toxin microinjection · Mesotherapy · SMAS · Topical botulinum toxin

Introduction

Microbotox is a term described by Dr. Wu, defined as the injection of multiple microdroplets of diluted onabotulinumtoxinA into the dermis or the interface between the dermis and the superficial layer of facial muscles. The intention is to decrease sweat and sebaceous gland activity to improve skin texture and sheen and to target the superficial layer of muscles that are attached to the undersurface of the dermis causing visible rhytides (Wu 2015).

Although initially injected with onabotulinum toxin, as it was the only one approved in some countries, we believe this technique can be done with any other toxin, respecting their biological characteristics. The terms microbotox and mesobotox do not really describe the procedure because they refer to the trademark Botox®. So we think that it would be better defined as botulinum toxin microdroplets or microbotulinum toxin, as the procedure can be performed not only with onabotulinum toxin, but also with abobotulinum toxin and incobotulinum toxin. The term "mesotherapy" is not suitable as well, because mesotherapy is used to describe the injection of solutions containing more than one ingredient for the treatment, but this technique uses only botulinum toxin.

Tamura et al. (2004) reported the surprising improvement in a patient with cutis laxa after botulinum toxin injection. The authors explained the action of botulinum toxin not only on the mimic muscle, but also on the most superficial layer of the mimic muscle fibers and reported its relationship with the SMAS. Thus, enough importance has not yet been given to the so-called "cutaneous muscles," attached to the dermis, which justify skin wrinkles.

Over the years, botulinum toxin injection techniques have evolved with the discovery of new anatomical sites and different layers of application, as well as lower dosage per site of injection. In 2007, Tamura reported the use of a very superficial and tiny amount of BTX in South America. The aim of such injections was to "disconnect" the muscle fibers that are joined to the dermis without relaxing the entire muscle, without losing their tonus. Through this technique, it is possible to have a natural result without a frozen look. The first site of injection was the "circumflex accent" sign area at the lateral superior portion of the eyebrows (a tiny wrinkle just above the lateral part of the eyebrow). At that time, doctors were still avoiding the treatment of the frontal lateral area, trying to prevent a possible dropping effect of the lateral eyebrow. After some strange and funny results called "diabolical" look, the tendency was to risk for an exaggerated drop instead of this undesired facial expression. Although the lateral lines could be treated at that moment, some of the patients remained unhappy because of a residual line just above the lateral side of the eyebrow, which is called a "circumflex accent" sign. Therefore, we ventured to inject microdroplets very superficially into the dermis (0.5–1 U) at each point on the wrinkle, exactly where the muscle inserted at the skin. This technique avoided not only the exaggerated dropping of the eyebrow, but also the puffy effect of the superior eyelids, with a very good cosmetic result.

After these initial results, we started to inject BTX at the eyebrow, over the mid-pupillary line, and intradermally to relax the superior portion of the orbicularis oculi muscle. We also began to treat the crow's feet under the zygomaticus arch and the risorius muscle insertion in patients with many and long lines at the malar area, without relaxing the zygomaticus muscles (Tamura 2005). At that time, we had suggested a greater amount of BTX per point, within a grid marked between the lateral eye angle, the mouth angle, the nostrils, and the tragus. For risorius treatment, toxin should be applied at the point that it inserts into the dermis. We started injecting 2 U per point every 1.5 cm (Fig. 1). The mimic improved, but it resulted in an unaesthetic smile (Fig. 2).

Despite the superficiality and small doses used for this technique, there is still a risk of undesired facial muscles relaxation. For this reason, topical

BTXA would be a better alternative for the treatment of risky areas. Probably, anytime soon, FDA will approve a new botulinum toxin for topical treatment. RT001 has been tested for topical use on the lateral canthal rhytids (crow's feet) and it seems to be promising. It will be presented as a cream, which should be applied at the physician's office, where patient should stay for about 15–30 min. This completely painless new topical treatment should eliminate injections for this area.

This treatment is being tested for other conditions, such as underarm hyperhidrosis (sweating), migraine, and rhinitis (runny nose). Off-label potential uses are reported for acne and for overall skin improvement in the face and neck. Unfortunately, for areas where muscle fibers are too deep (frown lines and forehead line), botulinum toxin should be injected. The treatment of upper lip lines, smoker lines, with topical RT001 has not been evaluated yet (Lee et al. 2015).

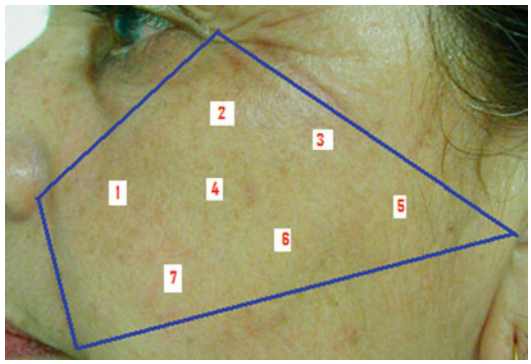

Fig. 1 Grid marked between the lateral eye angle, the mouth angle, the nostrils, and the tragus described in Tamura (2005)

Basic Technique

The technique varies among authors and doctors around the world. But we could consider the concept that the injections need to be placed very superficially into the dermis and in the area of the lines and can be injected virtually anywhere needed.

To obtain good results, we have to keep in mind that the aim is to relax the cutaneous muscle. It is fundamental to choose the right region and layer to be treated and superficially inject a low amount of toxin. The doses are lower compared to the ones usually injected to block facial mimics.

Before treatment, we should check patients' past history of bleeding and the use of medicaments to avoid ecchymosis. The general anamneses is very important every time we perform any aesthetic procedure. The characteristics of this technique might lead to unexpected and extensive ecchymotic area causing patient dissatisfaction.

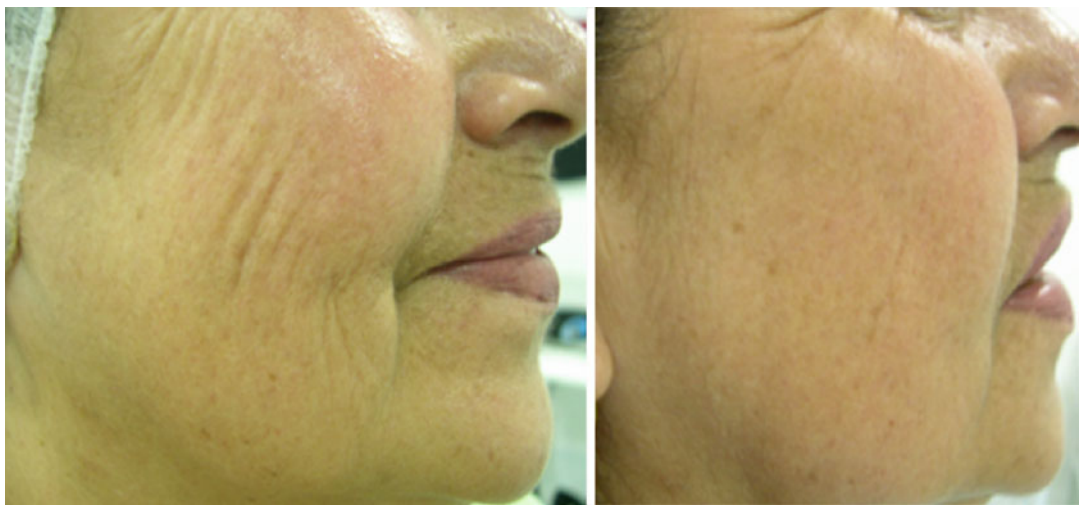

Fig. 2 Pre- and postmalar area treatment with BTXA (Tamura 2005)

Indications

In our experience, we suggest that the best indications are:

1. Patient with very thin skin thickness with a lot of fine lines.
2. Patient with excess of superior eyelid and not willing to be submitted to a surgical correction.
3. For crow's feet area, when patient has strong or volumized cheeks. With toxin microdroplets, we can avoid the "plateau" effect of the malar area or the so-called cartoon "Topo Gigio's" face, or "Disneyland's" smile.
4. To treat the crow's feet area in patients who had already been submitted to a blepharoplasty with the aim of avoiding temporalis muscle atrophy. The aim of the toxin microdroplets is to avoid temporalis muscle atrophy that can worsen the inner and lateral palpebrae malar sulcus.
5. Pretreatment for more wrinkles around the mouth, preparing the patient for fillers or for an abrasive medium or deep depth skin treatment.
6. Patients with exclusive "S" lines at the prejowl area caused by the contraction of the modiolus and the modiolar platysma.
7. Treatment of necklines to improve facial contour. It is difficult to decide between classical and microdroplets injection to treat this area (see chapter ▶ "Botulinum Toxin on the Neck"). For treatment of the lower face and neck, hundreds of microdroplets of diluted BTXA are injected into the dermis or immediate subdermal plane to improve the skin texture, smoothen the horizontal creases, and decrease the vertical banding of the neck, to achieve better apposition of the platysma to the jawline and neck, and finally to improve the contour of the cervicomental angle (Wu 2015). Although the results are good with this technique, we have faced a few adverse events, especially related to the dosage and the layer of application. The knowledge of the complexity of the muscles at the upper neck and lower neck with different repercussions is very important before any attempt to treat this area.
8. For the décolletage, toxin microdroplet gives an interesting result. However, in our experience, it is indicated when patient has a visible platysma extension over the "V" of the chest. This can be evaluated through examining and by asking the patient to contract the platysma muscle, making the chest lines visible. This is the safest area with minimum risks for the patient treated with this technique.
9. The muscles aimed with this technique are mainly the so-called cutaneous muscles. It can also improve the area at the insertion of other important muscles such as the risorius, the depressor anguli oris, and the mental. Besides, good improvement can be achieved when treating the frontalis, crow's feet, and the orbicularis oris at their skin adhesion site.
10. For both active lesions of acne or acne scars, microdroplets of botulinum toxin can be indicated (Tamura 2007).

Procedure

Dr. Wu suggests to dilute onabotulinumtoxinA in a classical way with 2.5 mL of saline solution and add a small amount of lidocaine to this solution. Each 1 mL of the solution contains 20–28 units of BTXA which is used to deliver at least 100–120 injections for the treatment of the cervicomental angle contouring. The lower face and neck will usually require 1 mL per side. The injections are delivered intradermally using a 30G or 32G needle raising a tiny blanched weal at each point. The author has treated the following areas: the forehead, the glabellar, the crow's-feet, the infraorbital, the cheeks, and the neck.

In our experience, we dilute 100 U of onaBTXA or incoBTXA in 1 mL of saline, then aspirate 5 U of BTXA of the solution in a 0.3 mL syringe, and dilute again the solution adding 0.25 mL of saline, thus, resulting in a total of 0.3 mL of syringe solution with 5 U of BTXA.

We prefer to have an exact idea of the number of units that should be injected in each chosen area. With this technique, we can individualize

each patient and quantify the minimal amount injected per area, per muscle activity. We can also predict the result and the effect duration. We write down the units injected per area in each session to achieve a better and longer result at every new appointment.

We named this technique "planned microinjection technique," and we can reproduce the results every time the patient receives a new treatment without any reference to commercial brands. In Fig. 3, we analyzed the patient's pretreatment mimics asking her to move the muscle to show static (left) and dynamic (right) lines at the frontal region. In Fig. 4, we planned the injection sites at the frontal area, with anterior and lateral view pictures. In Fig. 5, we checked the posttreatment result showing the static (left) and the dynamic (right) mimic of the frontal region.

The injections are planned to be really intradermally placed with the classical little white papule. We suggest injecting 0.01 mL per point within 5 mm distance between the points. For those doctors who do not have practice with this technique, topical anesthetics, vibration, or cooling should be used to give comfort (reduce pain) to the patient. At the beginning, it is common to lose part of the solution during injections. We particularly do not recommend the "nappage" technique, as the amount of BTXA cannot be really quantified with this method, and lot of product can be lost between the punctures.

Liew (2015) goes further by combining 10 U of onabotulinum toxin with 1 mL of non-cross-linked hyaluronic acid (12 mg). He has injected the solution in much less punctures (50–100) for the whole face and neck with much better results.

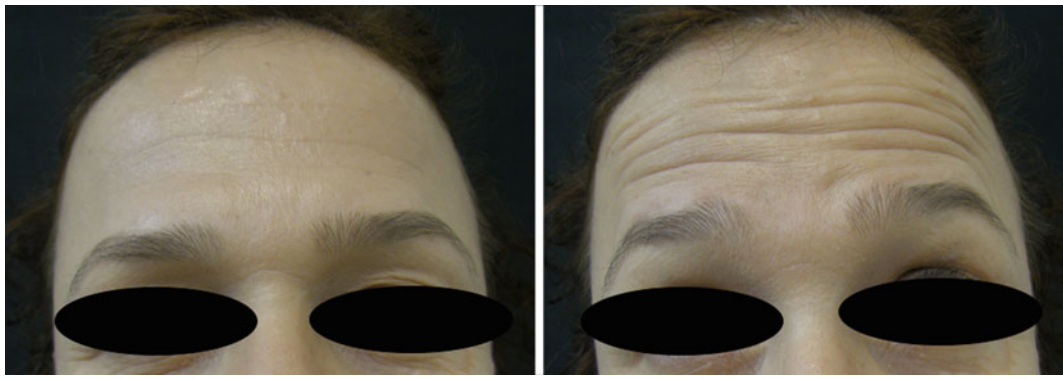

Fig. 3 Pretreatment photo at the frontal area

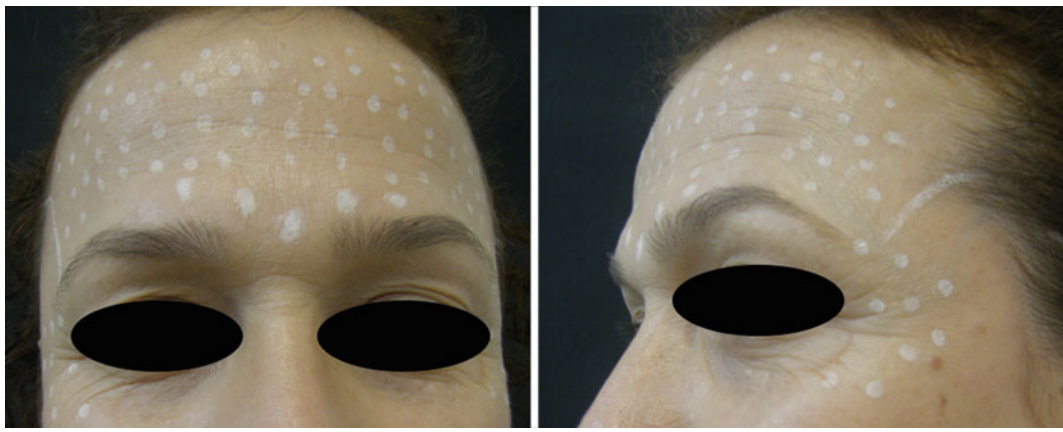

Fig. 4 Frontal area microinjection plan

Fig. 5 Posttreatment photo of the frontal area

In our experience, it is a really good idea, but we need to be aware that only non-cross-linked HA (hyaluronic acid) can be injected with this technique, not cross-linked. The cross-linked HA should not be applied very superficially.

Complications Related to the Technique

As it is not a standardized technique yet, there is no defined protocol for dilution, number of punctures, or dose (unit per punctures) for each area of treatment, which hinders the treatment plan and the predictable result. The procedure is painful and ecchymosis is frequent.

We can inject about two-thirds of the total volume usually injected with the classical BTXA treatment, to have a clinical effect, but the results are not long lasting. Strong and thick muscles are less responsive and clinical results are shorter.

If the BTXA solution is not well diluted, we might induce a nonhomogenous muscle relaxation. Ideally, a separate vial should be prepared with this specific hyperdilution of BTXA for the microinjection technique, avoiding the delivery of different concentrations at each point of injection, which can occur when saline solution is just added in a syringe.

With Liew's technique, micropapules and papules are expected and they might last for a few hours to 2 days depending on the HA composition. If the HA is pure, it is absorbed faster, and if HA is combined with mannitol or glycerol, and depending on the size of the papule, it can last for 24–72 h. HA with glycerol or mannitol is used for mature or photodamaged skin as they last longer and, in theory, attract much more water to hydrate the skin.

Discussion and Conclusion

The newest buzz about "Botox®" is this technique called "microbotox." Diluted botulinum toxin is injected in multiple, very small and superficial doses in the area to be treated. The theory here is that the effects of botulinum toxin spread more over the areas of injection and that the chance of overtreatment is diminished.

We believe that one of the most notable areas treated with microdroplets of toxin botulinum is the forehead, which shows a more natural look, avoiding the frozen effect. Wu (2015), Liew (2015), and Steinsapir et al. (2015) also reported very good results in neck treatment, showing mild improvement of the necklines and skin texture.

Serious complications of classical BTXA injections for the treatment of platysma's bands, such as dysphagia, respiratory impairment, and speech difficulty, can be avoided with this technique. Actually, it can be considered a very good option for platysma and for facial contour treatment.

If we are doubtful about which muscles should be treated, we should just think about the mimic muscles. Those that have literally cutaneous

adherence would be the first choice. Sometimes we do not need to inject at all its extensions, but at the skin over the strongest connection of the muscle to the dermis; one good example could be the insertion of the depressor anguli oris lateral to the chin.

Adopting the real term mesotherapy, intradermal injection through the "nappage" technique (Jager et al. 2012), the hypothetical effect of microneedling (Doddaballapur 2009), and the described collagen stimulation by BTXA (Oh et al. 2012), we could go further and say that depending upon the technique the doctor chooses, a muscular relaxation and a notable improvement of the skin could be achieved.

There is no consensus about microdroplets botulinum toxin, and studies to define a protocol are necessary. However, it is, for sure, an innovative, creative, and promising method, opening many other therapeutic possibilities. Microdroplets of botulinum toxin isolated or associated with hyaluronic acid through injections (microneedling, mesotherapy, micropunctures) at the dermis can also be used to induce neocollagenesis.

Take Home Messages

- Basically the technique still varies between authors and doctors around the world. But we could consider the concept that the injections need to be placed very superficially, at the dermis, on the lines.
- The advantage of using this technique is to treat wrinkles without relaxing the whole targeted muscle. The aim is to relax the fibers that adhere to the dermis.
- Best indications include: very thin skin thickness with a lot of fine lines, frontal area, crow's feet area, necklines, facial contour, and décolletage.
- With this technique, we can individualize each patient and quantify the minimal amount injected per area, per muscle activity and strength.
- It is very important to apply a very small dose intradermally, performing the classical little white papule at dermis. This papule must be seen after each puncture.
- This technique can be considered a new approach for botulinum toxin treatment; therefore, new studies to define protocols are necessary.

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Botulinum Toxin for New Indications

Doris Hexsel, Patricia Caspary, and Carolina Siega

Contents

Abstract

Since it was first approved by FDA for the treatment of glabellar frown lines, botulinum toxin rapidly became one of the most popular cosmetic procedures. In the last decade, its use has increased with improved techniques and new indications in the medical and cosmetic field. These include the treatment of asymmetries, muscles hypertrophy, and different conditions aggravated by sweating, keloids, and some diseases, as depression, rosacea, oily skin and associated conditions, and Raynaud's phenomenon. Besides its

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_14

effects in different conditions, new uses might be developed in the future.

Keywords
Botulinum toxin · Rejuvenation · Natural look · Asymmetries · Hailey-Hailey disease · Inverse psoriasis · Depression · Rosacea · Sebum · Oily skin · Hypertrophic scars · Keloid · Cicatrization · Raynaud's phenomenon

Introduction

Injections of botulinum toxin type A (BoNT-A) became one of the most popular cosmetic procedures in the world. Since its discovery for aesthetic use, BoNT-A has had a remarkable increase in cosmetic indications, mainly propelled by its popular use among physicians, more knowledge available from a huge number of publications, and rapid development of the new techniques and indications.

Nowadays, the aesthetic treatments with BoNT-A increasingly target a natural look. Besides, it has been found that the effects of BoNT-A enable not only the muscles' chemical denervation but also neurologic modulation in sweat and sebaceous glands, decreasing their production, as well as vascular regulation.

This chapter discusses new treatment approaches and some of the new indications of BoNT-A referred in the literature up to the beginning of 2016.

Current Uses and Goals in BoNT-A Treatments

The first indication described for BoNT-A in the cosmetic field was the improvement of hyperkinetic glabellar lines (Carruthers and Carruthers 1992), followed by the treatment of other facial dynamic wrinkles. Many experienced injectors are currently using BoNT-A to treat not only hyperkinetic muscles of various facial and extra facial areas, located at the glabella, orbicular, nasal, perioral, neck and décolleté areas, but also to improve the aesthetic appearance of hypertrophic masseter, gingival and asymmetric smile, eyebrows shape and position, and muscle-related asymmetries.

The "frozen look" had been considered the optimal result for a considerable time. In general, the goal of current treatments is to improve rhytides and skin quality preserving patients' expressiveness. Nowadays, approaches using BoNT-A for aesthetic treatments are shifting their target to a more natural look, although the concept of natural beauty is still a matter of debate (Dayan and Ashourian 2015). The three-dimensional aspects of the face, the way patients use their muscles, and how these can be improved are considered essential in one's expression and beauty (Dayan and Ashourian 2015).

Best results are obtained with careful evaluation of each patient and suitable strategies to specific patient needs. To reach these needs, physicians can use specific approaches, including the following:

- **Avoid frozen look or mask appearance:** Partial treatment of some facial muscles are considered the best option for more natural look. The *frontalis* m. are important muscles of facial expression. Low doses and partial treatment of these muscles may be the best option for some patients. Treating the upper part of the *frontalis* m. with less injection points and small doses of BoNT-A results in a more natural look and keeps the expressiveness (Ascher et al. 2010).
- **Avoid "Botox sign":** Caused by the excessive recruitment of the *nasalis* m. when smiling, it is sometimes aggravated by the treatment of the upper third of the face. Treating the *nasalis* m. concomitantly to the upper face indications confers a more harmonic appearance, and is always recommended for patients who already present these lines before treatment.
- **Prevention of side effects:** The consensus doses and the ideal injections sites are described in the literature, always considering patients' anatomy and desired results. As an example, injection points below an imaginary line between zygomatic arch and malar

eminency can reach the *zygomatic* m., giving an undesirable elevation of malar region. It is important to avoid injections that might target the *zygomaticus major* m., as they may also provoke the drooping of mouth corners (Carruthers et al. 2008; Ascher et al. 2010). Multiple injections and higher doses in the perioral area can cause side effects, the reason the lowest effective dose should be used. As an example, when treating gingival smile, high doses can cause the "joker's smile," a cosmetic side effect.

- **Treat asymmetries:** The treatment of natural asymmetries sometimes can result in a more harmonic and natural look.
- **Preserve the gender features:** The male and female features differences have been described by de Maio (de Maio 2015) because they are considered very important in performing cosmetic treatments. Injections in the glabella can change the brow shape and position giving the patients unwanted results. Straighter eyebrows are a typical male feature. It is important to prevent a feminine look for men, with arched eyebrows or, the excessive elevation of the brow tail.
- **Combined treatments:** The combination of BoNT-A and hyaluronic acid was showed to result in longer treatment effects than BoNT-A alone (Carruthers et al. 2010). Deep glabellar lines may require combined procedures, such as Subcision® and/or fillers (Hexsel 2002). Periorbital lines can also be adjunctively treated with fillers (Coleman and Carruthers 2006), lasers (Semchyshyn and Kilmer 2005), lights (Carruthers and Carruthers 2004), and peelings (Landau 2006). For better and more natural results, the treatment of the perioral area is best managed by combining BoNT-A with laser resurfacing and fillers (Gassia et al. 2013; Raspaldo et al. 2011).

Micro Injections of BoNT-A

Discussed in detail in the chapter ▶ "Microbotox, Mesobotox, Botulinum Toxin Microdroplets" (Bhertha Tamura). Microbotox, a technique that uses microdoses of BoNT-A, is being used, also helping the goal of a natural look. It consists in delivering multiple intradermal or subdermal injections of diluted BoNT-A into the overlying skin and superficial layer of the facial and neck muscles (Wu 2015). This technique promotes aesthetic improvement to the upper face without the unnatural forehead paralysis associated with conventional treatment (Steinsapir et al. 2015). Steinsapir et al. diluted a 100U-vial of onabotulinumtoxin A (ONA) in 3 ml saline solution and treated each patient with 1 ml of this solution divided in 60–100 microdroplets of approximately 0.01–0.02 ml, corresponding to a total dose of 33U per patient, and 0.33U–0.66U of ONA per injection point. According to the authors (Steinsapir et al. 2015), the toxins' solution containing small doses is placed more precisely to the target muscle, allowing the product to be used more efficiently, whereas the usual injections may cause the excess or focal forehead paralysis, among other cosmetic side effects. Iozzo et al. also reported the use of small doses distributed in multiple points in the forehead, periocular, glabellar, and nasal areas. They treated 223 patients with an average of 125U of abobotulinumtoxin A (ABO), distributed in intramuscular injection points, receiving 3U each, and subcutaneous or intradermal injections receiving 2U each. The authors reported high patient satisfaction and observed that the level of injections can regulate the potency of effect on the muscle (Iozzo et al. 2014).

Asymmetries

Asymmetries are particular of each person. They may be not only due to genetic inheritance but also caused by trauma or diseases as stroke and facial palsies as Bell's syndrome with contralateral hyperkinesis. Some asymmetries affect quality of life and even facial function and beauty. Therefore, the treatment has to be considered, being always discussed and individualized according to the individual anatomic variations (Bartoli et al. 2015).

Botulinum toxin type A is a safe and efficient option to treat asymmetries exacerbated by

muscle contraction or caused by muscle asymmetric movements. By injecting the BoNT-A in different muscles and using different doses and points of injection, experienced physicians are able to correct different asymmetries on the eyes, mouth, and/or brows. Doses vary depending on which muscles need to be treated and the degree of asymmetry and hyperfunction.

To balance asymmetric position and obtain brow lifting in some patients, brow depressors and *frontalis* muscles are treated in specific sites with selected doses (Tiryaki and Ciloglu 2007). By treating the opposite side, it is possible to partially relax the contraction strength, resulting in more facial symmetry. Benedetto reported successful treatment with injection of small doses of BoNT-A in five patients presenting smiling asymmetry due to ipsilateral hyperkinetic *depressor labii inferioris* (Benedetto 2007).

Asymmetries caused by tumors and surgical procedures can also be corrected with BoNT-A with high level of patient satisfaction, (Sadiq et al. 2012) sometimes combined with different techniques, such as fillers.

Masseteric Hypertrophy

The masseter muscles are located deeply in each side of the lateral portion of the lower face. When they present asymmetry or hypertrophy, they may give to the face an unattractive squared or asymmetric appearance. Botulinum toxin type A can be injected into these muscles aiming to cause some atrophy, but not a complete paralysis. Cha et al. treated ten patients with unilateral masseteric hypertrophy with BoNT-A injections. Total dose of 25U of ONA were divided in two injection points of the inferior part of the hypertrophic masseter m. They measured the thickness and volume of the muscle over a period of 12 weeks showing progressive decrease in volume and thickness with less asymmetrical lower face over time (Cha et al. 2013). Other studies report facial thinning with masseter volume reduction after BoNT-A injections, even in cases of asymmetry (Lee et al. 2013; Klein et al. 2014; Bhattacharjee et al. 2015). Nevertheless, no high level evidence is found in the literature for the effectiveness of efficacy and safety of intra-masseteric injections of botulinum toxin for people with bilateral benign masseter hypertrophy (Fedorowicz et al. 2013).

Conditions Aggravated by Sweating

Botulinum toxin is capable to reduce or even cease sweating in hyperhidrotic areas through the blockage of sympathetic nerve fibers. Excessive sweat may exacerbate some dermatoses, such as Hailey-Hailey disease and inverse psoriasis (Bessa et al. 2010; Saber et al. 2011), and provide a propitious environment for the development of cutaneous infections (Walling 2009).

Hailey-Hailey disease, also called familial chronic benign pemphigus, is characterized by acantholysis and the presence of flaccid blisters and erosions on intertriginous regions, as axillae and inguinal areas (Hohl et al. 2003). Different reports presented good or optimal improvement of this condition with reduction of sweating after BoNT-A injections (Lapiere et al. 2000; Koeyers et al. 2008; Bessa et al. 2010; López-Ferrer and Alomar 2012; Chiaravalloti and Payette 2014; Ho and Jagdeo 2015). So far no clinical trials have been developed to define how long effects can be sustained.

Inverse psoriasis, or flexural psoriasis, is characterized by erythematous, sharply demarcated, thin, shiny plaques that often itch and burn (van de Kerkhof 2003; Saber et al. 2011). It appears only at flexural sites and often presents as a chronic intertrigo. This type of psoriasis usually lack the scales associated with the more common form of plaque psoriasis (Wang et al. 2005). Zanchi et al. reported the treatment of 15 patients with 2.4U of ONA per injection point, placed 2.8 cm apart each other. The total dosage ranged between 50 and 100U per patient depending on the extent and severity of the psoriasis. The therapy resulted in improvement in patients' symptoms (Zanchi et al. 2008). These authors suggest that the reduction of sweating would not be the only mechanism implied in the improvement of the condition. Saber et al. reported improvement

of inverse psoriasis in one patient who concomitantly presented with hyperhidrosis in the axillae after treatment with 100U of ONA. These authors infer that sweat reduction probably contributed to the improvement of inverse axillary psoriasis (Saber et al. 2011).

Depression

Major depressive disorder (MDD) is a very common disease. Lifetime prevalence is estimated to be higher than 15% depending on the population (Kessler et al. 2003; Williams et al. 2007). It directly influences the mood and may cause functional impairment, worsening of quality of life, and risk of mortality (Katon 2011). Despite the new and safer antidepressant drugs currently available on the market, many patients are not able to completely control the disease.

The positive effects of BoNT-A injections in mood and depressive symptoms have been suggested in the last decade (Heckmann et al. 2003; Finzi and Wasserman 2006; Lewis and Bowler 2009). However, randomized controlled trials to evaluate the clinical outcomes of BoNT-A injections in the glabella in patients suffering from MDD are very recent (Wollmer et al. 2012; Hexsel et al. 2013; Magid et al. 2014; Finzi and Rosenthal 2014). The results of those trials support that a single treatment of the glabella with BoNT-A can alleviate symptoms of depression in patients with MDD. Patients of the active groups presented significant clinical improvement over time, while no significant difference was observed for the placebo groups (Wollmer et al. 2012; Magid et al. 2014; Finzi and Rosenthal 2014). Women were treated with 29U of ONA and men with 39U–40U of ONA. Outcomes were assessed at different time points in each study, with follow-up periods varying from 6 to 24 weeks (Wollmer et al. 2012; Magid et al. 2014; Finzi and Rosenthal 2014).

The exact mechanism of action of BoNT-A in the improvement of MDD symptoms is not completely understood. One of the hypotheses is that facial expression may influence emotional perception. The glabellar muscles, responsible for expression of sadness and other negative feelings, when treated with BoNT-A injection may decrease these feelings (Alam et al. 2008). The results of a recent study support the concept that facial musculature not only expresses but also regulates mood states (Wollmer et al. 2012). Other studies (Hexsel et al. 2013; Magid et al. 2014) showed that some patients still improve even after the chemical denervation is ceased or even if the self-esteem scores do not correlate with the improvement in depression symptoms. Thus, it is speculated that other neuromodulator mechanisms may be involved.

Up to now, only ONA has been evaluated as a possible treatment for MDD. Randomized, double-blind, controlled studies are needed to confirm the potential application of other preparations of botulinum toxin for that purpose.

Other important questions regarding the treatment of MDD with BoNT-A have been raised. Kruger and Wollmer speculate that other facial muscles involved in the expression of sadness, like the *mentalis* muscle or the *depressor anguli oris*, may also be targeted with BoNT-A to treat disorders associated with negative emotions (Kruger and Wollmer 2015). However, further studies are required to explore and identify the remaining open questions on this matter.

Flushing and Rosacea

Rosacea is a very common cutaneous disease that presents with different clinical features, which occur concomitantly or not. A classification has been established and defined four rosacea subtypes. The erythematotelangiectatic subtype is characterized by persistent central facial erythema and flushing (Wilkin et al. 2004). Laser and light therapies, oral tetracyclines, topical immunotherapy, and brimonidine topical gel are often prescribed (Weinkle et al. 2015).

Intradermal injections of BoNT-A is an emerging therapy for rosacea. Sterodimas et al. reported improvement of flushing in anterior chest and neck after injections of 2U of ONA each 1 cm^2 (Sterodimas et al. 2003). One year later, another case report presented good improvement of

persistent facial flushing after injections of ONA 1 cm apart each other. A total dose of 10U was used in this case (Yuraitis and Jacob 2004). In both cases, patients noted considerable improvement after 2 weeks.

Other successful cases have been reported using intradermal injections of ONA to treat facial flushing and erythema (Dayan et al. 2012; Park et al. 2015). Dayan reported the use of 8–12U of ONA per affected area, split in microdoses of 0.05U per injection point, placed 0.5 cm apart each other (Dayan et al. 2012). Park et al. used 15U of ONA per cheek in the first treatment and 5U in the second treatment, 1 week after. Injection points were placed 1 cm apart each other (Park et al. 2015). A proof-of-concept study presented significant improvement in erythema scores up to 3 months after treatment in 15 patients presenting with rosacea-associated erythema. Patients were treated with intradermal injections of 15–45U of ABO depending on the severity of each case (Bloom et al. 2015).

The doses of BoNT-A used to treat erythema and flushing should be lower than the regularly used for other cosmetic treatments, to prevent side effects in the muscles located where the toxin will be injected. Large volumes should be used to reconstitute the toxin to treat these indications. The concentration that has been reported is from up to 2U/0.1 ml for ONA and up to 10U/0.1 ml for ABO. The total doses vary according to the area. For each cheek, 10–15U can be used (Yuraitis and Jacob 2004; Park et al. 2015). For the chin, 5U is the recommended dose (Park et al. 2015). For the neck and anterior chest wall, 100U can be used (Sterodimas et al. 2003). Injections points are placed 0.5–1 cm apart each other (Sterodimas et al. 2003; Yuraitis and Jacob 2004; Dayan et al. 2012; Park et al. 2015; Bloom et al. 2015).

The mechanism of action is supposed to be related to the chemical denervation caused by BoNT-A inhibition of acetylcholine (ACh) and by the interference over other mediators also involved in the cutaneous vasodilatation process (Khan et al. 2013). Other possible mechanisms, also raised by Khan et al., are the attenuation of the thermogenic response by BoNT-A or the transient interference of the injection trauma or the drug properties with the skin's response to heat stress. A study using botulinum toxin type B to treat facial flushing suggests it is not effective for that purpose (Oh et al. 2011).

Evidences suggest that intradermal injections of BoNT-A are effective to treat rosacea, but further studies are needed to establish the efficacy in different types of rosacea, the mechanisms of action, and duration of effects.

Oily Skin and Associated Conditions

Sebum production is a natural and healthy process of the skin. However, excessive sebum production may cause discomfort and can even contribute to other clinical conditions as enlarged pores, acne and, seborrheic dermatitis. In 2008, Shah first raised the possibility of using intradermal BoNT-A for oily skin treatment. The author performed a restrospective study and presented improvement in skin oiliness and reduction in enlarged pores in 17 out of 20 patients treated with ONA. No objective methods were used for this assessment (Shah 2008). Two other publications also refer the reduction of skin sebum content after BoNT-A injections assessed by objective measurements (Rose and Goldberg 2013; Min et al. 2015). Twenty-five patients, 5 men and 20 women, presenting mild to moderate oiliness in the forehead area were treated with intradermal injections of 30–45 U of ABO distributed along 10 points. The best improvement was observed at 1 month follow-up, corresponding to a reduction of 80% in sebum production; at the end of the study, most patients were satisfied (Rose and Goldberg 2013).

On the other hand, Min et al. assessed the effects of BoNT-A in sebum production after intramuscular injections to treat forehead rhytides. The authors compared the effects of 10U and 20U injected in five standard sites. Reduction in sebum production was observed up to 8 weeks and was not dose related. Besides, the sebum production presented a positive correlation with the distance away from the injection point. The closer to the injection point, the lower was the sebum production (Min et al. 2015).

The exact mechanism of action is not clear. Rose and Goldberg suggested that that blockade of local ACh receptors in the pilosebaceous unit could alter the rates of sebum production. Indeed, it has been shown that ACh plays an important role in sebum production (Li et al. 2013).

Cicatrization and Scars

Cicatrization is the healing process that replaces normal skin after injury. When this process is abnormal, excessive fibrosis may lead to hypertrophic scar or keloids. Keloids and hypertrophic scars are challenging conditions, as they result from abnormal excessive scar tissue formation and lead to unaesthetic appearance. Many treatments available nowadays, as surgical procedures, cryotherapy, steroid injection, and lasers, are not always successful and lack evidence of efficacy (Davis et al. 2013).

The unattractive appearance of keloids and hypertrophic scars and poor efficacy of the available treatments propel the search for new techniques with better results. Repeated injections of BoNT-A have been proposed as an alternative option to expand the therapeutic range of keloids and hypertrophic scars (Gassner et al. 2006; Tollefson et al. 2006; Ziade et al. 2013; Chang et al. 2014; Kim et al. 2014; Shaarawy et al. 2015).

Although a previous study with four patients who received intralesional administration of BoNT-A did not result in regression of keloid tissue (Gauglitz et al. 2012), Shaarawy et al. conducted a randomized double-bind study comparing the effects of triamcinolone 10 mg/ml injection every 4 weeks in keloids of 12 patients to the effects of 5 U of BoNT-A injected every 8 weeks in keloids of other 12 patients, for 6 months. They demonstrated similar efficacy with better satisfaction in the latter group (Shaarawy et al. 2015). Recently, it was observed that BoNT-A affects the expression levels of five genes relevant to invasive growth in keloid fibroblasts (Xiaoxue et al. 2014). Results of another in vitro study, on the other hand, did not suggest a significant therapeutic role of BoNT-A after testing the effects of BoNT-A on cell proliferation and expression of cytokines and growth factors of keloid fibroblasts (Haubner et al. 2014).

Other publications report the effects of BoNT-A over hypertrophic scars and cicatrization. In 2009, Xiao et al. reported improvement in 19 patients that had their hypertrophic scars treated with 2.5UI of BoNT-A (Lanzhou Biochemical Companie, Lanzhou, China) per cubic centimeter of lesion, not exceeding 100U per patient per application. The injections were repeated every month for 3 consecutive months and patients were followed for 6 months (Xiao et al. 2009).

It is well known that distrophic scars can appear in areas of movement. Gassner et al. conducted a prospective, blinded, randomized, placebo-controlled trial to assess the effects of ONA injections in scar formation of traumatic forehead lacerations. The authors suggested the use of BoNT-A improves the appearance of scars (Gassner et al. 2006). Improved cosmesis of facial wounds was also reported in another prospective, blinded, randomized, placebo-controlled trial. Thirty patients were assigned to receive either ONA injections or no injections. The mean dose used was 20U, injected up to 72 h following the suturing. According to the authors, early injection of BoNT-A appears to enhance healing of facial wounds (Ziade et al. 2013). The use of BoNT-A has also been suggested to improve the quality of scars secondary to cleft lip repair surgery, even in children (Tollefson et al. 2006; Chang et al. 2014), and also in scars secondary to thyroidectomy (Kim et al. 2014). Despite the reports of successful use to improve wound scars with BoNT-A injections, a recent systematic review, which included ten studies, stated that the current evidence does not support the usage of botulinum toxin for this purpose (Prodromidou et al. 2015).

It is not yet completely understood how BoNT-A influences the scar formation. One of the possible mechanisms of action, and the most plausible up to now, is the reduction in skin tension forces with the muscle paralysis, which reduces microtrauma and inflammation (Gauglitz et al. 2012). Another possible mechanism could be the influence of BoNT-A in fibroblast cell cycle and differentiation, as demonstrated in some in vitro

studies (Zhibo and Miaobo 2008; Xiao et al. 2010; Xiao et al. 2011; Jeong et al. 2015). However, this is still to be clarified. Other recent research concluded that there is no evidence to suggest a significant effect of BoNT-A injections in fibroblasts proliferation and cytokines and growth factors related to wound healing (Haubner et al. 2012).

It seems that BoNT-A may collaborate for better scaring processes. Further studies need to be conducted to clarify whether the effects of BoNT-A are related only to the chemo immobilization of the affected area or whether the BoNT-A molecule is also capable of interfering in cell cycle. Irrespective of the mechanisms involved, the definition of ideal doses and treatment frequency is of great relevance for better outcomes and patient safety, since BoNT-A injections in certain muscles, or the use of excessive doses, can cause cosmetic side effects and even functional impairment.

Raynaud's Phenomenon

Raynaud's phenomenon is a condition that affects extremities, most commonly fingers and toes, causing alteration in color and temperature. The reduction of blood flow to the digits, which occurs due to an exaggerated vasospastic response, causes pallor and cyanosis and may also cause pain, disability, and ischemic ulcers, even leading to amputation in more severe cases. Raynaud's phenomenon can be primary or secondary to some other disease (Iorio et al. 2012).

Recently, BoNT-A was presented as a treatment option for this condition. Different authors reported improvements in the symptomatology of Raynaud's phenomenon after injections of BoNT-A and the safety of this procedure (Fregene et al. 2009; Neumeister 2010; Zhang et al. 2015). The improvements were also noted after BoNT-A injections also in cases of Raynaud's phenomenon secondary to other diseases (Serri et al. 2013; Uppal et al. 2014; Motegi et al. 2015; Zhang et al. 2015).

Treatment doses reported are variable. Zhang et al. 2015 used 50U of ONA in the palm of each hand, distributed along the artery supply (Zhang et al. 2015). Zhao and Lian reported two patients with severe disease, refractory to other treatments, that had good results with the cumulative doses of 200U and 280U of BoNT-A (Lanzhou Biological, Products Institute, Lanzhou, China) in the palm of both hands (Zhao and Lian 2015). They injected 20U of BoNT-A per digit divided in four points. The use of lower doses has also been reported (Motegi et al. 2015).

The development of further studies could help to better understand and standardize the technique.

Take Home Messages

- In the last years, the improvement of some medical and cosmetic conditions after treatment with BoNT-A have been reported by different authors.
- Botulinum toxin can offer alternatives for conditions of difficult treatment. In many cases, it can be used as adjunctive treatment.
- New indications of botulinum toxin must be object of randomized, controlled trials to support and strengthen their use.
- Some new indications described in this chapter are not yet approved by regulatory agencies. For this reason, they should be considered as off -label indications.

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Botulinum Toxin for Migraine

Maria Eduarda Nobre, Marcelo Cedrinho Ciciarelli, and Jano Alves Souza

Contents

Abstract

The use of onabotulinumtoxinA in headaches starts in 1997 with exploratory studies for migraine and other headache subtypes. At the same time, laboratory research explored the nonmotor effects of onabotulinumtoxinA.

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However, the efficacy was demonstrated just for chronic migraine (CM) and the use was approved in 2010 based on two studies, PREEMPT 1 and 2. These studies consisted of a 24-week randomized, double-blind, placebo-controlled phase followed by a 32-week onabotulinumtoxinA open-label phase. Study injections were given at 31 fixed and 8 optional sites with 5U in each site (total 155U to 195U, mean 165U) across seven head and neck muscle areas (procerus, corrugator, frontalis, temporalis, occipitalis, cervical paraspinal, and trapezius), each 12 weeks.

OnabotulinumtoxinA has shown a safe and effective prophylactic treatment option for patients with CM. Accurate target muscle localization and injection angles and depths

M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_42

are required to achieve optimal outcomes and to minimize adverse events.

Keywords
Headache · Chronic migraine · OnabotulinumtoxinA

Introduction

Botulinum toxin was first described by its effect in the autonomic peripheral nervous system in a case of botulism. The beneficial effect of botulinum toxin for strabismus was reported many years later, with subsequent expanding therapeutic use in medicine. The US Food and Drug Administration (FDA) first approved OnabotulinumtoxinA in 1989 for blepharospasm and strabismus. Nowadays, onabotulinumtoxinA is very well indicated for several non-cosmetic uses, including cervical dystonia, severe primary axillary hyperhidrosis, upper limb spasticity, overactive bladder, urinary incontinence from neurogenic detrusor overactivity, and chronic migraine (CM) (Erbguth and Naumann 1999).

Chronic migraine has been estimated to affect approximately 1.4–2.2% of the population globally and is often associated with substantial disability, functional impairment, and decreased quality of life. In a pioneering program, the US Food and Drug Administration approved onabotulinumtoxinA for the CM prevention. It was licensed specifically for the treatment of CM in July 2010 by the Medicines and Healthcare products Regulatory Agency (MHRA) (Lipton and Silberstein 2015).

History

In the early nineteenth century, Justinus Kerner published the first case study of botulism and described the clinical effects of botulinum toxin derived from sour sausages; he postulated that botulinum toxin could act on the motor and autonomic peripheral nervous system (Erbguth and Naumann 1999). Some decades later, in 1895, the *Clostridium botulinum* was isolated by Emile Pierre-Marie van Ermengem, a bacteriologist from University of Ghent (Brin and Blitzer 2013).

The first classification of toxin in serotypes A and B was published in 1919 by professor Georgina Burke from Stanford University. The bacterial exotoxin was purified and crystalized in the 1920s, followed by continued refinement of the isolation and purification process throughout the mid-century (Lamanna et al. 1946).

Nearly 60 years later, the ophthalmologist Alan Scott described the beneficial effects of botulinum toxin A for strabismus, which paved the path to regulatory approval and the subsequent expanding therapeutic use of botulinum toxin in medicine. The name of Scott's original product, Oculinum, was later changed to Botox, and in 2011, this biological substance was assigned the nonproprietary name onabotulinumtoxinA (Scott 1980).

The US Food and Drug Administration (FDA) first approved onabotulinumtoxinA in 1989 for two therapeutic indications: blepharospasm and strabismus. Nowadays, onabotulinumtoxinA is very well indicated for several non-cosmetic uses, including cervical dystonia, severe primary axillary hyperhidrosis, upper limb spasticity, blepharospasm, strabismus, overactive bladder, urinary incontinence from neurogenic detrusor overactivity, and chronic migraine (CM) (Erbguth and Naumann 1999).

In the 1990s, a facial plastic surgeon observed that, when treating patients with botulinum toxin A for cosmetic enhancement, some of his patients with an incidental history of migraine reported a reduction or elimination of the number or intensity of their headaches concurrently with the cosmetic effect (Binder et al. 1998a, b). In 1998, the first open-label study of onabotulinumtoxinA reported efficacy in patients with frequent migraines, and the first peer-reviewed publication appeared in 2000 (Binder et al. 2000).

At the time, some clinical studies evaluated the use of onabotulinumtoxinA for migraine and other headache subtypes. In addition, laboratory research explored the nonmotor aspects of onabotulinumtoxinA effects, which as a novel mechanism, supported clinical development decisions and, ultimately, regulatory filings. The

results from the phase II program demonstrated decreased headache in some patients, and the drug was well tolerated. Nevertheless, the most consistent efficacy in phase II studies was in patients with more severe disease, characterized by frequent headache days per month and with headaches that had migraine characteristics and symptoms. Based on these observations, a refined patient population was pursued for the phase III clinical trial program, from which it was proposed that onabotulinumtoxinA might be a therapeutic option for patients with transformed migraine, which would later be further defined as chronic migraine (CM). Until this point, these severely affected, complex patients were explicitly excluded from other headache treatment registration programs (Mathew et al. 2005).

Migraine

Migraine is a common disabling primary headache disorder, affecting approximately 18% of women, 7% of men, and 4% of children worldwide and is one of the world's leading causes of disability (Lipton et al. 2001). Migraineurs commonly experience restricted activity, decreased productivity, and missed work or school days. Migraine-related disability may lead to reduce health-related quality of life and increased depression. The worldwide burden of migraine to society is substantial, with upward of billions of dollars spent in direct costs (utilization of healthcare resources) and indirect costs related to disability, reduced productivity, and missed work days (Lipton et al. 2002).

Migraine has two major types: (1) migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms; (2) migraine with aura is primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. It is a recurrent headache disorder manifesting in attacks lasting 4–72 h. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia (Headache Classification Committee of the International Headache Society (IHS) 2018).

Migraine pain is the result of the activation of the trigeminovascular system (TVS), which releases vasoactive neuropeptides, mainly calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) around leptomeningeal and extracranial vessels (Ho et al. 2010). It is hypothesized that cranial pain pathways become sensitized by repeated episodes of TVS activation, leading to migraine chronification (Riesco et al. 2017).

Chronic migraine has been estimated to affect approximately 1.4–2.2% of the population globally and is often associated with substantial disability, functional impairment, and decreased quality of life. In many cases it may be associated with medication overuse (Straube et al. 2010; Weatherall 2015). It is defined as a headache occurring on at least 15 days per month for >3 months in which headache with features of migraine occur at least on 8 days per month, according to International Classification of Headache Disorders. The last classification included CM in code 1.3 – chronic migraine (Fig. 1) (Headache Classification Committee of the International Headache Society (IHS) 2018).

The risk of progression is affected by both modifiable and nonmodifiable factors. Nonmodifiable risk factors include older age, female gender, Caucasian ethnicity, low educational level, low socioeconomic status, and genetics. There are also a number of potentially modifiable risk factors for CM onset. Obese individuals with EM are two to five times more likely to develop CM than are persons of normal weight. Persons with snoring are more likely to progress to CM. Other risk factors include the frequency of the attacks, head or neck injury, comorbid depression (especially moderately severe or severe depression), and stressful life events or major life changes (Weatherall 2015).

There are three broad approaches to treating chronic migraine: lifestyle and trigger management, acute treatments (i.e., those taken during attacks or exacerbations of chronic pain), and preventive treatments (medication or other

Classification

ICHD-3 code Diagnosis
1. Migraine
1.1 Migraine without aura
1.2 Migraine with aura
- 1.2.1 Migraine with typical aura
  - 1.2.1.1 Typical aura with headache
  - 1.2.1.2 Typical aura without headache
- 1.2.2 Migraine with brainstem aura
- 1.2.3 Hemiplegic migraine
  - 1.2.3.1 Familial hemiplegic migraine (FHM)
    - 1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)
    - 1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)
    - 1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)
    - 1.2.3.1.4 Familial hemiplegic migraine, other loci
  - 1.2.3.2 Sporadic hemiplegic migraine (SHM)
- 1.2.4 Retinal migraine

1.3 Chronic migraine
1.4 Complications of migraine
- 1.4.1 Status migrainosus
- 1.4.2 Persistent aura without infarction
- 1.4.3 Migrainosus infarction
- 1.4.4 Migraine aura-triggered seizure

1.5 Probable migraine
- 1.5.1 Probable migraine without aura
- 1.5.2 Probable migraine with aura

1.6 Episodic syndromes that may be associated with migraine
- 1.6.1 Recurrent gastrointestinal disturbance
  - 1.6.1.1 Cyclical vomiting syndrome
  - 1.6.1.2 Abdominal migraine
- 1.6.2 Benign paroxysmal vertigo
- 1.6.3 Benign paroxysmal torticollis

Fig. 1 ICHD-3 code Diagnosis for Migraine types

interventions designed to reduce the tendency to have attacks). While many patients find that lifestyle adjustments such as regularizing meals and sleep can reduce the frequency of their attacks, some form of medication or other treatment is almost invariably necessary in patients with chronic migraine. Numerous medications have been shown to be effective in the preventive treatment of migraine. The choice of treatment can be influenced to varying degrees by the pattern of headaches, patient comorbidity, tolerability, teratogenicity, potential side effects, ease of use, and patient choice (Blumenfeld et al. 2013).

If first- or second-line preventives fail, the patient should be referred to a specialist headache clinic for reevaluation, and consideration of other therapeutics interventions such as greater occipital nerve blockage and onabotulinumtoxinA injection should be offered (Weatherall 2015).

Botulinum Toxin in Headache

In a pioneering program developed for a treatment, the US Food and Drug Administration approved onabotulinumtoxinA for the CM prevention. It was licensed specifically for the treatment of CM in July 2010 by the Medicines and Healthcare products Regulatory Agency (MHRA) and has not been shown to be effective for any other headache type (e.g., episodic migraine, tension-type headache, and cluster headache) as yet, but many studies are in course (Lipton and Silberstein 2015).

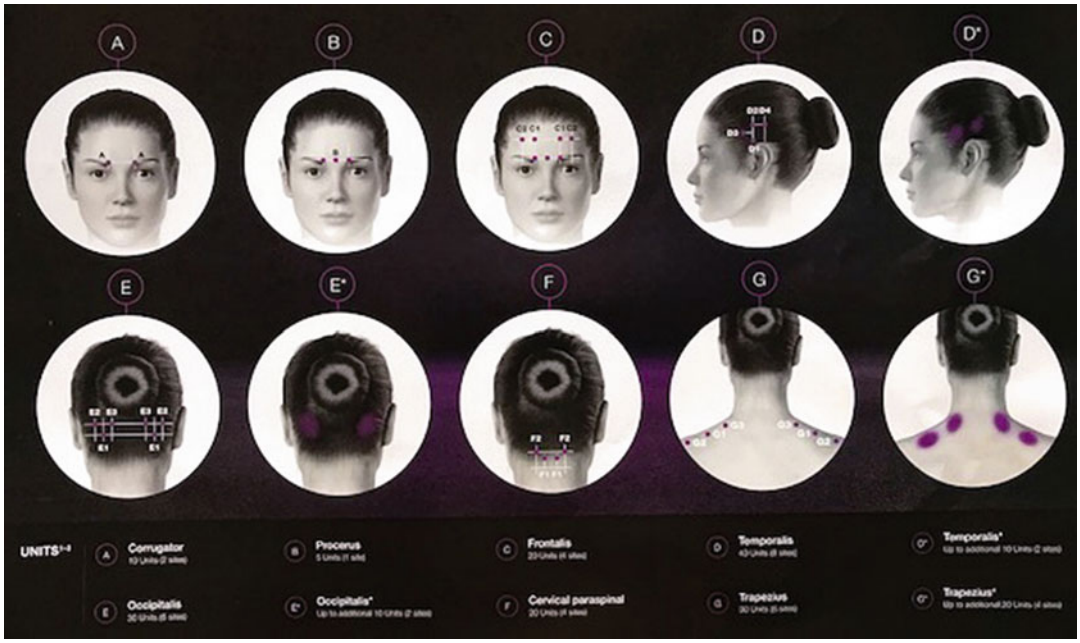

Fig. 2 Recommended injection sites for chronic migraine using fixed-site, fixed-dose injection site locations. Cordially provided by Allergan.

Historically, treatment paradigms have not concentrated on CM and have been divided into acute treatment of migraine (analgesics, triptans, opioids, ergot derivatives) and prophylactic treatments (beta-blockers, calcium-channel blockers, antiepileptics, antidepressants). However, many of these treatments have considerable side effects and do not work well in CM.

To date, the only treatment approved by the FDA for CM prophylaxis is onabotulinumtoxinA, which was established in two phase III trials. The phase III program that led to regulatory approval of onabotulinumtoxinA for the treatment of CM included the PREEMPT 1 (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) and PREEMPT 2 clinical trials (NCT00156910; NCT00168428). These studies consisted of a 24-week randomized, double-blind, placebo-controlled phase followed by a 32-week onabotulinumtoxinA open-label phase and were published both as individual studies and as a pooled data set. Patients were recruited from 56 North American sites in PREEMPT 1 and from 66 European and North American sites in PREEMPT 2 (Diener et al. 2010; Aurora et al. 2010).

Study injections were given at 31 fixed and 8 optional sites with 5 U in each site (total 155 U to 195 U, mean 165 U) across 7 head and neck muscle areas (procerus, corrugator, frontalis, temporalis, occipitalis, cervical paraspinal, and trapezius) (Fig. 2).

OnabotulinumtoxinA Versus Oral Preventive Treatment

Several studies have compared the efficacy of onabotulinumtoxinA with that of oral migraine medications for prophylaxis of chronic headache. One group of investigators randomized 72 patients with chronic migraine to two groups and treated them with 25 or 50 mg of amitriptyline or 250 U of onabotulinumtoxinA. They concluded that onabotulinumtoxinA was as effective as amitriptyline for the prophylactic treatment of chronic migraine in that there was no significant difference in endpoints, including the percentage of patients who reached a 50% reduction in headache days [67.8% in the onabotulinumtoxinA group and 72% in the amitriptyline group,

p = 0.78; relative risk (RR) = 0.94; confidence interval (CI) = 0.11–8.0] and the reduction in pain intensity (50% in the onabotulinumtoxinA group and 55.6% in the amitriptyline group, p = 0.79; RR = 1.11; CI = 0.32–3.8) (Magalhaes et al. 2010).

Other than onabotulinumtoxinA, topiramate is the only other treatment option that has undergone double-blind placebo-controlled studies to support its efficacy for CM prophylaxis. The researchers used data from the PREEMPT trial and the topiramate trial to compare the safety and efficacy of onabotulinumtoxinA with topiramate, noting the limitations for a cross-trial comparison. They compared outcome measures by using the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) framework and concluded that there were significant and clinically relevant treatment benefits for both onabotulinumtoxinA and topiramate and there is evidence to support similar efficacy of both treatments as preventive therapy for patients with CM. Ultimately, individual patients will decide which treatment is of more clinical meaningfulness to them (Diener et al. 2007).

Mechanism of Action of OnabotulinumtoxinA in Pain

The mechanism of action of onabotulinumtoxinA in treating pain is most likely related to the inhibition of nociceptive mediator release from afferent neurons, thereby attenuating peripheral pain signaling to the brain. The efficacy of onabotulinumtoxinA as a prophylactic treatment for CM may be attributed to the notion that extracranial administration decreases the release of the neuropeptides and decreases the sensitivity of meningeal receptors through downregulation of their activity (Blumenfeld et al. 2017).

When injected intramuscularly at therapeutic doses, onabotulinumtoxinA produces a temporary graded chemical denervation of the muscle resulting in a localized relaxation and/or reduction in the activity of the muscle. The effect on sensory neurons relies upon the same biochemical mechanism of impairing synaptic vesicle fusion by cleaving SNAP-25. OnabotulinumtoxinA plays a role in regulating pain pathways by impairing release of CGRP, substance P peripherally, and glutamate centrally, as seen in nonclinical pain models (Lawrence and Dolly 2002). Although the exact mechanism of action of onabotulinumtoxinA in the prophylactic treatment of CM has not been fully elucidated, the current notion is that one component comprises inhibition of neuropeptide and neurotransmitter release from peripheral trigeminal sensory nerve terminals and consequently mitigates development of peripheral sensitization and, secondarily, central sensitization. The distribution of peripheral nerves is described below (Fig. 3) (Blumenfeld et al. 2017).

Comments

At present, the use of onabotulinumtoxinA for headache treatment is restricted to a few specialist headache centers and approved just for CM, but as time goes on, there should be increasing numbers of trained injectors available, and its efficacy may be demonstrated for other types of headache and facial pain (Blumenfeld et al. 2013).

The injector should receive appropriate training, both in the diagnosis and management of chronic migraine and in the delivery of injection according to the proven PREEMPT schedule. This manuscript emphasizes the importance of understanding the anatomy behind each injection site to optimize efficacy and minimize unwanted outcomes and adverse events (Diener et al. 2010; Aurora et al. 2010).

Based on the PREEMPT clinical trial program data, the most commonly reported injection-related adverse events were neck pain, muscular weakness, ptosis, and headache. These may be minimized not only by identifying the correct injection sites and implementing the advised injection techniques but also by thoroughly assessing the patient before treatment (Diener et al. 2010).

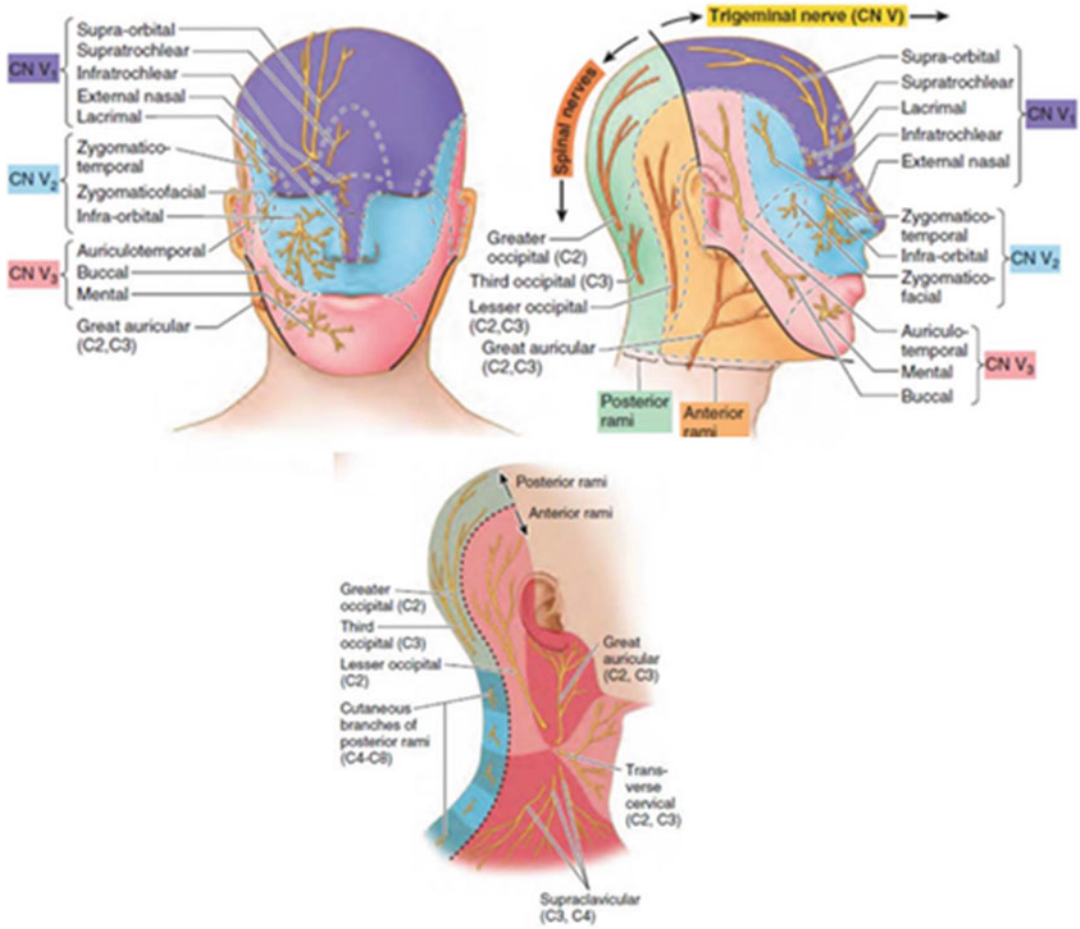

Fig. 3 Distribution of peripheral nerves. Anterior and lateral view of the trigeminal (CN V) and occipital (C2, C3) sensory nerves. Cervical sensory nerves (C2, C3). Reproduced with permission

Prior to the first injection of onabotulinumtoxinA, it is critical to first assess the patient's head and neck anatomy, since variation in anatomy will lead to variations in target muscle locations.

Treatment expectations, including risk of unwanted and/or adverse events, should be discussed with the patient prior to treatment. This will help to avoid omission of injection sites based on concerns.

OnabotulinumtoxinA is a safe and effective prophylactic treatment option for patients with CM. Accurate target muscle localization and injection angles and depths are required to achieve optimal outcomes and to minimize adverse events. Firm knowledge of the functional anatomy of the head and neck muscles is essential.

Take Home Messages

- The efficacy of the botulinum toxin A for the treatment of patients with headache was first observed by a plastic surgeon, when treating patients for cosmetic enhancement; some of his patients with an incidental history of migraine reported a reduction or elimination of their attacks.
- The botulinum toxin A acts in chronic migraine, probably, inhibiting the release of the neuropeptides and glutamate preventing the neurogenic inflammation.
- It is currently approved just for chronic migraine.

- The efficacy and security of the botulinum toxin A for prophylactic treatment of the chronic migraine is proven.
- OnabotulinumtoxinA is also approved for other neurologic diseases such as blepharospasm, strabismus, cervical dystonia, spasticity, blepharospasm, overactive bladder, and urinary incontinence from neurogenic detrusor overactivity.
- The injector should receive appropriate training in the diagnosis and in the delivery of injection according to the proven PREEMPT schedule, understanding the anatomy behind injection site to optimize efficacy and minimize adverse events.

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Botulinum Toxin: Complications and Their Management

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_15

Abstract

In 2014, the International Society of Aesthetic Plastic Surgery published the numbers of non-surgical cosmetic procedures performed around the world, showing that the most popular procedure was botulinum toxin A (BTXA) injections. Although the most popular treatment, complications and adverse events relating to BTXA are rare as knowledge improves every day due to various anatomic studies, clinical studies, and the improvement of doctors' skills. Due to the mechanism of action of BTXA, its adverse events tend to be transitory and short in duration, but have a negative impact on the patient's quality of life that needs to be minimized or avoided. Knowledge of facial anatomy, injection techniques, complications, and adverse events is paramount. In this chapter we discuss the possible complications and adverse events of BTXA, how to avoid them, and how to minimize them when they do occur.

Keywords

Botulinum toxin · Complications · Adverse events · Ptosis of the lids · Asymmetry · Hypersensitivity · Onabotulinum toxin · Abobotulinum toxin · Incobotulinum toxin · Pain

Introduction

In the last 30 years few drugs have been studied and tested in relation to their efficacy and safety as much as botulinum toxin A (BTXA), both for its aesthetic and therapeutic indications (Coté et al. 2005). The efficacy of BTXA is well-established and unquestionable but, as with any other drug, its use may lead to adverse events and complications, which are well-accepted when treating diseases but not when related to cosmetic treatments (Cavallini et al. 2014). Although these effects have a short-term duration, they can impact negatively on the quality of life of patients, especially undesirable asymmetries. There are few alternatives for minimizing them but often there is no solution other than waiting for the improvement as the action of BTXA on the muscles fades away.

According to the International Society of Aesthetic Plastic Surgery (2014), BTXA injections are the most popular non-surgical cosmetic treatment around the world. Although used worldwide, complications and adverse events resulting from this therapeutic modality are very rare due to improvement of anatomy knowledge, clinical studies, and better training of the injectors. A recent publication has associated one-third of complications with off-label treatments in cosmetic use. On the other hand, in the same study, therapeutic injections were revealed to have

complications seven times more frequently than cosmetic indications (Lolis et al. 2015).

Few papers in the scientific literature describe complications of BTXA used for aesthetic treatments and they are mostly related to injections in the superior third of the face. The number of articles describing complications of lower-face treatment is low, but they seem to be more frequent than in other regions of the face. Review articles consider similar adverse events with the use of onabotulinum toxin A, abobotulinum toxin or incobotulinum toxin, differing slightly in duration, severity, frequency, or dosage (Cavallini et al. 2014). Some of the adverse events and complications described in this chapter are from our everyday observations over many years of experience with BTX for cosmetic treatments.

Didactically, we could separate the adverse events into those related to the drug and puncture of the skin during the injection; and complications resulting from the effects of the BTXA, i.e., unexpected muscle relaxation or neural-sensitive complaints due to the BTXA action, the injection site, or the technique itself.

Another issue that can be considered a complication is any patient dissatisfaction with the results. The best way to prevent complaints is to begin with a correct and complete anamnesis and understand the patient's expectations. Photographs should be taken of the patient with all facial mimics to be treated well documented. Frontal and lateral pictures should be taken – 45° pictures are also advised – with a resting face and showing all of the mimics the patient wants to treat. With patients who show any sign of doubts or psychological issues, a short film should be taken to ensure all different facial mimics and asymmetries are available for evaluation, since photographs can't capture patients' movements with accuracy. Previous asymmetries should be emphasized and the expected results should be discussed, with the aim of recognizing the patient's desires and detecting false expectations, avoiding overcorrections, and planning the treatment to achieve a natural look, the result that most doctors recommend.

Adverse Events Related to the Drug

Adverse effects related to the drug are independent of the injection technique and are associated with an individual sensitivity to the chosen BTXA. It should be remembered that different brands have different excipients and they need to be diluted in different amounts of saline. The final solution used must be checked as doctors tend – sometimes following anecdotal publications – to use other diluents such as lidocaine and buffered saline solutions and also forget that there could be reactions due to the diluent or topical products applied before or after the procedure such as anesthetics creams or antiseptic solutions.

Hypersensitivity

Cosmetic treatment almost always requires a low BTXA dosage in total and hypersensitivity for BTXA itself is very rare; when it does occur, it is generally related to the excipients. Lactose and gelatin have been described as sensitizers leading to drug reactions such as fixed pigmentary reaction, cutaneous rash, and urticaria, and other reactions could occur due to the toxoid (inactive part of the toxin).

Allergic reactions commonly occur a few minutes after the injection and affect, in general, previously BTXA-sensitized patients, especially those receiving frequent and premature touch-ups, rather than allergic reactions being related to the dosage itself. A reaction may present as an erythematous papule at the injection site or as a cutaneous rash (Tamura et al. 2008). Anaphylactic reactions can begin as a small urticaria lesion or generalized edema followed by dizziness and evolving to systemic shock (Ricciardi et al. 2013). If medical intervention is immediate, patients should recover well; cortisone, antihistamine, and adrenaline might be necessary. Incobotulinum toxin is a pure toxin that does not have protein complex added to it, only having albumins as the excipient, and it is described as the best choice for sensitized patients (Ricciardi et al. 2013). Albumins are not considered to be allergens but they can potentially be contaminated

by various infectious viruses; however, the main trademarked products have proven trustworthy to date, with no cases of infection described.

Nausea and Flu-Like Symptoms

Nausea and flu-like sympoms might be observed in some patients; while their cause is not clear, they could be related to the excipients or toxin hypersensitivity. These symptoms only last a short time and there is no need to treat them (Coté et al. 2005).

Headache

Although BTXA has been used as an alternative treatment for migraine and tensional headache, mild to moderate headache can be considered an adverse effect and occurs in approximately 16% of patients receiving treatment for glabellar lines. Headache lasts a few hours to days, is poorly responsive to analgesics, and has spontaneous recovery. The etiology is still not understood but might be related to periosteal needle trauma, intramuscular hematoma, anxiety, and temporary muscle spasm (Vartanian and Dayan 2005); it has also been noted in patients who have had palmar BTXA injections (Cavallini et al. 2014).

Adverse Events Related to the Puncture

Pain

Puncture and injection pain can be alleviated with topical anesthetics, different formulations containing lidocaine, procaine and/or prilocaine in various concentrations, fresh pads, ice packs, vibration devices, massage, and the choice of very thin needles such as those produced specifically for BTXA injection. However, these methods will not alleviate the pain produced by the solution's muscle distention, which shows almost no improvement with anything other than asking the patient to try to relax the muscle as much as he can and injecting slowly.

Ecchymosis and Hematoma

While hematoma is quite rare, ecchymosis is a very frequent adverse event as the areas that we treat with BTXA are fully vascularized (Cavallini et al. 2014). In addition to the worse aesthetic view of these effects, there is also the possibility of spreading BTXA to undesired areas, leading to the impairment of other muscles and resulting in asymmetries, paralysis, or ptosis and also of losing some BTXA with the blood reflux. It is important to always remember to check whether patients are using any drugs, medicines, or vitamins that change coagulation and use alternative tools such as cold pads and ice packs before the injections, firm local compression immediately after the injection, and intense pulsed light or other light-based devices that may be useful to minimize the ecchymosis or hematoma, especially at the inferior lid.

Intravascular Injection

Although there are no concerns about emboli, frequent intravascular injections could potentially stimulate neutralizing antibodies or provoke systemic effects; however, to date, it seems that the amount of BTXA injected for cosmetic purposes is too insignificant to be clinically proven (Coté et al. 2005).

Edema and Erythema

Edema and erythema are generally transient, with a short recovery time. Edema is usually related to the volume of the injected solution, i.e., dilution with more than 1 mL of saline (Cavallini et al. 2014). If the signs are intense and do not reverse quickly, other causes such as allergy or dermographism due to a patient's history of urticaria should be considered.

Local Infection

Local infection following BTXA is very rare and is related to inadequate antisepsis and the consequent contamination of the puncture sites (Lowe et al. 2005). In addition to correct local

disinfection, the patient must be advised to avoid topical sunscreen, makeup, or creams that might contaminate the skin. Herpes simplex can follow any invasive skin treatment.

Others

Dyschromia has also being described at the puncture site. In addition, a few authors have anecdotally described rare cases of bone hypertrophy at the injection site during the early use of BTXA, when the technique for forehead injection was inserting the needle until it touched the frontal bone and injecting the BTXA after pulling the needle back a few millimeters (Kim and Byrne 2007; Tamura 2007).

Muscle Motor Impairment

Undesirable motor muscle impairment is one of the most feared complications after BTXA treatment as it directly affects the quality of life and aesthetic results of the patients, being noticeable and evident to anyone in their social circle. This complication might be due to one of the following: injection of BTXA into the wrong muscle, individual anatomy, site of injection, incorrect dosage, poor training and knowledge of the injector, excessive volume of saline dilution, lack of familiarity with the chosen toxin, or diffusion of the product. Diffusion might occur because of the characteristics of the toxin, an ecchymosis or local hematoma, or edema, especially after skin ablative procedures such as medium or deep peelings, lasers, or collagen-stimulating fillers that are diluted and injected into areas already treated with BTXA (Lolis et al. 2015).

It should be noted that there are many articles and reviews regarding BTXA complications following cosmetic treatment for the lines of the upper third of the face but there are few for the medium and inferior third of the face and neck as most of the injections at these sites are still off-label; however, dysphasia, neck weakness, dry mouth, speech impairment, difficulty retaining food and liquids in the mouth, and pseudo-aneurysm of the superficial temporal artery have been described to date (Tamura 2010a, b; Skaf et al. 2012; Dayan 2013; Hassouneh and Newman 2013).

Eyebrow Ptosis

Eyebrow ptosis is the most frequent complication of BTXA when treating the rhytids of the superior third of the face (Cavallini et al. 2014). Frequently misinterpreted by the patient as an eyelid ptosis or sometimes as 'puffy' eyes, eyebrow ptosis is related to an exaggerated paralysis of the frontal muscle, especially at the area above the eyebrows where the muscle often acts as a tool to elevate the brows as aging tends to drop them. Excessive relaxation of the frontal muscle in this area leads to an inability to raise the brows, causing a 'tired look' – heavy and overhanging lids – while the opening of the eyes is normal (Fig. 1).

The solution to avoiding such complications is to determine the patient's forehead muscle extension and strength prior to the procedure and carefully check the mimics of the eyebrow movements, and their relationship to the contraction and height of the eyebrows, and inject an appropriate number of units, usually a lower dosage, to relax the muscle enough to soften the lines but not so much as to paralyze it (Hexsel and De Almeida 2002; Gassia 2009).

Eyelid Ptosis

Actual eyelid ptosis reflects an inability to open the eyes properly due to a dropping of the superior lid as a consequence of an inadvertent paralysis of

Fig. 1 Left eyebrow ptosis

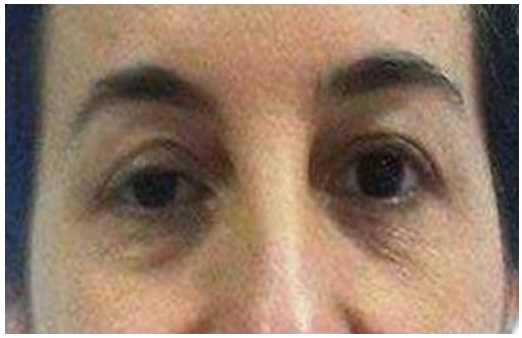

Fig. 2 Ptosis of the right upper eyelid

the levator palpebrae muscle. During the early use of BTXA, this complication was relatively common, occurring in as often as 10% of cases, but is a very rare effect nowadays due to the evolution of anatomy knowledge and improvement of the injection technique (Ferreira et al. 2004; Lolis et al. 2015) (Fig. 2). The muscle at the superior palpebrae inserts to the bone at the internal wall of the superior orbit and does not cross or pass under the corrugator; it directs inside the orbit, does not connect to the orbicular muscle, and is deep inside the orbit at the brow level. Understanding the anatomy is the best way to avoid undesirable effects; the old suggestion to avoid injections until 2 cm above the brows at the pupil level has been abandoned in our clinic, resulting in various advanced injection points to soften perpendicular eyebrow lines and elevate the brow with BTXA at the orbicularis oculi, molding the shape of them in a much more attractive look and even injecting into a higher point at the upper site of crow's feet during their treatment without any cases of eyelid ptosis occurring (Klein 2002, 2004; Pena et al. 2007; Gassia 2009).

To avoid such complications, we need to understand what to do, what not to do, and how to perform the treatment in the superior third of the face. Tamura (2007) and Tamura and Odo (2011) have described three easy ways to cause eyelid ptosis: injecting the BTXA inadvertently at what we 'think' is the corrugator; injecting in the periosteum; or neglecting the diffusion halo of different toxins. The suggestion of where and how to inject BTXA into the corrugators is to localize the muscle and the superior border of the orbit, hold the muscle between the fingers, directing the needle upward into the muscle, and not into the bone or the palpebral area, and be careful when injecting at the lateral extension of the muscle.

It should always be remembered that the eyebrow level is not a reference to localize a safe injection as the eyebrow might be located above, at, or under the orbital bone level. The orbit bone should be palpated and the corrugator pushed upward as it is held, injecting far from the levator palpebrae muscle. Avoid injection on the bone because the risk is higher at the level of the orbit rim as the solution might flow down at the layer of the periosteum, dissecting easily towards the rim and into the orbit at which the levator palpebrae is inserted. The characteristically larger abobotulinum toxin diffusion halo requires that the injection at the corrugators be higher and injections at the orbicularis muscle to elevate the brows be avoided or the dosage reduced drastically.

Apraclonidine, phenylephrine, or brimonidine eye drops could be used to contract the Müller's muscle, which is located under the levator palpebrae muscle, without acetylcholine-mediated innervation (Kirkpatrick et al. 2016). In our experience, electrostimulation with microcurrents and/or facial aesthetic ultrasound towards the superior orbicular rim has also been helpful to stimulate the Muller's muscle and the fibers of the levator palpebrae that are not affected by BTXA.

Eyebrow Contour

The upside-down medial and lateral 'V' shape and the 'diabolical look' are the most common complications of unnoticed frontal muscular localized strength. The upside-down 'V' shape can occur at the middle of the eyebrow or laterally, depending on the location of the stronger contraction area. It commonly occurs at the middle of the brow after the treatment of the forehead of Asian patients. The final effect results in a look somewhat like a clown's eyebrow makeup; to avoid such a result we suggest that, for flat eyebrows and Asian patients, the injection be planned to begin at the forehead at the projection of an imaginary line from the pupil about 2 cm above the eyebrow. If

at the first appointment the patient has an angular contour on the lateral sides, the injection marks should also begin at the strongest part of the frontalis that pulls the angle of the brow. After marking these key sites, we suggest marking the other areas within a distance of 1.5–2 cm apart, injecting at least 2 U at the strongest sites.

The 'diabolical look' was a very common result after forehead treatment in the early years of BTXA because doctors considered the frontal area lateral to the pupil to be a no BTXA injection zone. After some time, many doctors began to treat the lateral area of the frontal muscle if it is very active and strong to avoid this complication. We suggest injection of 1–2 U at a site higher than 1.5 cm above the eyebrow for a natural result without dropping the lateral aspect of the eyebrow.

Exacerbation of the Infraorbital or Nasojugal Sulcus Pads

The use of BTXA in the inferior portion of the orbicular muscle of the eyes or the lacrymal area near its insertion to treat inner canthus lines (Fig. 3) might weaken this area's musculature, leading to an exacerbation of the infraorbital fat pads or the nasojugal fold expressed as a 'tired look' (Fig. 4) and/or a 'double' smile line at the medial malar area. A technique to avoid this effect but still treat the area is to lower the dosage to less than 1 U and inject it into a unique site at the medial inferior palpebrae right inside the fine lines. When the patient develops a 'double' smile, add about 2 U at the levator alaeque nasi anguli oris m. branch, lateral to the nasal dorsum muscle.

Diplopia

Diplopia is a consequence of the injection of BTXA in one or more of the extrinsic motor muscles of the eye or the spread of the toxin to them. These muscles are responsible for the movement of the ocular globe and their paralysis is represented as 'blurry vision' or 'double vision' and diplopia might be seen clinically with divergent or convergent eyes. To avoid this complication, injections around the eye should respect the orbital rim, which is easily identified when we

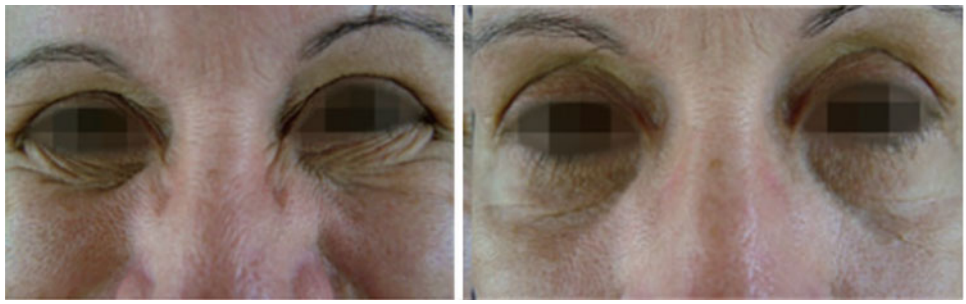

Fig. 3 Exacerbation of the infraorbital fat pads

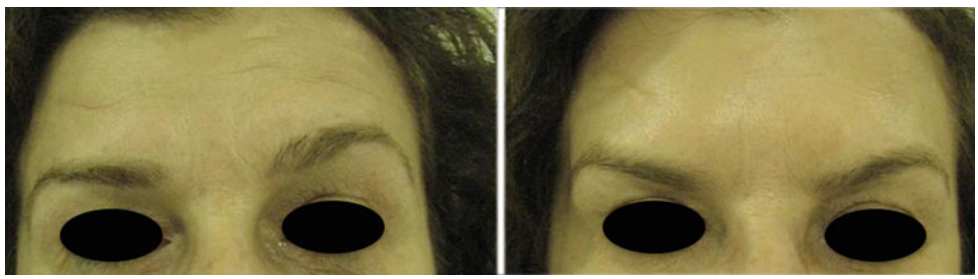

Fig. 4 Undesirable dropping of the eyebrows. Pre and post treatment

palpate the area, and when injecting BTXA in advanced and delicate sites, inject a small amount, less than 1 U per point, and very superficially. The palpation and identification of the orbital limits should never be neglected in any treatment as each patient has unique and personal small anatomical nuances. There is no treatment for diplopia at this time other than waiting for the effect of BTXA to end (Zagui et al. 2008; Gassia 2009).

'Plateau Smile' or 'Topo Gigio's Smile'

A 'plateau smile', or 'Topo Gigio's smile', is very frequent when crow's feet are treated with abobotulinum toxin or when an excessive quantity of units of another BTXA are injected to treat them. It is typical for the crow's feet area to be very flat and the lines completely relaxed; when the patient smiles, only the malar structures rise up, creating a horizontal medial line, and the malar area becomes rounded like a 'plateau smile' or the cartoon character Topo Gigio's face. We can minimize this undesirable effect injecting too many units at too many points in the crow's feet area when the patient shows these kind of results. An easy test can be performed to predict this effect: hold both sides of the crow's feet area simultaneously using pressure and ask the patient to force a smile; this gives an idea of the future results of the treatment. Patients with a rounded malar area are more prone to this effect than other patients.

Facial Asymmetries

All muscles of the face are susceptible to inadvertent treatment and one of the most adverse impacts is the paralysis of the zygomaticus m.; although all muscles are very important and are clinically visible, the relaxation of these muscles causes an almost hemifacial lack of expression. Clinically, it depends whether both zygomaticus muscles – minor and major – are relaxed or only one of them. If one side is affected, it results in an attenuation of the crow's feet lines and an asymmetric smile with a drop of the buccal rima very similar to Bell's paralysis. If both sides are paralyzed, the patient seems to have an emotionless face. Treatment of the lower crow's feet with a third point too lateral to the zygomaticus bone or a fourth point lower than the classical lower site of injection to treat crow's feet almost at the inferior border of the zygomaticus bone are the most common causes of undesirable zygomaticus m. relaxation. The best method to inject safely in this area would be to always localize the zygomaticus arch and the injections should be at the top of the arch, not on the side or under it (Hexsel and De Almeida 2002; Gassia 2009; Tamura and Odo 2011).

The most frequent complication of the treatment of the nasociliary area is a local, mainly unilateral asymmetry caused by the injection of BTXA at the periosteum and not at the orbicularis oculi m., which is quite thin at this region; to correct it, the BTXA should be reinjected at the location that the muscle still moves.

Injection of BTXA at the nasalis area might also lead to paralysis of the levator alaeque anguli oris m. as well as the levator anguli oris m. The best technique to avoid these complications is to inject BTXA by directing the needle to the middle line of the face, inserting it medially to an imaginary line from the lateral aspect of the nostrils.

There are different approaches to soften the peribuccal lines – the 'bar code sign' – by varying the number of injection sites and dosage, as well as their location. In our experience, 4 U at the upper lip and 2–4 U at the lower lip is more than enough to have some improvement without weakening the muscle to a point that the patient experiences complaints such as an incapacity to close the lips, inability to contain food in the mouth properly, or difficulties in pronouncing 'b' or 'p' or pursing the lips. Authors vary significantly in the recommended techniques but we reinforce the need for comprehensive anatomy knowledge. At the lateral area of the lips, fibers of the levator anguli oris m. and the alaeque nasi anguli oris m., and even in natural anatomical differences, fibers of the zygomaticus and risorius m. could be affected by BTXA, leading to a worse scenario with functional and aesthetic disability. We prefer to aim for a slight relaxation of the perioral muscle and to plan to inject fewer points and units.

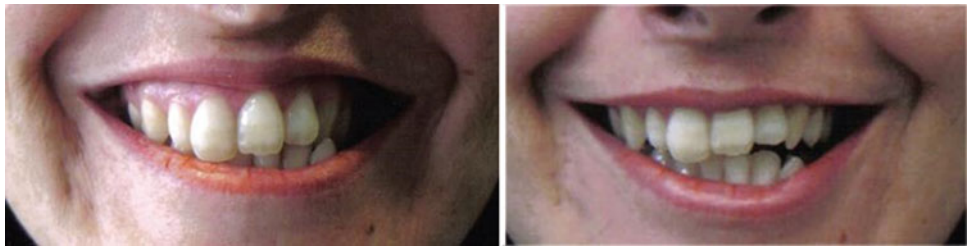

Fig. 5 Diminished volume of the superior lip

However, there is an exception for the indication of higher doses: when BTXA is injected as "prior" treatment to dermabrasion, phenol peelings, or even CO_2 resurfacing for deep lines of the perioral zone.

Superior Lips Ptosis

The levator labii m. is also treated when we prepare patients in advance for a phenol peeling, CO_2 resurfacing, or dermabrasion at the superior lip lines 2 weeks prior to the procedure, and over-relaxation of the muscle is sometimes desired and planned with the patient in these exceptional indications. Ptosis of the superior lip also occurs when the dosage of BTXA is higher than needed to correct a gummy smile. Excessive treatment of the muscle also leads to an elongation of the lip, flattening the labial philtrum and diminishing the volume of the superior lip, and worsening the aging signs of the perioral area (Fig. 5).

Changes of the Smile

The patient's smile characteristics may be changed when an intradermal BTXA injected using a 'mini doses' technique is chosen for the treatment of the peribuccal lines, as well as relaxing the zygomaticus, risorius levator labii, levator alaeque nasi and anguli oris, depressor labii, depressor anguli oris, and/or mental muscles. The relaxation of any of these will cause asymmetries and if relaxation occurs on both sides there will be almost no facial expression, leading to a sad linear and horizontal smile.

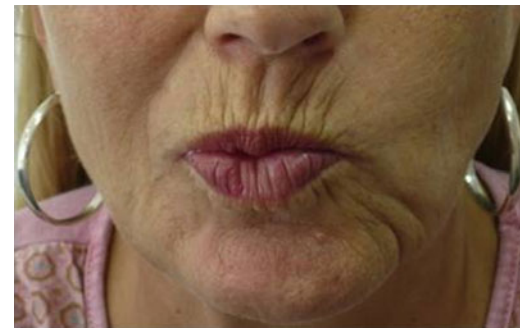

Fig. 6 Smile asymmetry after treatment of the depressor anguli oris muscle

Oral Rim Deviation

When the depressor anguli oris is relaxed, the levator anguli oris m. acts to pull up the corners of the lips. Excessive bilateral relaxation of the depressor anguli oris m. leads to a 'joker's smile' and asymmetries (Fig. 6) occur if only one side of the depressor is relaxed. We treat the depressor anguli oris to soften the downward angle of the corner of the lips but need to find a balance between the dosage and results. Thus, 2 U can be used to improve it, but if the improvement is not adequate, an additional 0.5 U intradermally at the exact point that the muscle adheres to the skin relieves the muscle but does not paralyze it. The modern approach to the treatment of the facial contours is to not inject more than 2 U for the mentalis m. and depressor labii m. when treating the platysma bands, avoiding an unpleasant effect where the chin becomes stiff and the speech sounds like a forced whisper with the teeth a little crunched.

Food Retention

Relaxation of the depressor anguli oris and sometimes the masseter muscle leads to food accumulation at the jugal mucosa between the teeth and inferior lips, and the patients need to use the tongue to remove the food to masticate it. To address this, fewer units should be injected at the next treatment or the balance between the side effect and the benefit of the treatment should be explained to the patient.

Chin Herniation

A curious and unattractive complication of BTXA is also herniation of the chin (Fig. 7) due to relaxation of the lower part of the mental muscle and contraction of the depressor labii, sometimes added to contraction of the depressor anguli oris. Herniation of the relaxed mental muscle occurs with the mimic of the lower face. We suggest that 2 U injected into two sites or a maximum of 4 U is advisable. If there is a residual contraction of this muscle when re-checking the results, 1 U as a complementary treatment at the site of maximum contraction could be used as a touch-up procedure. The lower face muscles are more responsive to BTXA and treatment of the whole group is tricky, often leading to weakness of the entire inferior face and contour muscles. A lower dosage is a safe option.

Weakness of the Masticatory Function and Speech Difficulties

Weakness of the masticatory function and speech difficulties can be a complication after the treatment of masseteric hypertrophy as a greater quantity of BTXA is required for an efficient result (Park et al. 2003).

Dysphagia, Cervical Muscles Weakness, and Respiratory Impairment

Treatment of the platysma m. with a high dosage of BTXA, different techniques, deep injections, or diffusion of the BTXA might result in dysphagia, cervical muscles weakness, and respiratory impairment (authors' personal experience) (Cavallini et al. 2014; Tamura 2012). Injections at the cervical area should be very superficial and it is essential to be aware that the dangerous zone is at the anterior medial portion of the neck where the most important deglutition muscles are located (stylohyoid, sternohyod, thyrogloss, and hyoglossus muscles). Besides injecting BTXA very superficially in this area, lower doses and sites are advisable as well as chosing a smaller halo action BTXA.

Epiphora

Epiphora has also been described in a few papers as well as the current authors having seen it in their personal experience (Ozgur et al. 2012; Kim and Baek 2013). Epiphora resolves spontaneously in 1–2 weeks.

Sensitive Complications

Dry Eye and Ocular Discomfort

Dry eye and ocular discomfort are related to an exaggerated amount of BTXA at the glabellar area as well as during treatment of the depressor cilia and nasociliary orbicular muscles. An excessive amount of BTXA in the muscles in this area might result in the entire glabellar area dropping, causing some difficulty in closing the eyes tightly

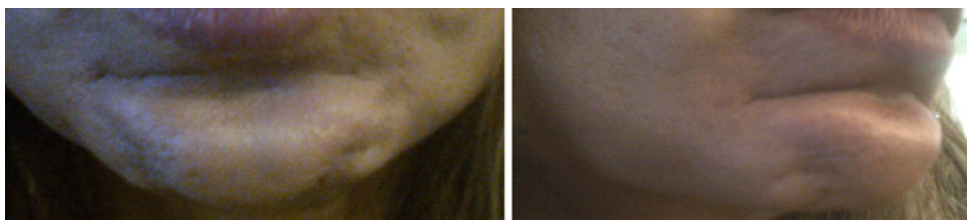

Fig. 7 Herniation of the chin due to relaxation of the lower part of the mental muscle and contraction of the depressor labii

(Ozgur et al. 2012; Cavallini et al. 2014). These effects are not common and tend to improve without treatment in few days. Ocular moisturizer drops could help to improve this problem and, technically, very superficial and tiny amounts of BTXA injected into the periocular area instead of a greater quantity should help to avoid such complications (Gassia 2009).

Other Sensitive Complications

Sensitive alterations including 'burning', paresthesia, or numbness along the sensitive nerve innervation area might occur when the puncture traumatizes the nerve. These symptoms are transitory and the best technique to avoid them is good anatomic knowledge. In addition, any patient complaints regarding unusual pain during the injection should be valued, and reinsertion of the needle more superficially or just beside the first site will prevent any future problems. In fact, in BTXA treatment for general aesthetics, superficial injections are required as the aim is to affect the mimic muscle and not the foramens and sensitive nerves located deeper in the muscular layer.

Injections at the wrong site, inadequate dosages, and lack of anatomy knowledge are less frequent among dermatologists and plastic surgeons today. The choice of BTXA brand is personal, although some papers suggest that abobotulinum toxin, due to its diffusion halo, should be avoided in the inferior portion of the face and neck. Understanding potential complications and side effects might drastically lower the number of post-procedure problems and increase patients' confidence. Care should be taken with simultaneous procedures that cause edema, heat, and erythema as they can change the normal outcome of BTXA injection (Lorenc et al. 2013).

Efficacy Issues

A total or partial lack of effect might happen *ab initio* or after several or a few treatments. The *ab initio* lack of BTXA response has some considerations, most of them theoretical or anedoctal case reports, or personal experience. In theory, this lack of effect might occur because of a previous botulism infection in a patient with mainly serotype A or a genetic enzymatic deficiency of any substance in the principal pathway between adhesion, internalization, and blockage of the acetylcholine in the neuromuscular plaque. The expected duration of the BTXA effects varies between 3 and 6 months, although the patient should know that the clinical results last an average of about 4 months (most studies are based on about 120 days). Other factors that are of extreme importance are variables such as injection dosage, muscle strength, number of injection points, and the muscle, but the duration should be around 4 months if the total dosage injected follows at least the minimum suggested in some good consensus papers (Lorenc et al. 2013).

A few patients might have short-duration results or even, rarely, no results at all after their first treatment, which could be explained by the presence of specific neutralizing antibodies against the BTXA due to previous exposure to *Clostridium* (Klein 2002) or, hypothetically, to a genetic-specific neuroreceptor enzyme deficiency or antibodies sensitized against the protein complex added to the active 150 kDa toxin (Tamura 2005). When the lack of response occurs after years of BTXA treatments, it should be investigated whether the cause is a real sensitization with antibodies against the toxin or the protein complex added to BTXA (Hefter et al. 2012). The recommendation to avoid shortening the duration of the effects or to stimulate antibodies is to respect a minimum interval of 1 month for touch-ups, even with very low doses, and 3 months for a new treatment. Recently, authors defended the choice of incobotulinum toxin due to its low antigenicity and purity and (Hefter et al. 2012) have published an interesting paper about the successful response to injection of this BTXA in the treatment of patients with detectable antibodies against BTXA and no clinical response to onabotulinum and abobotulinum toxin (Hefter et al. 2012). On the other hand, other authors claim that neutralizing or non-neutralizing antibodies have not been detected and that there is no therapeutic duration reduction with the long-

term treatment with BTXA for cosmetic purposes (Schlessinger et al. 2014).

In theory, the effect of BTXA can be reduced when drugs such as 4-aminoquilones are prescribed as antimalarials and joint diseases and can be increased by antibiotics such as aminoglycosides (Santos et al. 1981; Molgó et al. 1987). Drugs that interfere with neural impulse transmissions to the muscle, such as tubocurarine due to its relaxant effect, can also interfere in theory, increasing the duration of the BTXA as well as the phytase enzyme intake.

Heat does seem to inactivate BTXA at the site of injection, although patients can be treated with light equipment or radiofrequency devices after BTXA injection without affecting its efficacy (West and Alster 1999).

In summary, we do not consider the adverse events or complications of the different halos of efficacy of abobotulinum toxin and its slight differences in technique to be reasons to avoid BTXA, rather being just a matter of knowledge and skills. This is a different issue to local edemas caused by the injection performed by the doctor leading to diffusion of BTXA and sometimes resulting in asymmetries. The recommendation for avoiding BTXA resistance is to not inject it frequently and to try and keep intervals between injections of at least 3 months.

Take Home Messages

- Complications and adverse events relating to BTXA for aesthetic treatment are rare, transient, and of short duration but create a strong negative impact on the quality of life of the patient.
- The incidence of complications might be lowered with improvement in the knowledge of the facial anatomy and proper training of the injector as most complications occur due to an incorrect injection site and depth, over- or under-correction, lack of awareness of the diffusion properties of the BTXA, and outdated knowledge of the evolution of techniques and local fashion, and the differences between the needs of women and men as well as patients of different ages and ethnicities.
- Frequent touch-ups should be avoided and intervals between the injections kept to a minimum of at least 3 months to avoid possible sensitization against BTXA as much as possible (Naumann et al. 2013).

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My Personal Experience with Botulinum Toxin

Mary Sheu

Contents

Abstract

Facial rejuvenation and enhancement with neurotoxin injections can produce results that can appear dramatic as well as natural. A thorough knowledge of facial anatomy in repose and with animation is critical for optimal outcomes. Communicating with patients regarding the agreed-upon goals, realistic expectations and limitations of this therapy is important for patient satisfaction. The purpose of this chapter is to provide clinical pearls to optimize results for the cosmetic use of botulinum toxin in the face and neck. We will also review practical considerations such as reconstitution, injection technique and pre- and post-procedure patient education.

Keywords

Botulinum toxin · Neurotoxin · Neuromodulator · Injection technique · Glabella · Brow lift · Practical tips · Reconstitution · Dilution · Combination therapies

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_36

Introduction

Since the inception of botulinum toxin for cosmetic improvement almost four decades ago, its popularity has risen dramatically. Worldwide, it is estimated that botulinum toxin injections account for over 45% of minimally invasive procedures (ISAPS 2014). In the USA, the number of neurotoxin procedures increased over 700% from 2000 to 2014 (ASPS 2014).

Botulinum toxin often serves as a first foray into aesthetic procedures for both patients and cosmetic providers. For patients, the procedure is quick, associated with minimal discomfort, and results are visible within days. It is an ideal procedure for patients who prefer to be discreet about undergoing aesthetic procedures: there is usually no downtime, and the results can be enhancing and rejuvenating without altering one's fundamental appearance. For providers, it is a good gateway procedure in that it does not require specialized equipment and the startup investment is minimal. However, to characterize botulinum toxin as an "easy" procedure belies the nuance of this craft. To perform this procedure well and deliver results that are aesthetically balanced, injections must be tailored to the individual anatomy and aesthetic goals of each patient. A thorough knowledge of facial and neck anatomy, as well as the interactions of facial muscles with surface structures, is critical.

This chapter is meant to supplement the previous chapters on botulinum toxin and provide practical perspectives on treating the face and neck. In this chapter, the terms botulinum toxin, neurotoxin, neuromodulator, and toxin are used interchangeably. Dosing is provided in terms of onabotulinum and incobotulinum units, as there is variability in conversion to abobotulinum units among providers. This chapter will begin with practical tips and then delve into pearls for treatment of specific anatomic areas.

Practical Considerations

Dilution

In our clinic we, employ a 1 cc preserved saline per 100 unit dilution in order to achieve a concentrated solution. Other commonly used dilutions include 2–2.5 cc per 100 unit bottle. The advantage of the more concentrated reconstitution is that it minimizes diffusion and allows for a tighter radius of effect. With a concentrated solution, precise placement of the toxin is extremely important. One must become very comfortable with injecting small volumes using a small syringe with precision, since each 1/100 of 1 mL contains 1 unit of toxin. We draw up the toxin with 0.3 cc tuberculin zero waste syringes, taking care not to touch the needle to the walls of the glass bottle, to avoid bending the tip of the needle. We encourage those who are new to these syringes and the concentrated dilution to practice drawing up and pushing saline through the needle prior to injecting patients, as there is a learning curve for those who are accustomed to a larger volume dilution and 1 cc syringes.

In our clinics, we stock the three type A botulinum toxins approved by the US FDA for cosmetic indications: onabotulinum, abobotulinum, and incobotulinum toxins. For unit conversion, we employ a 1:3 onabotulinum to abobotulinum conversion ratio (the generally accepted range of conversion is 1:2–3.) and a 1:1 onabotulinum to incobotulinum ratio. We reconstitute the 300 unit abobotulinum with 1 cc preserved saline, which streamlines preparation of syringes as all three toxin types have equivalent functional unit per volume dosing and reduces the potential for error.

Onabotulinum and incobotulinum toxins are available in 50 and 100 unit vials. If your clinic stocks both size vials, it is important to educate your staff on proper reconstitution for each size.

Proper Positioning

Ergonomic factors are important to ensure consistent, precise, and reproducible results. Proper patient positioning helps ensure comfort for the patient and injector. I prefer to have the patient seated in an adjustable procedure chair, with the back mostly upright (very slightly reclined for comfort), and I place a pillow behind the head so that the head is perpendicular to the horizontal plane. This allows the patient to fully rest his/her head, stabilizing it to reduce head movement. This position is especially helpful when injecting the

glabella, as it helps to keep the needle perpendicular to the plane of injection to ensure proper placement of the toxin. The location of the tip of the needle, not the entry point, is most important, as this determines where the toxin is being delivered.

Make use of the contralateral hand to palpate the muscle to be injected. To increase stability for trainees and new injectors, or those who have a tremor, the pinky finger of the injecting hand can rest on the thumb of the contralateral hand which is stabilizing the muscle to be injected. In areas where diffusion is unwanted, be careful not to inadvertently apply pressure to the injected areas. This is especially important over the corrugators, to avoid unwanted diffusion to adjacent muscles. In certain areas where diffusion is desired, such as the procerus or lateral orbicularis oculi, gentle massage can help disperse the toxin.

Patient Communication

Prior to injecting botulinum toxin, one must ascertain the patient's goals for treatment and ensure that they align with realistic expectations. Do they wish to have a completely natural look, and simply appear well rested, or would they like to enhance the arch and height of their brows? Patients need to be educated on the onset of action, the expected duration, and the limitations of this procedure. For example, deep static glabellar rhytides may require a few sessions over several months of toxin injections to gradually improve or may require combination treatment with both neurotoxin and filler to resolve these creases.

When discussing botulinum toxin injections, one should avoid using words such as "paralyze" or "freeze," as this conjures negative images of "overdone" faces. We refer to these medicines as "wrinkle reducers" that "relax" the hyperactive or overworked muscles and reduce the stress and worry in our facial expressions.

One should provide proper informed consent and ensure that patients are aware of the risks and potential complications of botulinum toxin prior to treatment. Patients should know how to contact the provider after office hours should an issue arise. Postprocedure access to the provider is important for patient retention.

One of the greatest challenges of botulinum toxin is that the results are not immediate and take days to develop. Patients may or may not return for follow-up or contact the provider to give feedback if the results are less than satisfactory. As botulinum toxin results are not quickly reversible, it is better to take a conservative approach and not overtreat. For challenging cases, or if one is a novice injector, consider having patients to return 10–14 days after injection to evaluate the effects and administer touch ups as needed. I encourage all of my patients to contact me if they feel that they need a touch up or have any concerns.

It is important to note the pretreatment appearance prior to injection and document abnormalities that may be of significance, such as preexisting eyelid or eyebrow ptosis, which may be subtle. Asymmetry often exists at rest and/or with animation, and this should be pointed out and discussed with the patient. Pre- and posttreatment photographs are strongly encouraged.

Postprocedure Instructions

To limit unwanted diffusion of toxin, we ask patients to avoid strenuous physical activity until the next day and to stay upright for at least 3 h postprocedure. We also recommend avoiding manipulation or applying pressure to the treated areas and to avoid facials, peels, and laser procedures over treated and adjacent areas for 2 weeks.

Tips for Injection by Anatomic Region

Upper Face

Glabella

Treatment of the glabella is often where patients begin their cosmetic journey. A smooth brow and glabellar complex can convey youth, serenity, and confidence. Static rhytides may convey moods and emotions that do not reflect the patient's frame of mind. Patients often report that they

look tired, stressed out, sad, or angry, when they actually feel the opposite. There is a wide range of anatomic variability in glabellar anatomy and rhytides. Utilizing the standard five-point injection listed in the botulinum toxin package insert will not produce optimal results in every patient. At least two published works have identified glabellar rhytid patterns, with recommendations on injection points for each pattern (de Almeida et al. 2012; Kim et al. 2014). Due to the vast diversity of wrinkle patterns across individuals, I find it most effective to observe the pattern and location of rhytides and musculature in each patient at rest and with animation in order to determine the injection points. I ask the patient to furrow their brows, scrunch their nose, raise their eyebrows, and sometimes repeat it several times to ensure proper identification of their musculature.

Procerus: This fan-shaped muscle originates from the nasal bone at the superior nasal dorsum and inserts in the dermis in the lower medial forehead between the medial brows and the superior fibers interdigitate with the lower frontalis as well as the medial portion of the corrugators. The standard injection point for the procerus is determined by visualizing an "X" with the arms of the "X" connecting each medial canthus to the contralateral supero-medial orbital rims, with the center of the "X" forming the injection point. Note that this point is not on the same horizontal plane as the medial eyebrows but is usually below it; a too-high injection point may result in diffusion of neurotoxin to the medial lower frontalis, resulting in medial brow ptosis. Typically four to five units are injected at a depth of 3–4 mm below the skin surface. Massaging laterally may promote diffusion of toxin to the depressor supercilii, to aid in medial brow elevation. Some individuals, particularly women, have a longer procerus with horizontal rhytides that extend inferiorly along the nasal bridge to the nasal dorsum (Macdonald et al. 1998). In cases of a long, inferior extending procerus, a second injection point lower on the procerus may be needed (two to five units). In some patients with more resistant horizontal lines at the nasal bridge, an additional two injection points laterally (two units each) may produce more complete procerus blockade.

Corrugators: In addition to the procerus, the corrugators are the other major muscle that contributes to glabellar rhytides. Depending upon the length and bulk of the corrugators, one to three injection points on each side may be used. The corrugator is thickest in the medial portion above the medial canthus and becomes thinner laterally (Macdonald et al. 1998; Benedetto and Lahti 2005); therefore, I generally inject more units medially (four to five units) than laterally (one to three units). Medially it lies deep to the frontalis, and therefore medial corrugator injections should be placed deeply. The landmark for the medial most injection is typically located superior to the medial canthus, outside the orbital rim. Some individuals have shorter, more vertically oriented corrugators, whereas some have longer, horizontally extending corrugators. It is important to have the patient animate to identify the lateral insertion of the muscle. If the corrugators extend horizontally, then a second and possibly third injection along each corrugator may be warranted (one to four units each point, with fewer units as the muscle becomes thinner laterally). One can often visualize the insertion of the lateral corrugator fibers by observing the patient's skin retract with when they contract their glabellar complex – the lateral most injection should be placed medial to this muscular insertion. The lateral corrugator injection is more superficial as the muscle inserts onto the underside of the dermis at this location. If the corrugators have a more vertical orientation, the superior portion of the corrugator may be treated.

For patients with short or delicate corrugators, the corrugator injections may be limited to just the one medial point. Likewise if there is concern for medial brow ptosis due to diffusion into the lower frontalis (especially in older patients), then I limit injection of the corrugators to just the medial portion and avoid lateral corrugator injections. If the patient desires a more natural appearance and would like to retain some muscle movement in the glabella, then limiting the injections to just the medial corrugators will help to achieve this partial reduction in muscle movement.

When injecting the corrugators, it is important to avoid injections in the "danger zone" which is

the 1 cm zone above the superior orbital rim, in order to avoid diffusion of toxin to the levator palpebrae muscle, as this may result in eyelid ptosis. The hair of the eyebrow is not a reliable landmark since eyebrow position varies greatly across individuals and changes with age and grooming practices. Instead, it is better to use the bony landmark of the orbital rim which is much more reliable.

In patients who have had a previous upper eyelid blepharoplasty, oftentimes, the orbital septum has been breached, and there is more of a risk of diffusion of toxin into the levator palpebrae of the upper eyelid. In these patients, it is especially important to remain superior to the danger zone.

Other Muscles Contributing to Glabellar Creases

The depressor supercilii are small muscles that lie just lateral to the nasal bridge and serve as medial brow depressors. Injection of the depressor supercilii may also result in mild medial brow elevation (one to two units per side). The medial and superior fibers of the orbicularis oculi also contribute to glabellar rhytides in some patients. Some patients also recruit the superior and superolateral orbicularis oculi muscles when furrowing their eyebrows and will form vertical/radial creases above the mid eyebrow, sometimes extending to the lateral eyebrow. Microdroplets of very superficially placed toxin above the brow can address these creases, using a small number of units and taking care to avoid the danger zone to avoid eyelid ptosis. When injecting this area, consideration should be given to whether treatment of this area could worsen existing brow ptosis and perhaps avoid concurrent injections in the lateral forehead.

Nasalis

The so-called "bunny" lines caused by nasalis contraction may be present at baseline or appear or worsen after neuromodulator blockade of the glabella due to compensatory contraction of the nasalis. Generally two units to each of one to two points on each side of the nasalis will produce excellent results. Injections should be located on the nasal sidewall, staying more medially, and away from the nasofacial sulcus, as injections that are too lateral can result in diffusion of neurotoxin to the lip levators, resulting in lip ptosis.

Forehead

Neurotoxin injection of the forehead may be the most nuanced of cosmetic toxin injections, as it can greatly affect brow position and impacts the overall appearance of the face. It is very helpful to discuss with patients prior to injections what their aesthetic goals are for this region.

As the use of neurotoxins has evolved over the past few decades, the goals of therapy have shifted away from complete forehead immobilization. In our practice, most patients prefer a more natural-appearing forehead with retention of some frontalis activity. There are exceptions, and some patients prefer to have no movement at all.

Several factors affect the placement of injection points and the number of units used including the height and width of the forehead, muscle mass, brow position, and anatomic variations in the frontalis. It is important to note that the duration of effect in the forehead is longer than in other areas of the face.

In general, for a female forehead with average muscle thickness, height, and width, 8–12 units will produce reduction in the forehead rhytides without giving the "frozen forehead" appearance. In men, usually there is more muscle mass, and a higher number of units may be needed. For patients with a smaller/shorter forehead or thin/delicate muscles, it is best to err on the side of starting with fewer units.

Care must be taken to avoid the 2 cm zone above the eyebrow as the resting tone of this portion of the frontalis determines the shape of the brow. Injections that are too low may result in loss of the eyebrow arch or result in a heavy appearing brow.

One must take into account sexual dimorphism with regard to eyebrow shape. In general, it is best to avoid feminization of a male brow so lateral forehead injections should be placed to maintain a horizontal brow. Women who naturally have an arch in their brow usually wish to retain this

feminine contour and therefore it is best to avoid over-injection of the portion of the forehead above the apex of the arch (usually above the lateral limbus of the eye) in order to retain this shape. However, some women have a more horizontal brow at baseline and do not wish to alter their appearance with a more arched brow, and therefore it is important to ascertain this prior to treatment.

Occasionally, blockage of the glabella and/or medial forehead will result in a compensatory increased resting tone of the lateral frontalis resulting in an exaggerated lift of the tail of the brow or "Spock brow." This is easily remedied with one to two units injected into the upper lateral forehead to help address the exaggerated lift of the brow. Likewise an overarched brow can give an unnatural appearance that some associate as a sign of being "overdone" with neurotoxin. Management of this unwanted effect would be one to two units in the mid- to mid-upper forehead above the arch to make the brow's shape appear more natural. Placing one to two units in the lateral mid-upper frontalis on each side can also treat or prevent the overly wide-spaced eyebrows that can result from treatment of the glabella.

For my older patients as well as patients with some degree of eyebrow or eyelid ptosis who rely on their frontalis to help keep their eyebrows in a favorable position, or their eyelids lifted off the lashes, I educate them on the need to retain some muscle tone in order to avoid having a heavy brow. Most patients prefer to keep their brows in a favorable position despite having some forehead rhytides, rather than have a smooth forehead with low-set brows.

In most patients, I do not treat the forehead alone without also treating the glabella, as it would render the brow depressors unopposed and could lead to brow heaviness. An exception would be a relatively young patient without baseline brow ptosis who has isolated forehead rhytides without glabellar rhytides; starting with a low dose is advised.

Some patients find that treatment of the upper and mid-upper forehead results in dynamic rhytides in the lower forehead, particularly the lateral portions above the arch of the eyebrow. Patient selection and education are important when addressing this area. If the patient does not have baseline brow ptosis that requires resting frontalis tone to keep the eyebrows elevated, then one can consider injection of a small amount (0.5–1 unit) to address these lower forehead rhytides. The patient must be made aware that this may result in a lower brow or reduction in the brow arch. Prior to treating this area, I show patients a mirror to demonstrate how this will affect eyebrow position and the appearance of the eyelid. If the patient has brow ptosis at baseline, or does not wish to risk loss of the eyebrow arch, other minimally invasive alternatives would include filler injections to fill in these lines and lift the brow or to treat with a tissue tightening device or surgical brow lift to address the brow ptosis before attempting neuromodulator to this region.

Crow's Feet/Periorbital Region

Anatomic variations occur in the periorbital rhytides, and injections should be tailored to each patient. Some individuals have more rhytides in the superior periorbital region, while in others the rhytides are concentrated on the lower portion, and some have them throughout the entire area. Dosing is on average 12 units on each side but can range from 6–18 units on each side. Some patients require two rows of injections for complete blockade.

Injections should be in the superficial subcutaneous plane, making note of superficial vessels to avoid bruising. The lateral injection point is approximately 1 cm outside the orbital rim; the points superior and inferior to this may follow the curve of the orbicularis. I prefer to use my non-injecting hand to palpate the rim and anchor my injecting hand onto my non-injecting hand, which in turn is resting on the patient. This way, if the patient moves, the hands move with them. I inject at approximately a 45° angle to ensure a superficial injection. This is a sensitive area, rich in cutaneous sensory nerves, and patients can inadvertently flinch; therefore, it is best to angle the needle away from the globe to prevent eye injury.

In the lower periorbital area, care must be taken to ensure the injections are very superficial in

order to avoid spread of the neurotoxin to the lip levators and abductors, which can result in a change in the patient's smile. I inject only one to two units per injection point in this area to further limit diffusion.

Injection of a small amount (two units) of neurotoxin in the lower eyelid (2–3 mm below the lash line) may help reduce a prominent infraorbital roll and can result in a wider eye. It can also help as reduce the crepey texture that can develop in this area. One must perform a snap test prior to injection in order to avoid ectropion or worsening of dry eye symptoms. In some patients, injection in this location can result in a small temporary bulge of the skin, and patients should be warned of this possibility. This may be due to temporary edema which resolves after several days; however, it may also be due to reduced muscle tone and skin laxity, which would take longer to recover.

In patients with significant lower eyelid laxity, over-injection of the lateral orbicularis can result in worsening of the lower eyelid region as there is decreased resting muscle tone to keep the skin taut. In these patients, fewer units placed laterally would be recommended.

Brow Lift

Elevation of the brows with botulinum toxin can open up the eye/eyebrow area and enhance one's appearance. The position of the brows is determined by the balance of brow depressors and the brow elevator; neuromodulator treatment can result in a modest elevation of both the medial and lateral brows (Carruthers and Carruthers 2007).

Relaxation of medial brow depressors (procerus, depressor supercilii, corrugators, and medial portion of the orbicularis oculi) with neurotoxin can result in modest elevation of the medial portion of the brows.

The superolateral and lateral portions of the orbicularis oculi pull the lateral brow downward when contracted, and relaxation of these muscles will allow the lateral frontalis to lift the brow. When injecting the tail of the brow, are must be taken to avoid injection of the lateral frontalis as this would result in lateral brow ptosis; therefore, injections must be lateral to the temporal suture line. Typically two to four units are used on each side.

Lower Face

Mentalis

Treatment of the mentalis can refine the texture of the chin, as some patients will subconsciously contract this muscle, resulting in a pebbled chin appearance. Relaxation of the mentalis also results in a more favorable anterior projection of the chin. Injections in the mentalis should be kept inferior and medial, as injections that are too superior or lateral carry the risk of diffusion into the depressor labii inferioris (DLI), which lies just lateral to the mentalis. We typically inject three units in each of two points in the mentalis; more units may be required for a larger or more resistant chin. Unilateral diffusion into the DLI will result in an asymmetrical smile due to inability to lower the lower lip to show the lower teeth. Should this unfortunate side effect occur, one may inject a small number of units the contralateral DLI to restore symmetry to the smile.

Depressor Anguli Oris

The depressor anguli oris (DAO) is a triangular shaped muscle; the base of the triangle originates inferiorly on the mandibular bone lateral to the chin, and the tip inserts superiorly on the oral commissure. Injection of the DAO can help improve the contour of the lips by releasing the downward pull of downward turning oral commissures, resulting in a more pleasing neutral lip position. Some patients contract this muscle involuntarily when they smile or speak or at baseline. Over time, this can result in downward turning lips, an unintentionally disapproving appearance or static horizontal rhytides overlying the DAO. Contraction of the DAO can also be distracting when a patient speaks. Typically two to three units are injected at the lateral inferior margin of the muscle. Treatment of the DAO is often combined with filler treatment of the marionette lines to enhance the lower face. The DAO and mentalis are often contracted simultaneously to

produce a frown, so I often treat both areas with neurotoxin concurrently. I employ three methods to localize the DAO:

1. Ask the patient to frown and turn down the corner of the lips. It can help to demonstrate this expression to the patient yourself or show him/her a photo of someone with this facial expression. If the patient finds it difficult to produce a frown voluntarily, I ask them to pull their lower lip laterally and down to show their lower canine teeth and pre-molars. The contraction of the DAO will allow visualization of the boundaries of the muscle; the injection should be at the lateral and inferior portion of the muscle, aiming perpendicular to the skin and slightly posterior toward the angle of the mandible, in order to avoid injection or diffusion into the depressor labii inferioris (which could result in an asymmetrical smile).
2. Ask the patient to bite down while you palpate the anterior border of the masseter muscle. The injection point of the DAO should be approximately 1 cm or one fingerbreadth anterior to the anterior border of the masseter. I use this technique if the patient has difficulty contracting the DAO voluntarily.
3. Follow the diagonal line of the nasolabial fold to the mandible. This should correspond to the approximate location of the lateral portion of the DAO. I use this method of localization to corroborate the other two methods, but I find the other two methods to be more reliable.

Perioral Rhytides

The orbicularis oris forms a sphincter around the lips; contraction causes radial lip lines. A small amount of neurotoxin injected in the upper and lower lips about 2 mm from the vermillion border can reduce the overactive resting tone of this muscle and soften the radial lip lines. It can also result in a slightly fuller appearing lip as the sphincter muscle is released. The number of units should be low, as higher doses can affect speech and function: 0.5–1 unit for each of two to four points just outside the upper and/or lower vermillion borders. I avoid the cupid's bow area to retain lip shape. I usually perform this in conjunction with a hyaluronic acid filler designed to be placed superficially. Studies have shown that employing both and HA filler and neurotoxin leads to better results and improves patient satisfaction over just one modality (Carruthers et al. 2010). Prior to injection, I warn patients that certain activities may be more difficult temporarily, such as drinking from a straw, whistling, or playing musical horn or wind instruments.

Masseter

Neurotoxin injections into the masseter can reduce an overly square jaw. Large masseter mass may be a normal anatomic variant or the result of bruxism. In women, reduction of an overly square jaw can lead to a more feminine facial contour, with a more oval and tapered lower one third of the face. In men, there may be masseter hypertrophy leading to an exaggeratedly square facial shape. Some individuals have hypertrophy on one side, leading to asymmetry of facial contours. There are often two phases to the response to neurotoxin; within the first 1–2 weeks, there may be a subtle improvement due to relaxation of the resting tone of the masseter. Over several months with repeat injections, the masseter also undergoes atrophy, resulting in more profound changes in facial contour. For masseter injections, we typically use a higher dilution to allow for more diffusion, as well as a longer needle in order to reach the masseter muscle. As the patient bites and clenches the jaw, one can palpate the location and boundaries of the masseter muscle. I typically inject 15–30 units into each masseter, divided over 3 points, and then massage the area to distribute the toxin. Injections may be performed every 1–2 months until the level of correction is reached and then maintained at longer intervals. The main side effect is the potential for food to collect in the lower lateral gingival sulcus, so patients should be warned that they may need to rinse their mouths after eating to address this.

Neck

Neurotoxin treatment of the platysma can result in improvement of the neck and jawline. Platysmal

bands can become prominent over time and detract from the appearance of the neck. The bands may be located anteriorly and/or more laterally. If they are located anteriorly, care should be taken to limit the dose to prevent over-injection which could potentially lead to dysphagia. To inject, we pinch the skin lightly between the thumb and index finger of the non-injecting hand and inject two units every 1–1.5 cm along the length of the platysmal bands.

In some patients, the contracted resting tone of the platysma results in prominent horizontal lines and/or a "bunched up" accordion appearance primarily in the anterior neck. Diffuse injection of neurotoxin injection throughout the area can relax and improve the texture and appearance of the neck by relaxing muscle tone (two units every 1–1.5 cm).

The platysma extends superiorly and inserts along the mandible. In some patients, relaxation of the platysma along the jawline just below the mandible can improve contour and definition of the jawline. We inject two units every 1–1.5 cm under the inferior border of the mandible.

Combining Botulinum Toxin with Other Procedures

Combining neurotoxin injections with other procedures has become the norm in many practices. Neurotoxins and fillers can work synergistically and the toxin can extend the duration of effect of the filler. The combination of procedures has been shown in studies to provide a better outcome than either procedure alone, such as for radial lip lines (Carruthers at al. 2010). Regarding timing of the procedures, when treating patients with both filler and neurotoxin on the same day, there are a couple reasons to inject filler first and toxin last. For filler, I often position the patient semi-reclined for comfort and ergonomics, whereas following botulinum toxin injections, patients are asked to stay upright for at least 3 h, so it is best to do the toxin injection last. I also often massage and palpate after filler placement, whereas I avoid applying pressure to most places treated with botulinum toxin to avoid the spread of toxin to other muscles. For locations such as the glabella and radial lip lines, if the patient is willing to have the procedures on separate days, it is best to do the botulinum toxin injection first and then wait at least 1 week for the muscles to relax before placing filler. This may allow the filler to stay in place longer since toxin will reduce the muscular movements that can displace the filler.

Botulinum toxin can improve the results of resurfacing procedures such as lasers (West and Alster 1999) or peels. The toxin will reduce dynamic rhytides in areas that are resurfaced, and neocollagenesis can occur in a smooth plane rather than in wrinkle patterns of facial expression. When combining neurotoxin with lasers or chemical peels in the same location or adjacent locations, it is recommended to separate the procedures to avoid inadvertent diffusion of the toxin (which may occur from increased blood flow, inflammation, or edema following lasers or peels). Ideally the toxin is placed 2 weeks or more prior to the resurfacing procedure.

Take Home Messages

- A thorough knowledge of facial anatomy is crucial for success. Attention to individual anatomic variability separates excellent from suboptimal outcomes.
- Avoid complications. Know the danger zones.
- Adhere to postprocedure protocol.
- Know how to troubleshoot and address less than ideal outcomes should they arise.
- To have high patient satisfaction, listen to your patients' wishes, discuss mutual goals, and educate them on the possibilities and limitations of botulinum toxin. Be available to your patients post procedure.

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Part II

Anatomy View, Indications, Complications, and Management of Fillers and Collagen Stimulators

Facial Anatomy View for Aesthetic Fillers Injections

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Contents

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_16

Abstract

The therapeutic armamentarium for facial rejuvenation has changed over the years. Fillers and the comprehension of the aging process have evolved rapidly. The techniques have changed and facial anatomy needs to be better understood. Fat compartments and bone aging and reabsorption are responsible for aging of the face. Therefore they are key for facial rejuvenation. The most important anatomical references for facial aging treatment are the fat compartment, the vasculature, and the bones, but also the muscular interaction, the neural complex, and even the subcutaneous and full skin thickness need to be studied. The risks and drastic consequences of arterial occlusion have haunted physicians. To get a successful outcome and to minimize complications, it is necessary to analyze the facial anatomy and to recognize which areas should be volumized or filled to promote lifting aspect. It is possible when fillers are deeply injected at specific points, acting as vectors.

Keywords

Fillers · Anatomy · Arterial occlusion · Amaurosis · Adverse events · Implants · Facial anatomy · Rejuvenation · Aging · Bone · Vascular · Necrosis

Introduction

The evolution of facial rejuvenation has advanced over the last few years, with new techniques and different approach of global facial aging. The main points to be considered are: bone absorption, mimic muscles contraction, fat compartments, which are influenced by environment and patient's habits. Special attention must be given to certain areas such as glabellar, ocular and nasal due to the risk of arterial occlusion, ischemia and embolism during filling procedure.

Botulinum toxin for muscle dynamics treatment is used for a long time in Cosmetic Dermatology, but the introduction of different types of fillers changed the concept of filling procedure. Nowadays, fillers are used not only to refill, but mainly to restructure the face and to replace facial fat pads. These new techiniques require a deep knowlegde of facial anatomy to avoid important complications, such as vascular occlusion.

Skin Anatomy

The skin is the widest barrier of the human body and besides protection, it does prevent dehydration. The superficial layer of the skin, the keratinized layer, can be exfoliated during treatments through chemical and mechanical peelings or by using different laser devices. The re-epithelization depends upon the basal layer's integrity and the pilosebaceous unit. The epidermis extends to the basal layer where melanocytes, Langerhans, and Merkel cells are located.

The dermis, one of the most important structures, plays an important role in the wrinkling process of the skin due to its collagen and elastic fibers, cellular components, and vascular supply. This area is resistant, for example, to needle punctures because of its firm, compact, and less distensible characteristics. This is also the layer that can sense pain due to its sensitive innervation. Any product injected at the dermis forms a painful and very superficial papule, and these are the signs that indicate we have reached this layer.

The subcutaneous layer comprehends the fat tissue, right under the dermis, divided into an areolar layer where the vessels and nerves are

mostly located, and under it, divided by a tiny fascia, the lamellar layer or the hypodermis. At this point, the fat compartments are also kept in their own location by their fascia. Its thickness, the fat compartments, and their position have an important role in the global facial aging process.

This paragraph about skin anatomy does not require a detailed histological description but should be considered to understand depth and the techniques for the injection of fillers to correct lines in the skin. Arlette and Trotter (2008) reported that the thickness of the dermis at the nasolabial fold varies from 1.32 to 1.55 mm. Considering that the needle bezel's length varies from 0.75 to 0.95 and the needle diameter varies from 0.3 to 0.4 mm, the old trick of inserting the needle at 30 ° to reach the superficial dermis and at 45 ° to reach the deep dermis, or to visualize the needle by skin transparency, does not represent the reality, especially considering that different areas of the body and face have variations. Therefore, the majority of fillers are injected into the superficial subcutaneous layer, and not the dermis, even by highly experienced doctors.

Dermis and Subcutaneous Tissue of the Face

The skin of the forehead is thicker than the inferior portion of the face. Under the skin, there are: the subcutaneous tissue; the galea-aponeurotic, part of the Subcutaneous Muscular Aponeurotic System (SMAS); the areolar subaponeurotic layer and the periosteum. Due to the local anatomy, overcorrection of the frontal lines is easily noticed with minimal excessive amounts of fillers, in the form of papules, nodules, or lines of the skin in the frontal area and the bone structure. Through the introduction of new products, as nonparticulate hyaluronic acids, and new techniques, it is possible to fill fine lines properly as well as to remold the forehead creases, caused by a fat loss in the medial and lateral frontal fat compartments.

At the temporal area, the skin is relatively thin, and many times the superficial temporal artery might be seen as quite a linear pulsing line with a thicker connective tissue, and also two extensive deep and superficial fat compartments. The superficial fat pad extends to the preauricular and posterior area of the mandible and the deepest fat compartment to the medial area of the face reaching the Bichat area (Gardner et al. 1978). At the subcutaneous layer, massive arterial branches of the temporal artery are found along the temporal neural branches. It is possible that the injection of fillers intravascularly might spread an embolus to any region of the face and the cranium and even cause amaurosis or necrosis. Due to these anatomic features, most physicians prefer to inject fillers with cannulas or in bolus at the supraperiosteal layer, right into the intersection point between 1 cm under the temporal crest of the frontal bone and 1 cm above the eyebrow. This point has been used for safer injection, as it avoids the artery and the migration of the filler, when injected in a greater amount, to the Bichat area.

The facial superficial fat layer is dense because of the fibrous septum and it is scarce at the forehead, glabella, and temporal and orbital areas (Fig. 1).

Fig. 1 The facial superficial fat layer is dense due to the fibrous septum and is scarce at the forehead, glabella, temporal, and orbital area

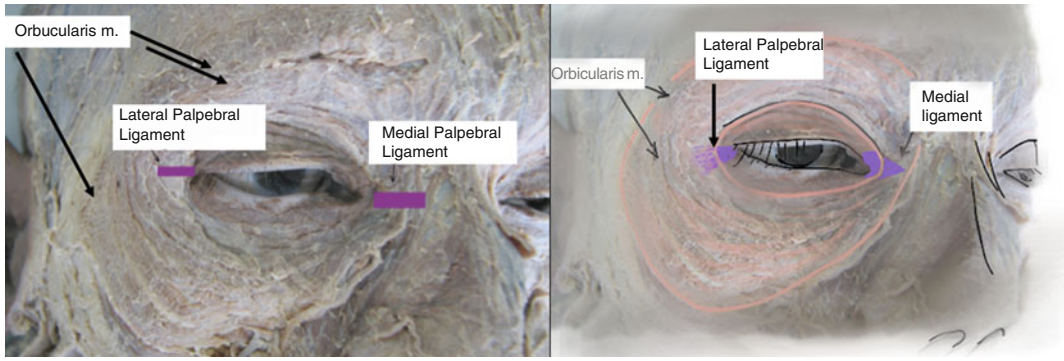

Fig. 2 Medial and lateral palpebral ligaments, the periocular muscle, and the medial ligament

The suborbicularis oculi fat (SOOF) is located inferiorly to the zygomaticus bone and under the muscle. It is separated from the periorbital fat through a thin orbital and malar septum. The ptosis of the SOOF could be responsible for the lateral malar ptosis at the orbital rim that might be seen during the aging process. When fillers are injected at the medial palpebral malar sulcus (tear trough) and the lateral palpebral malar sulcus, we need to remember the medial and lateral palpebral ligaments (Fig. 2). These ligaments must be considered when we are planning to correct not only the medial and lateral palpebral malar sulcus but also the upper lid orbital rim. They need to be filled separately as the filler cannot progress upward from the inferior orbital rim through the ligaments.

The eyebrows position also has basic parameters of normality that need to be respected when fillers, botulinum toxin, or facial sculpture are planned (Goldberg 2008). The eyebrows should be positioned 5 or 6 cm below the hair implantation, the medial portion at a perpendicular line that crosses the lateral nasal alae and 1 cm above the medial canthus of the eyes. The lateral portion of the eyebrow (in back – Fig. 1) ends at an oblique line of the base of the alar cartilage of the nose through the lateral canthus of the eyes (red line – Fig. 1). The medial and lateral areas of the eyebrow should be horizontal and at the same level (in blue – Fig. 1) (Fig. 3). Women's eyebrows are above the supraorbital margin and in an arch shape with the higher point at the lateral limbo of the eye, next to the junction of the medial two-thirds with the lateral third of the eyebrow. The arch is smaller and slightly below the supraorbital margin in men (Pessa and Rohrich 2012).

The fat tissue at the malar area, the nasolabial fold, and the mandible is dense. The fat pad at the malar area is divided into jugal and mandibular, and the deep portions might be found between the muscles. The Bichat fat pad is localized anterior to the masseter muscle and deeper to the posterior fascia of the buccal region. Their anatomic location should be analyzed balancing the shape of the face to correctly program the right volume and the depth for the injection of fillers thus planning a natural result and not as a huge artificial implant. Differences in men and women also need to be considered properly.

At the malar prominence, we face the musculocutaneous perforating vessels and one or two zygomatic nerve foramen depending upon individual variations. With aging, there is ptosis and pseudo herniation of the SOOF and the orbital fat pads. The laxity of the medial malar area leads to fat accumulation at the anterior and inferior portion of the cheeks and there is also fat loss at the lateral superior malar area. These changes lead to a deep nasolabial fold, multiple lines at the cheeks at smiling mimics, and a pseudo fold at the submalar area. The vector that pulls the face downward does also lead to a skeletonized appearance of the malar region and this is where the filling techniques mentioned come into play (Carruthers et al. 2009; Pessa and Rohrich 2012; Sadick et al. 2009). Fig. 4 shows the facial fat pads.

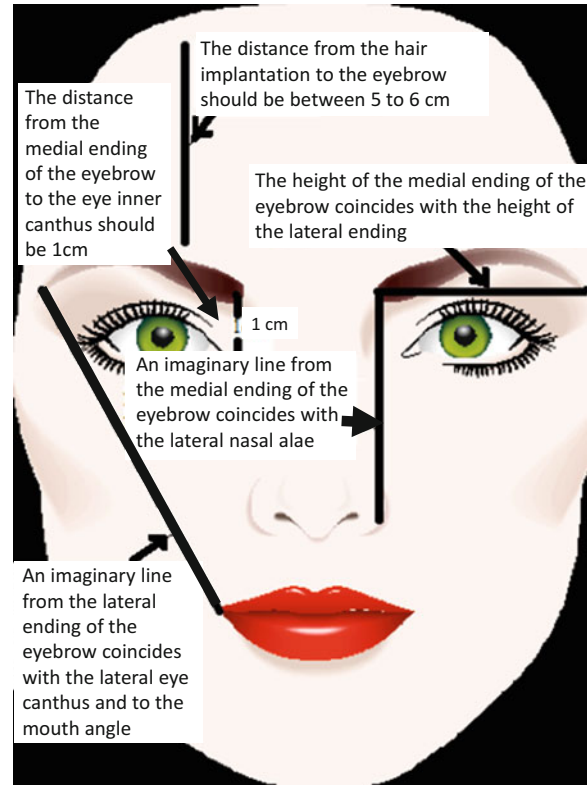

Fig. 3 Standard parameters of the eyebrows positioning

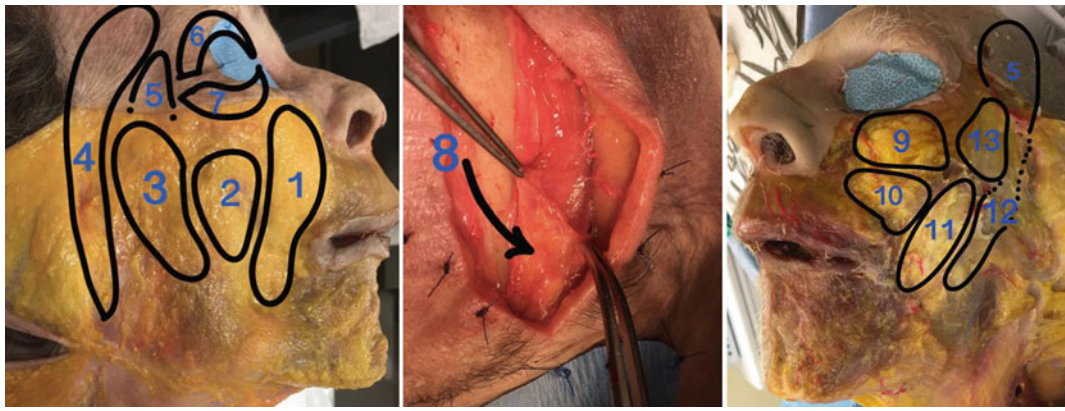

Fig. 4 The left picture shows the superficial facial fat pads; at the middle, the arrow points to the the retroorbicularis oculi fat (*ROOF*) (8); the picture on the right shows the deep facial fat pads. (1) nasolabial fat pad; (2) medial cheek pad; (3) middle cheek pad; (4) lateral temporal cheek pad; (5) Temporal fat pad; (6) superior palpebral fat; (7) inferior palpebral fat; (9) sub-orbicularis oculi fat (medial part); (10) deep medial fat pad (medial part); (11) deep medial fat pad (lateral part); (12) buccal extension of the bucal fat; (13) sub-orbicularis oculi fat (lateral part)

The skin adheres to the *risorius* and platysma muscles at the parotideal masseteric area. The facial nerve branches (Fig. 5) and the parotideal duct (Fig. 6) are located posterior to the SMAS and anterior to the masseter and the buccal fat pad. When we inject fillers at this area, we must remember that the parotideal duct is right under an imaginary line from the mouth corner to the

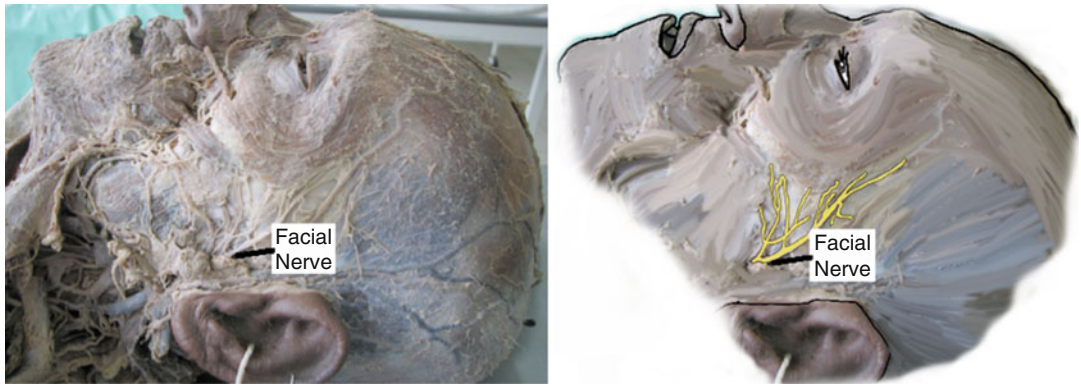

Fig. 5 Location of the facial nerve

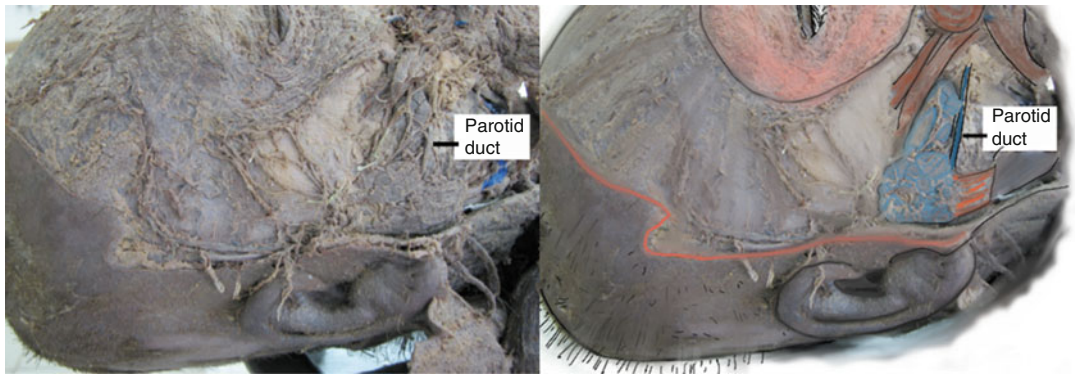

Fig. 6 Parotid's duct

tragus. We need to be aware of an accidental fistulae due to a ductal trauma during injections. The parotideomasseteric fascia (connective layer) that originates the risorius muscle also envelopes the parotid gland and the masseter muscle (Altruda Filho et al. 2005).

Skin, cartilage, and bone supporting a connective tissue and ligaments keep everything together at the nose. The skin is thick and adheres to the inferior third and it is thinner and mobile at the superior two-thirds of the nose (Fig. 7). Although these structures are intimately bonded, fillers can be injected without any problem and when well indicated, migration of the products is extremely rare (depending upon the volume, technique, or product).

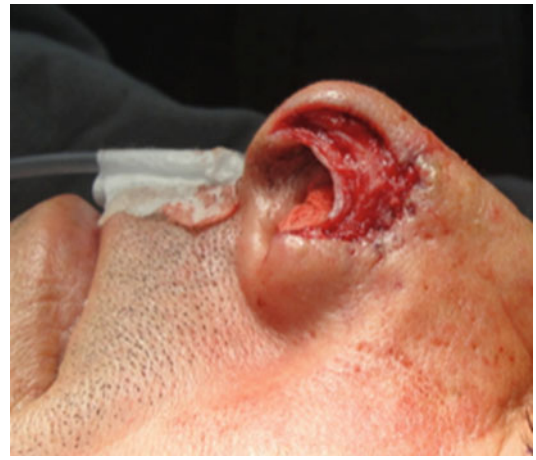

Fig. 7 The nasal structure combines the skin, the cartilage, and the bone

Around the lips, the skin is thick and just over the muscular layer. The vermillion of the lips has a transitional epithelium between the skin and the mucosa that is thin and delicate. On the other hand, at the lateral canthus of the lips, the subcutaneous tissue is important for the adherence of the local muscles and the lips mucosa. During the aging process, frequent perioral movements lead to mimic lines, so-called "bar codes," around the lips. Vessels are found at the medial area and the intimate adhesion of the mucosa and muscles explain why fillers must be injected at the dermis. Therefore, physicians must choose the right filler to get the best result, avoiding overcorrection and deformities of the superior lips without even smoothing the lines properly. The number of tortuous vessels at the deeper layer of the lips might result in hematoma, depending upon the technique of injection.

The chin's skin is thin and the mentual muscle is located right under it, depressor labia muscle is right beside, and the depressor anguli oris and the platysma muscle are located laterally to it and at the labiomarginal sulcus (Fig. 8). The adipose tissue that is superficial to the SMAS adheres firmly to the dermis through a fibrous septum and laterally all the tissues connect straight to the bone at the retainer ligament. This firm attachment leads to longer discomfort when higher amounts of fillers are injected to reshape the mental area.

Earlobes can also be corrected with fillers, improving laxity (aging process) or giving firmness after a plastic reconstruction. Fillers not only fill up the lobe and reshape it, but add an extra firmness to the preauricular area. Earlobes are delicate structures with thin epidermis and medium thickness dermis and subcutaneous tissue. The vessels at the subcutaneous layer are very thin and evenly distributed.

Limits of the Facial Zones

The superior third of the face is limited by an imaginary line from the tragus to the lateral canthus of the eyes, contouring the inferior eyelid bordering the nasal radix to the eyebrow line. The limits of the medium third are the line of the superior third, from tragus to the lateral canthus of the mouth, contouring the border of the upper lip to the tragus of the other side. The inferior third's superior limit is the medium zone contouring the inferior border of the lower lip until the mandibular line (Fig. 9).

The temporal area is anteriorly limited by the temporal portion of the zygomaticus bone, posteriorly by the supramastoid crest, superiorly by the temporal line, inferiorly by a horizontal line that crosses the zygomaticus arch, laterally by the skin, and medially by the frontal, sphenoidal, parietal, and temporal bones.

There is a temporal space limited laterally or superficially by the temporalis fascia (that covers the superficial branch of the temporalis muscle) and medially or deeply the superficial branch of the temporalis muscle. There is a superficial fat pad and a deep fat pad. The deepest communicates to the masticator and buccal area. It is also medially or deeply limited by the superficial branch of the temporalis muscle.

The infratemporal region is limited superiorly by the infratemporal side of the major branch of the sphenoidal bone, inferiorly the inferior line tangential to the mandible basis, laterally the internal side of the mandible branch, medially the lateral aspect of the lateral lamina of the pterygoid process and the superior and medium constrictor muscle of the larynx, anteriorly by the maxillae tuber, and posteriorly by the parotid gland (Tamura 2013).

The orbicular area is divided into lateral portion, medial canthus, superior and inferior lacrimal area, and superior and inferior lid.

The infraorbicular, zygomaticus, and the cheeks limits are anteriorly the external nose, nasolabial and labiomarginal sulcus, posteriorly the anterior margin of the masseter, superiorly the infraorbital margin, and inferiorly the mandibular base. The cheeks limits are the malar complex superiorly and inferiorly the mandible and its shape determined by the parotid gland, the muscles, and the buccal fat pad. Deeply to the muscles

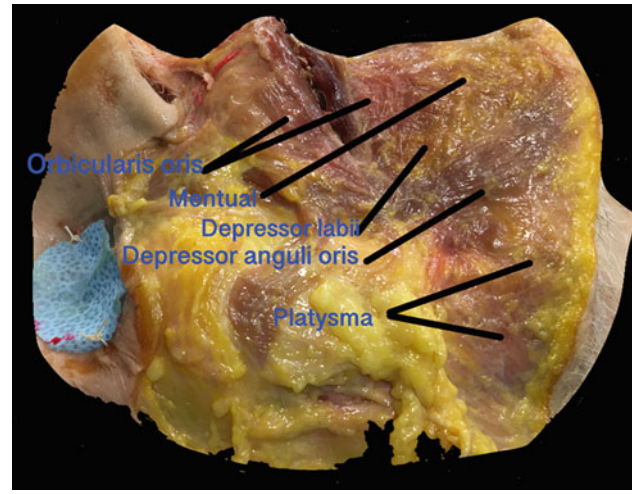

Fig. 8 Mentual, depressor labii, depressor anguli oris and platysma muscles intimately related at the chin

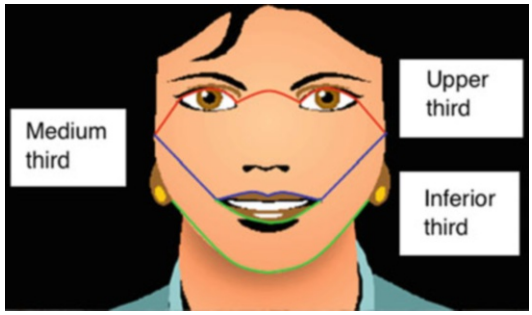

Fig. 9 Limits of the facial zones: superior, medium, and inferior thirds

of the infraorbital, zygomaticus, and cheek region, the mucosa extends between the superior and inferior fornix of the buccal vestibule and the periosteum that covers the bones of this region.

The ideal location of the malar prominence is 10 mm lateral and 15 mm inferior to the external canthus of the eye. Deficiencies of this measurement lead to an elongation of the maxilla added, most of the times, to a lack of projection of the medium third of the face. The submalar triangle is an inverted depressed triangle of the mid face limited superiorly by the zygoma prominence, medially by the nasolabial sulcus, and laterally by the body of the masseter.

The parotideomasseteric region is limited superiorly by the anterior margin of the masseter and posteriorly by the mastoid process and the anterior margin of the sternocleidomastoid muscle. The superior limit is the zygomaticus arch until the external acoustic meatus; the inferior, the tangential line of the mandible basis until the mastoid process, and the medial, the styloid process (posteriorly) and the lateral side of the pharynx (anteriorly). The pterygopalatine corresponds to the same named fossa, localized deeply at the face and superiorly to the palate, inferiorly to the sphenoidal sinus, anterior to the pterygoid fossa, posteriorly to the orbit and the maxillary sinus, laterally to the nasal cavity, and medially to the infratemporal fossa; it resembles an upside-down pyramid with a square base (superior) with an apex (inferior) and four walls.

Concerning the nasal area, it is limited superiorly by both eyebrows, inferiorly in a line designed tangential to the nasal basis, and laterally between the medial angle of the eye to the nasolabial fold. This area is divided into radix (superior part of the nose), the dorsum, and the apex of the nose (the tip) and nostrils. The dorsum corresponds to the right and left walls of the nasal basis; the dorsum that is the right and left lateral walls of the nose between the base, radix, and nostrils that correspond to the elevator of the inferior part of the nasal dorsum. The nasolabial angle stays between 90° and 100° in men and between 100° and 110° in women.

When analyzing the labial limits, the superior is the base of the nose; the lateral, the nasolabial sulcus; the superior lateral, the nasolabial fold; the

inferior, the labiomental fold; and the inferior lateral, the labiomarginal fold. The extension of the lips is greater than the red portion of the adjacent skin. It is an anatomical unit that extends superiorly to the nose and inferiorly to the mentum. The perfect lip structure includes a white line, or transitional, visible between the mucosa and the skin, a long median tubercle, a "V" shape (known as Cupid's bow), the vermillion, and the ascendant line of the buccal commissure. The golden proportion (the perfect measure) of the lips is 1:1618 (in width and thickness). The philtrum is an important reference at the central area of the upper lip outlined by two columns of the philtrum vertically oriented, and Cupid's bow is the concavity at the base of the philtrum.

The superior limit of the mental region is the labiomental sulcus, the interior is the mandible basis, and the lateral, the labiomarginal fold. It is limited between the mental foramens and the central part of the mandible. The lateral medium zone extends from the posterior mental foramen to the oblique line of the horizontal body of the mandible and the lateral/posterior is limited by the posterior half of the body, including the angle and the first 2–4 cm of the ascendant branch of the mandible. The submental zone is the lower area of the mentum and localizes between the platysma band and of the cervico-mental angle.

Facial Bones (Altruda Filho et al. 2005; Gardner et al. 1978; Tamura 2010a, b; Sobotta and Becher 1977)

The bones that delimitate the cranial cavity protecting the encephalon and the meninges are the frontal, the ethmoid, the occipitalis, the temporalis, and the parietal bones; the former two come as pairs. The frontal, nasal, lachrymal, zygomaticus, maxilla, and the mandibular bones are located at the facial area. The vomer is odd, and those in pairs (the palatines and the inferior nasal shells) are deeper. The deep grafts and fillers at the face are mostly located at the nasal, malar (zygomaticus and superior maxilla), and mental (gnathion and mental protuberance) bones (Figs. 10, 11, and 12).

Forehead

The forehead bone is the frontal bone; and at the caudal part, each side of the medial line articulates with the nasal bone. The nasion (Fig. 13) is the intersection of the frontal and both nasal bones, and the area above the nasion between the eyebrows is the glabella. From the glabella, the eyebrows extend laterally to both lateral sides.

Orbit

The eyes are located at the orbital cavity, which is divided into superior, lateral, interior, and medial border.

The frontal bone is the superior border or supraorbital area. The supraorbital vessels and nerve emerge from the supraorbital notch, medially to the notch and at the margin of the frontal bone (Fig. 13). Nowadays, the line that describes better the location of the three main sensitive foramens of the face is considered to be the one that crosses the limbo of the eyes, and not the medial pupillary line. The supraorbital margin ends laterally to the zygomaticus process of the frontal bone, and in each supraorbital margin, the frontal bone directs posteriorly as most of the ceiling of the pars orbitalis. The zygomaticus and frontal bone from the lateral side and the inferior are formed by the maxilla and the zygomaticus. The medial area of the orbit is shaped by the maxillaries, lacrimal, and frontal bone. Under the inferior border of the orbit at the pupil line, the maxilla has a foramen, the infraorbital foramen (Fig. 12) where the infraorbital vessels and nerve emerge.

Facial Prominence

The malar bone (zygomaticus) forms the facial prominence at the inferior and lateral border of the orbit and lies on the maxilla. Thus, there is a lateral surface, an orbital side that contributes to the lateral wall of the orbit and a temporal surface at the temporal fossa. The frontal process articulates with the zygomaticus process of the frontal

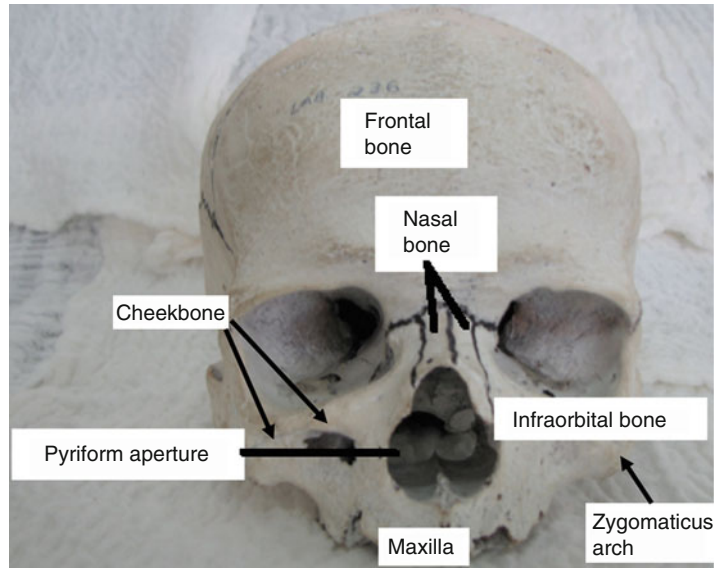

Fig. 10 Facial area bones

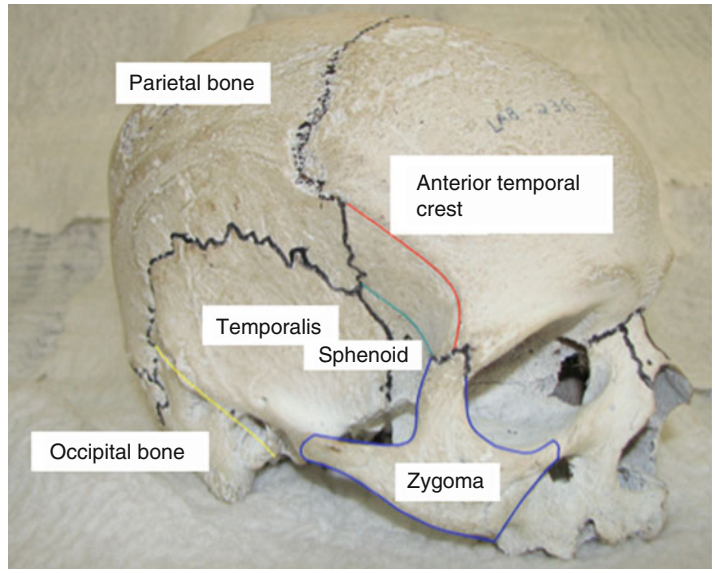

Fig. 11 Lateral vision of the cranial bones

bone and the temporal with the zygomaticus process of the temporal bone. At the lateral portion, the zygomaticus bone is perforated by the facial zygomaticus foramen (Fig. 13), and the nerve block performed in this area can reduce pain during malar procedures. (see chapter ▶ "Facial Nerve-Block Anesthesia in Cosmetic Dermatology").

External Nasal Bone

The external nasal bone is constituted by the nasal bones limited by the maxillaries and ending anteriorly at the piriform aperture (Fig. 10). The soft tissue of the external nose is formed by a cartilage structure (medium and lateral) that joins the piriform aperture through a fibrous tissue. The

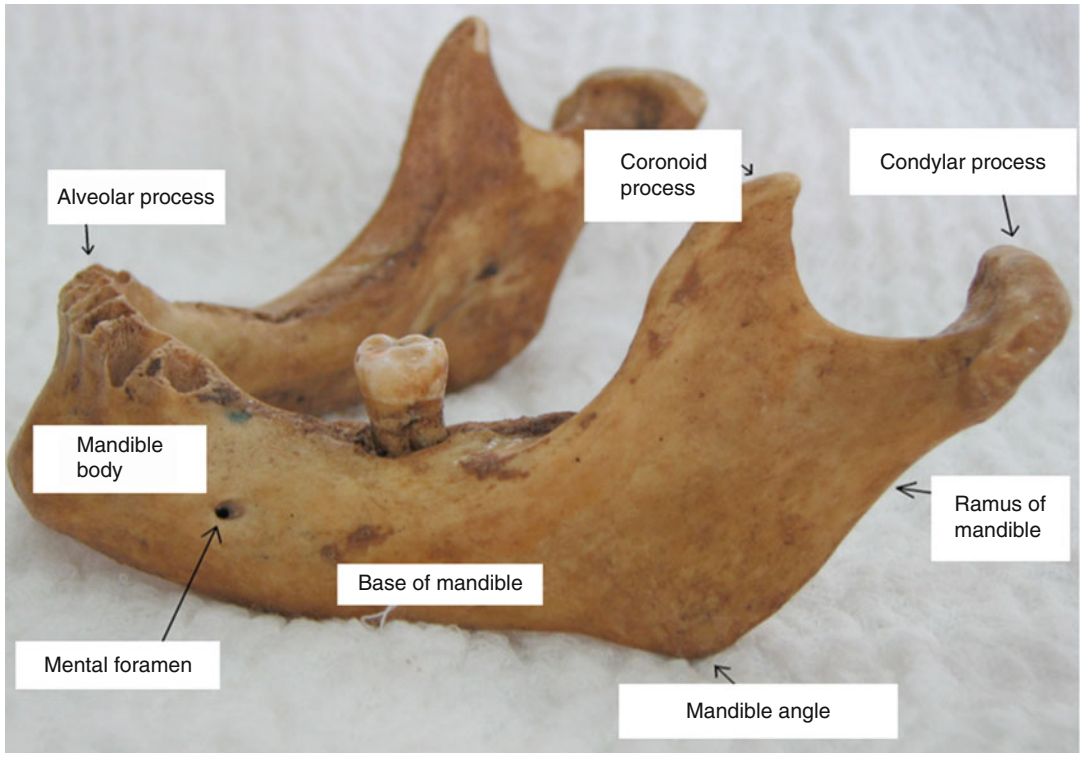

Fig. 12 Mandible. The mandibular angle is behind and below the inferior third of the molar tooth

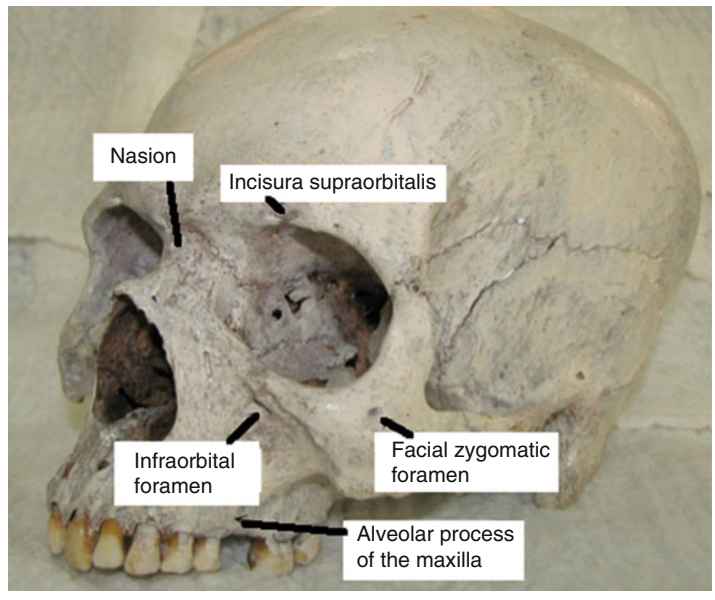

Fig. 13 Nasion, supraorbital notch, and the foramens

domus is the junction of the medial and lateral cartilages, the shape of the tip of the nose depends upon these structures and it is supported by the nasal skin, the ligaments, and the cartilage as a unit. The nasal bones are the superior limit of the nasal aperture and laterally and inferiorly are

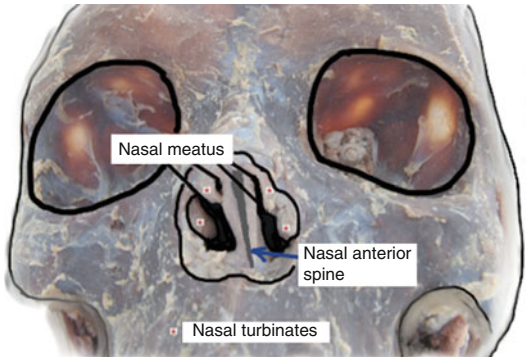

Fig. 14 There are three or four curved plaques (conches or turbinates) at the lateral walls of the nasal cavity

limited by the maxillaries. The nasal cavities are divided by the nasal septum; the anterior septum portion is formed by the cartilage and the posterior by the ethmoid and vomer bones. At the lateral walls of the nasal cavity, we find three to four curves of the bones: the turbinates; and the space under each one is defined as nasal meatus. The anterior nasal spine is found at the median area of the inferior border of the pyriform aperture (Fig. 14).

The nasal bones articulate superiorly to the frontal bone and laterally to the frontal process of the maxillaries and the inferior borders that join the nasal cartilage.

Maxilla

Both maxillaries form the maxilla, and its growth is responsible for the vertical elongation of the face between 6 and 12 years. During the aging process, bone absorption occurs at a lower degree, and the gravity and absorption of the fat of the malar region are mostly responsible for the descent of the face.

The maxilla sinus is located at the maxilla; the zygomaticus process extends laterally and articulates to the zygomaticus bone; the frontal process (superior direction) joins the frontal bone; the palatine process (horizontal) joins the opposite side (forms the palatine skeleton); and the alveolar process surrounds and supports the teeth. Its pyramidal shape with a nasal side or base forms the lateral wall of the nasal cavity; the orbital side consists of the orbit floor; the infratemporal side forms the anterior wall of the fossa infra temporalis; the anterior side is covered by the facial muscles.

The infraorbital artery and nerve emerge about 1 cm under the infraorbital margin across the anterior surface of the maxilla at the infraorbital foramen (sometimes multiple). This foramen is mostly localized at an imaginary line of the limbus (Fig. 13). The upper teeth are implanted at the alveolar process of the maxilla. The inter maxilla suture is the point of junction between both maxilla, and the maxilla portion that supports the incisor teeth is called premaxilla.

Mandible

The mandible, or the inferior maxilla, is the biggest and strongest bone of the face. The inferior teeth are located at the alveolar part of the mandible. Under the second premolar tooth, the mandible has a mental foramen from where the mental nerve and vessels emerge, and it is also localized at an imaginary line of the limbus as a reference to locate the foramen for anesthetic blockage. The mandible has a U shape with a pair of branches. The joint area behind and under the inferior third of the molar tooth is described as part of the branch and for others as a part of the body (Fig. 11). In this area, the mandible angle presents a medium value of 125° varying between 110° and 140°.

The greatest prominence directed laterally is called gonion, and the mental symphysis is the medial area of the mandible. The inferior mandible is the basis, and the digastric fossa is an irregular depression at the basis or near the symphysis. At about 4 cm anteriorly to the mandible angle, the basis can present a sulcus where the facial artery lays and pulsates. The lateral branch of the mandible where it turns to be flatter is where the masseter muscle inserts.

The alveolar portions of the mandible suffer serious reabsorption during the years leading to teeth loss, and these effects reflect at the aging of

Fig. 15 Aging of the cranium

Fig. 16 Aging of the mandible

the inferior third of the face. The mandible is reabsorbed and becomes thinner and narrower, resulting in an impression of the face falling down, worsening the prejaw area and leading to loss of facial contour. Although these areas have great importance, we cannot forget the bone loss at the orbit, the temporal area, the facial area, and the zygomatic arch as shown in Fig. 15 of the cranium and in Fig. 16 that shows the mandible in different ages.

Temporalis

The temporalis bone is divided as pars squamous, tympanic, styloid, mastoid, and petrosal. The squamous and mastoid pars are those of most interest and we can describe them in detail. The squamous part of the parietal bone joins inferiorly to the pars squamous of the temporalis (squamous suture). At the squamous portion, the zygomaticus process (the zygoma) projects anteriorly to join to the zygomatic bone completing the zygomaticus arch. The superior border of the zygomaticus arch corresponds to the inferior cerebral hemisphere where the temporal fascia inserts. The masseter originates from the inferior border of the deep surface of the arch. The lateral ligament of the temporomandibular junction inserts at the tubercle of the zygomatic root (inferior border of the arch) and posteriorly to the tubercle of the head of the mandible localizes at the mandibular fossa.

The external acoustic meatus (behind the head of the mandible) has in its interior the tympanum (tympanic membrane) with approximately 3 cm of length. The roof and the adjacent posterior wall of the acoustic meatus are formed by the squamous part of the temporalis, and the wall is formed by the tympanic part.

The posterior part of the temporalis bone is part of the mastoid and joins the squamous portion. It

is formed by the mastoid process with an inferior projection, and the mastoid process of the two sides of the head is lined with the magnum foramen. Each process results in insertion into many muscles. The anterior part of the mastoid process is separated from the tympanic plaque through the tympanic-mastoid fissure that might act as a pathway to the auricular branch of the vagus nerve.

Fossa Temporalis

The temporal line (where the temporal fascia joins) begins at the zygomaticus process of the frontal bone forming an arch in a posterior direction through the frontal and parietal bones. The posterior part joins the supra mastoid crest of the temporal bone. The temporal fossa, where the temporal muscle is accommodated, is localized between the temporal line and the zygomaticus line. The origin of the muscle occurs at its floor and has a pars parietal, frontalis, major wing of the sphenoid, the squamous pars of the temporalis, and the place where the four join is called pterion. It lies at the anterior branch of the meninges artery on the medium side of the cranium and corresponds to the surface of the lateral sulcus of the brain. The center of the pterion is about 4 cm above the medium part of the zygomaticus arch almost at the same distance behind the zygomaticus process of the frontalis.

The temporal muscle and the deep nerves and vessels cross the space between the zygomaticus space and the rest of the cranium, and where the temporalis fossa communicates with the infratemporal fossa below. The infratemporal fossa lies behind the maxilla, the temporal fossa stays medial, and the roof of the fossa is formed by the infratemporal surface of the major wing of the sphenoid. The medial limit of the infratemporal fossa is the lateral lamina of the pterygoid process of the sphenoid and the lateral is the branch and coronoid process of the mandible. The lateral and medial pterygoid muscle, the maxilla artery and its branches, and the pterygoid venous plexus are found at the inferior region of the temporalis. The mandibular nerve, maxilla, and tympanic cord are also part of it. The maxilla has a connection with the orbit through the inferior orbit fissure and it continues with the pterygoid maxilla fissure. In addition, its connection to the pterygoid maxilla fissure offers an intimate relationship with the maxilla artery and nerve at that location (below the apex of the orbit).

Description of the Main Facial Muscles

The facial muscles are important when we discuss fillers and aging process. Dynamic muscles are related to the behavior, durability, and maybe migration of the fillers injected in the face. The facial muscles details are described in the anatomy of the botulinum toxin chapter. (See chapter ► "Facial Anatomy View for Aesthetic Botulinum Toxin Injection").

The frontal muscle with the frontal and occipital belly inserts at the aponeurotic galea. At the forehead, they are separated in pairs and are involved by the superficial fascia. The frontal muscle's function is to elevate the eyebrow and create hyperkinetic frontal lines (Fig. 17).

The corrugators muscle originates from the internal and anterior portion of the superior and medial orbital margin above the nose and inserts to the frontal muscle and the eyebrow skin. Its contraction brings the eyebrow together as well as pulls down the glabellar wrinkles (Fig. 17).

The procerus muscle originates from the nasal bone at the glabella and inserts at the skin of the forehead. This muscle pulls down the eyebrow and is responsible for the transversal lines at the glabellar area (Fig. 17).

The orbicularis oculi muscle pars palpebral originates from the medial palpebral ligament and adjacent bone on the medial side of the orbit. The orbital pars comes from a slip of bone adjacent to the orbit on the orbital process of the frontal bone to the frontal process of the maxilla, and to the medial palpebral ligament between the two bony areas (Figs. 2 and 18) and it joins the transversal nasal muscles. It is a circular muscle that acts as a sphincter. The lateral orbicular oculi pulls down the eyebrow.

The temporal muscle has two parts: superficial and deep. The superficial temporal originates

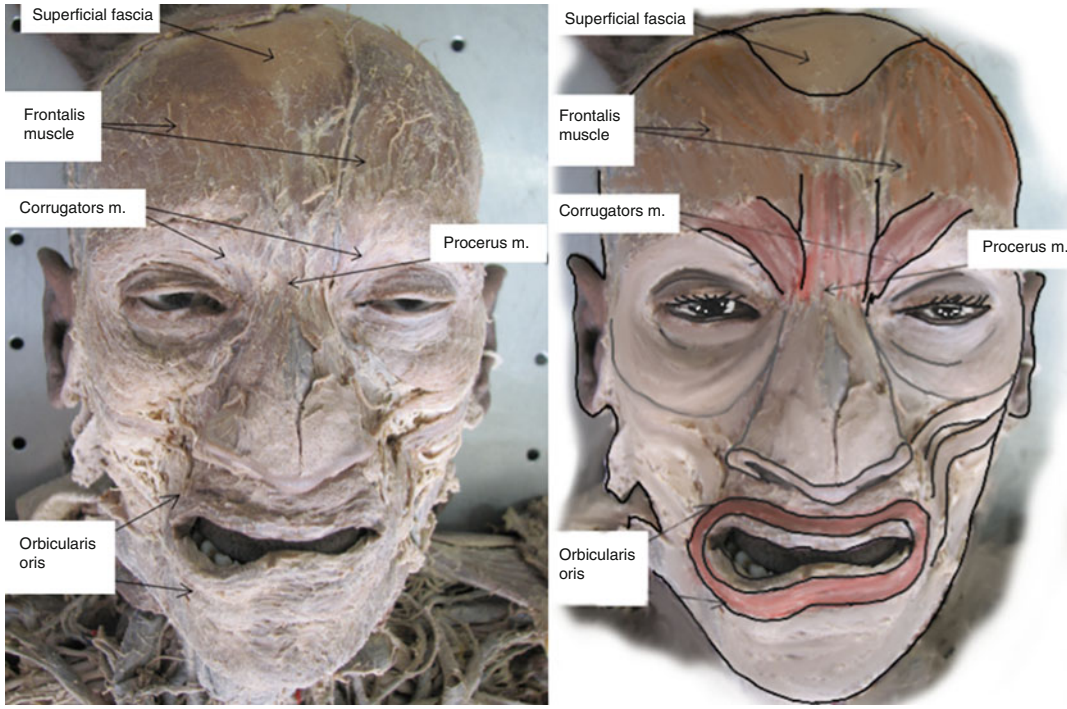

Fig. 17 Frontal superficial fascia and frontal, corrugators, procerus, and orbicularis oris muscles

from the fossa temporalis and the temporal fascia, and the deep temporal pars originates from the sphenoidal tubercle. It inserts at the margins of the medial side of the coronoid process and at the temporal crest of the mandibular. It elevates and contracts the mandible.

The medial and the lateral pterygoid muscle (superior and inferior branch) are located in the infratemporal region. The superior branch of the lateral pterygoid muscle originates from the lateral side of the lateral lamina of the pterygoid process and the infratemporal side of the major wing of the sphenoid bone and inserts at the capsule and the temporomandibular joint. The inferior branch of the lateral side of the lateral lamina of the pterygoid process, the pyramidal process of the palate bone, and the maxilla tuber insert at the pterygoid fovea. Their function is protracting, moving side to side, stabilizing the articular disc, and opening the mouth. The medial pterygoid muscle originates from the medial side of the lateral lamina of the pterygoid process, pterygoid fossa, pyramidal process of the palatine, and the maxilla tuber inserting to the medial side of the mandible, and its function is to elevate the mandible and act synergistically with the masseter muscle.

At the infraorbital, zygomatic and cheek region, we find the following muscles.

The orbicularis oculi muscle (pars inferior of the orbit), which closes the lids and squeezes them against the eyes and originates from the lacrimal bone, the frontal process of the maxilla and skin around the orbit. *The levator labii superioris and alae nasii* (Fig. 18) is responsible for the elevation of the upper lid, and the nasal alae also participates to dilate the nostrils and originates from the frontal process of the maxilla inserting at the superior nasal alae. The zygomaticus muscle pulls superiorly and posteriorly the upper lip, originates from the body of the zygomaticus bone, and inserts at the superior lip, and the zygomaticus major muscle (Fig. 18) pulls the angle of the mouth superiorly and posteriorly originating from the temporal process of the zygomaticus bone and inserting at the mouth angle (Haddock et al. 2009).

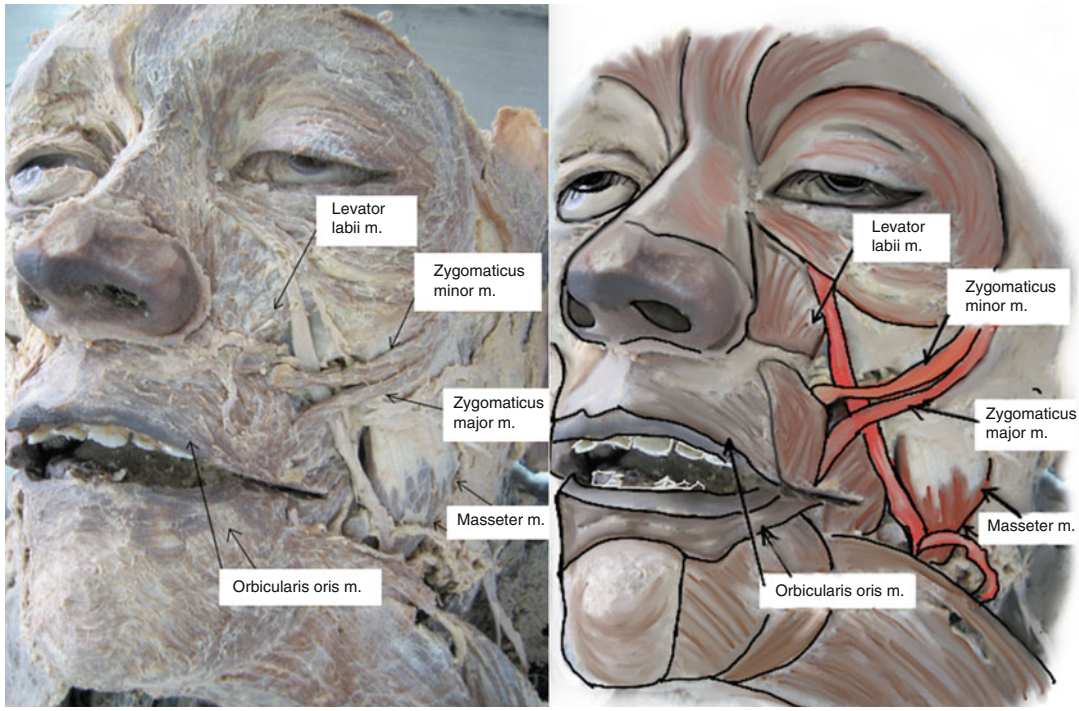

Fig. 18 The levator nasal alae and buccal angle muscle

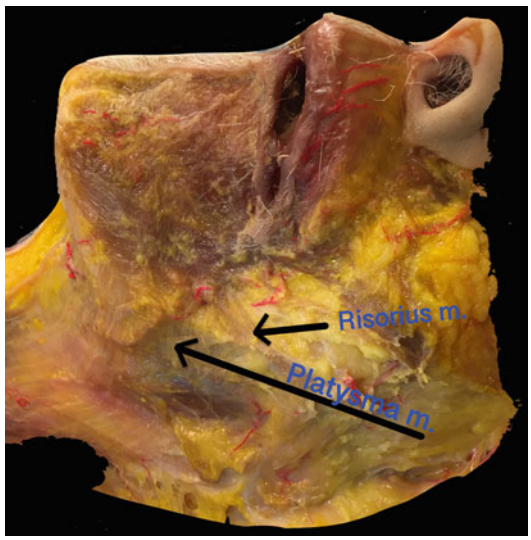

Fig. 19 Risorius and platysma muscles

The risorius muscle slightly pulls (Fig. 19) the angle of the mouth to a posterior position. It originates from the parotideomasseteric fascia and inserts at the angle of the mouth. The muscle that elevates the angle of the mouth is the levator anguli oris (Fig. 20). The platysma muscle stretches and pulls the neck skin and pulls laterally and posteriorly the angle of the mouth. The buccinator muscle emerges posteriorly in the pterigomandibular raphe, and it is responsible for pulling laterally and posteriorly the mouth angle and for keeping enough tension in the cheeks during mastication, suction, and whistling. It originates from the vestibular alveolar process of the maxilla at the molars, the maxillae tuber, pyramidal process of the palatine, pterygoid hamulus, pterigomandibular ligament, and the vestibular face of the alveolar process of the mandible at the molars area and inserts at the mouth angle. The bucinator muscle is located posteriorly in the buccal fat pad and extends anteriorly to fixate at the oral orbicularis. Finally, the masseter muscle (Figs. 17 and 20) at the parotideomasseteric area has a superficial and a deep portion. The superficial originates from the inferior border of the anterior two-thirds of the zygomaticus arch, and the deep pars originates from the internal surface

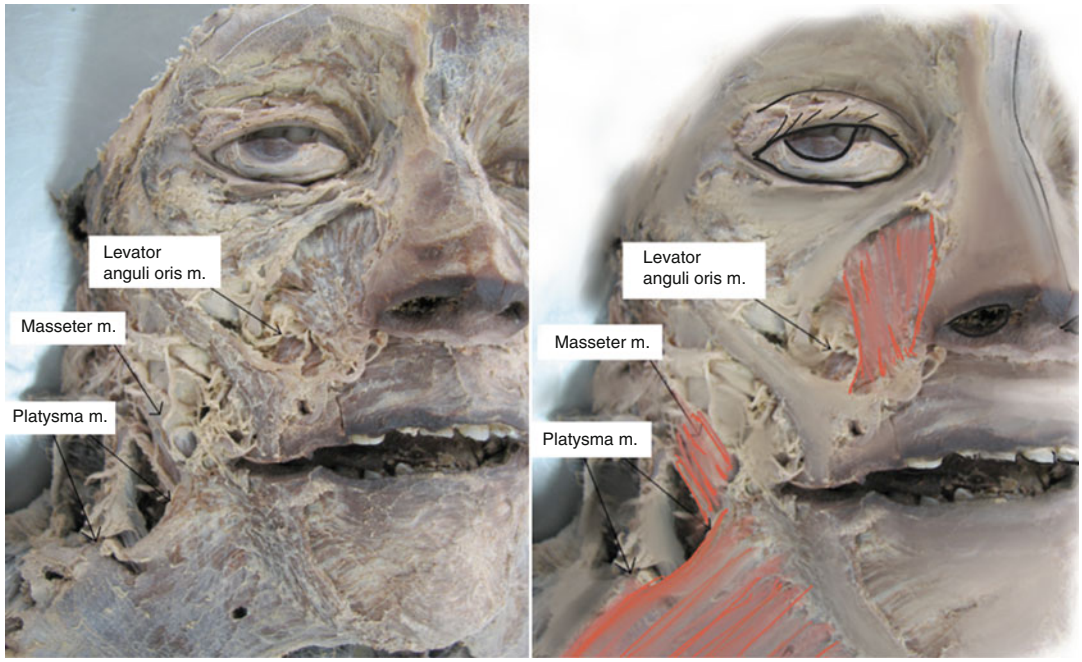

Fig. 20 Masseter and levator anguli oris muscle

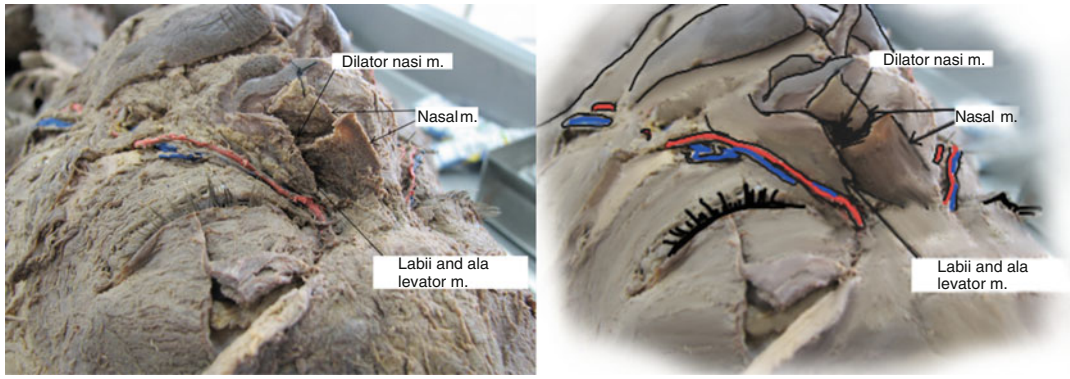

Fig. 21 Nasal and nasal dorsum transversal muscle

of the posterior third. It inserts at the lateral branch of the mandible and elevates the mandible.

At the nasal region, the nasal muscle inserts at the nasal alae, dilating the nostrils, and the transversal pars of the nasal dorsum compresses the nostrils (Fig. 21). The nasal septum depressor (Fig. 22) is the one that shortens the superior lip and depresses the tip of the nose with the smiling mimics.

At the lips area, the orbicularis oris (Figs. 17 and 22) lies very superficially around the buccal rim. It inserts at the skin and the lips mucosae acting as a sphincter, and with other local muscles intimately associated, it elevates, pulls down, and holds back the lips combining highly complex movements during its normal function. The incisor muscles are tiny muscular fascicles, and they are responsible to squeeze the lips against the teeth, projecting the lips anteriorly and closing them. The levator of the labial area includes from the medial to the lateral zone, the labia

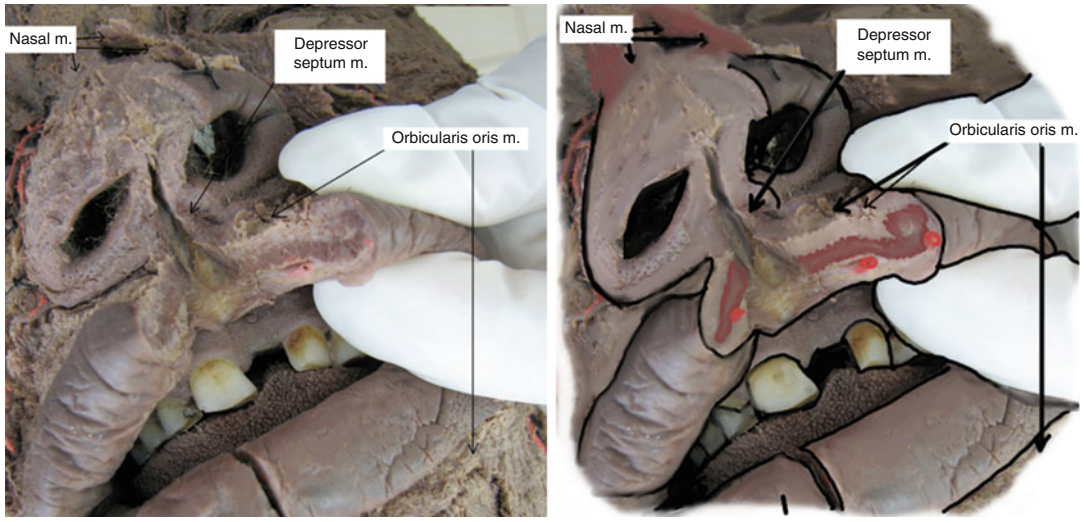

Fig. 22 Depressor nasal septum muscle

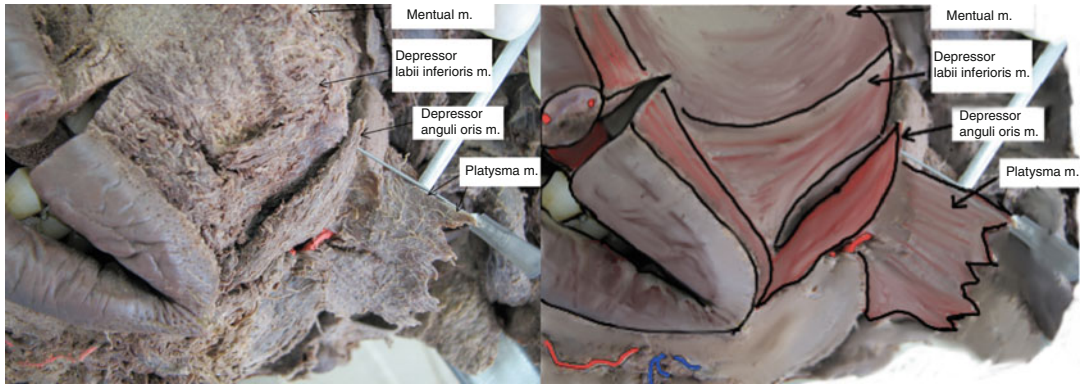

Fig. 23 Chin area muscles

superioris and the alae levator, the labia superioris levator, the major and minor zygomaticus, the risorius and the depressor, the anguli oris depressor, labia inferioris depressor, and the mentual muscle. The commissures are pulled down by the anguli oris depressor and platysma. The laxity of the SMAS at this area creates the so-called marionette lines during the aging process.

At the mental area, the depressor anguli oris originates from the basis of the mandible (first molar at the mental tubercle) and inserts at the mouth corner; the depressor labia inferioris originates from the mandible basis (superior to the origin of the anguli oris depressor) and inserts at the inferior lip. The mentual muscle originates from the mental fossa (superiorly to the mental tubercle) inserting to the chin, everts, and helps to pucker the inferior lip (Fig. 23). The mentual muscle contraction protrudes the inferior lip and originates below the central and lateral incisor inserting at the mental skin, wrinkling it.

Sensitive Innervation of the Face

The sensitive innervation of the face is a special target when leading with anesthetic blockage for surgery or fillers to avoid occlusive complications at the foramens when performing treatments with

implants (see chapter ▶ "Facial Nerve-Block Anesthesia in Cosmetic Dermatology").

Forehead

The forehead and the anterior portion of the scalp are innervated by the supratrochlear and supraorbital nerve (Figs. 24 and 25). The supraorbital nerve is responsible for the anterolateral portion of the forehead and the scalp's sensitive innervation. It emerges between the medial and central margin of the superior border of the orbit to the superior and lateral inner surface of the frontal and galea fascia.

Eyelids

The superior palpebrae and its conjunctiva are innervated by the ophthalmic nerve. The cornea, the ocular globe, and the dura mater of the

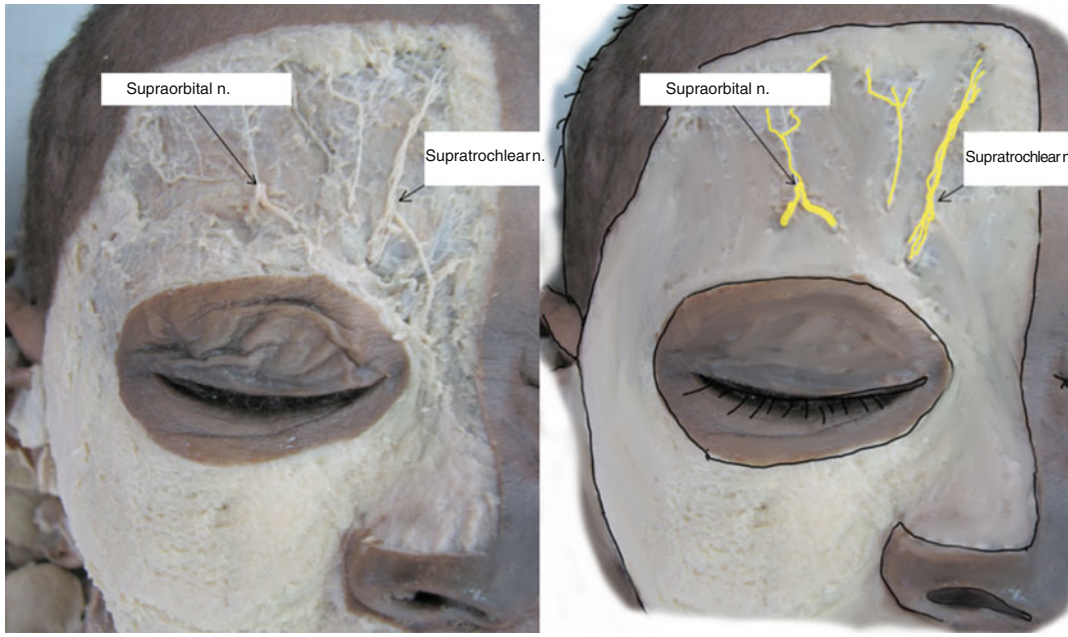

Fig. 24 Sensitive innervation of the frontal area

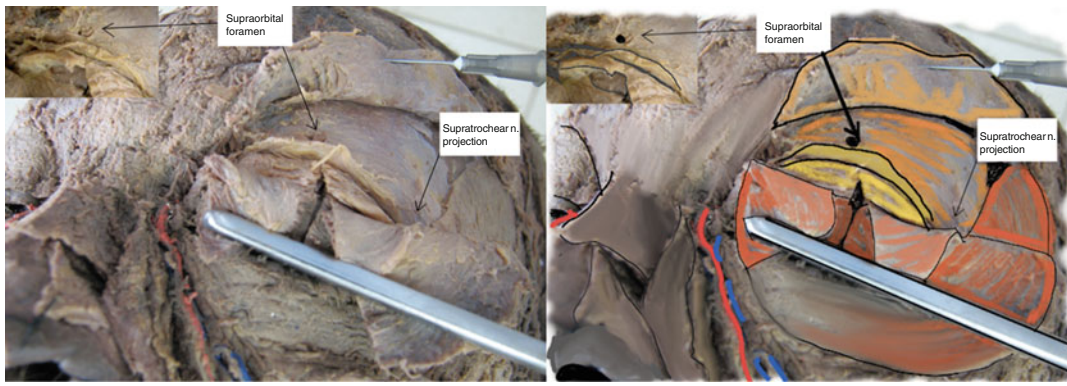

Fig. 25 Supraorbital foramen and the projection of the supratrochlear nerve

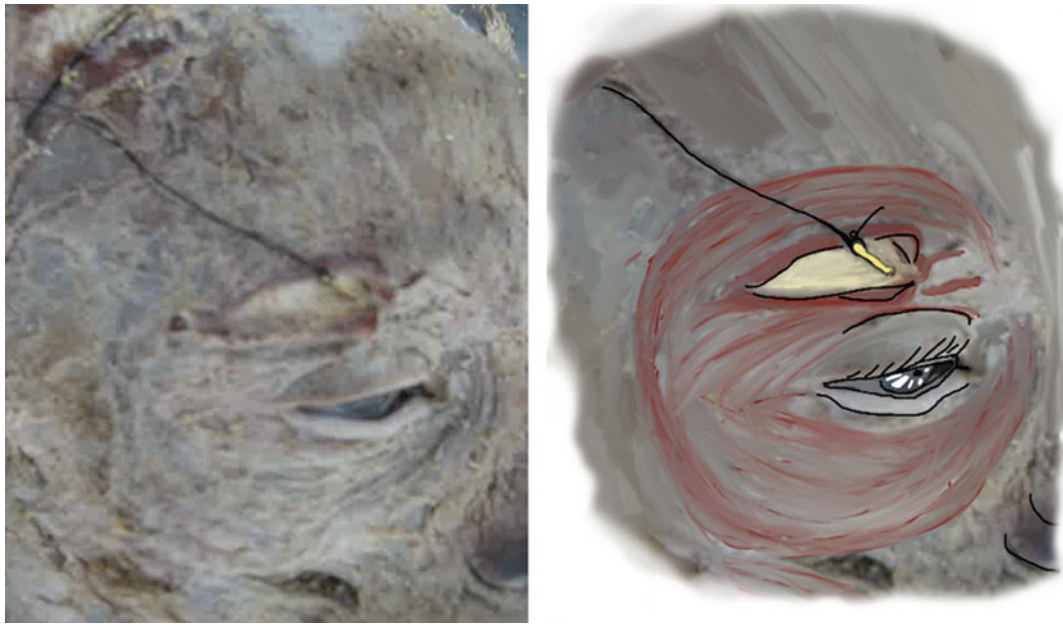

Fig. 26 The palpebral branch of the lacrimal nerve locates at the lateral superior orbital rim

cerebellar tent are innervated by the ciliary nerve and the frontal, ethmoidal, and sphenoidal sinus by the supraorbital and ethmoidal nerve. The lacrimal gland is innervated by the lacrimal nerve and its palpebral branch that is localized at the superior orbital rim (Fig. 26). The lateral areas of the inferior palpebrae and its conjunctiva, the lateral area, and the vestibule of the nose are innervated by the maxilla branch. The infraorbital nerve and its vascular branch emerge from the infraorbital foramen to innervate the skin and the inferior lid (Fig. 27).

Nose

The nasal area must be analyzed separately concerning sculpture with fillers. The nasal dorsum is innervated by the infratrochlear, dorsal nasal supraorbital, and anterior ethmoidal nerves. The septal mucosa and the superior area of the nose are innervated by the anterior ethmoidal nerve. The supratrochlear nerve (trigeminal branch) emerges from the orbit between the periosteum and the orbital septum at the medial supraorbital margin and innervates the medial and central area of the forehead and the nasal radix. The external nasal nerve is a branch of the anterior ethmoidal nerve (trigeminal nerve) and innervates the dorsum, apex, and the nostrils. The external nose is innervated by the infraorbital nerve (localized deeply through the central massif bone of the face) that has also a sensitive innervation of the maxilla area.

Auricle-Temporal, Cheek, Mandible, and Maxilla Areas

The auricle-temporal nerve originates from the mandibular branch of the trigeminal nerve directing posteriorly surrounding the meningeal media artery and then contouring the mandible neck to the temporal area in an ascendant trajectory crossing the temporomandibular joint, the auricle pinna, the external acoustic meatus, the tympanic membrane, and the parotid gland innervating the auricle-temporal, the mandible, and maxilla area. The great auricular nerve is at the cervical fascia, posteriorly to the mandible angle; the posterior auricular nerve that is a branch of the facial nerve, and innervates the external acoustic

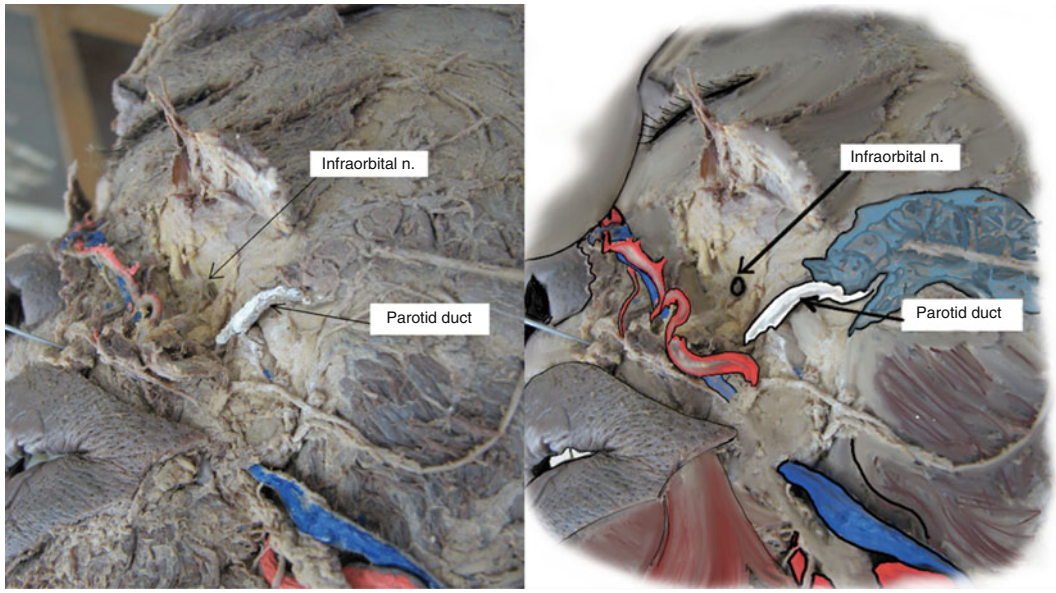

Fig. 27 Terminal branch of the infraorbital nerve and vessels emerging from the infraorbital foramen to innervate the inferior lid and the local skin

meatus skin and the ear pavilion. The magnum auricular nerve innervates the skin of the parotid gland. The nerve of the tympanic cord is a branch of the facial nerve that originates from this area through the petro-tympanic cleft. The zygomaticus-facial nerve (branch of the trigeminal nerve) that externalizes through the foramen of the same name, innervates the skin of the zygomatic area, and finally, the mandibular branch of the facial nerve that crosses the medial and anterior portion of the mandible. This nerve is localized most of the times at the angle of the mandible at the medium lateral zone. The pterygopalatine and nasopalatine nerves complete the maxilla area. The nerve that is responsible for the parasympathetic innervation of the parotid gland is the optic ganglion localized at the medial area of the mandibular nerve branch near the oval foramen (Goldberg 2009; Altruda Filho et al. 2005; Gardner et al. 1978; Tamura 2010a, b).

Buccal Area

At the buccal area, we need to take into account not only the buccal area, the peribuccal, and the cheek, but also the internal area of the mouth and the alveolus as they are intimately related. The buccal nerve is one of the branches of the mandibular nerve of the trigeminal nerve that crosses the adipose body of the cheek after crossing the infratemporal fossa. It is responsible for the mucosal, cheek skin, and the inferior vestibular molar mucosa sensitivity.

The terminal branches (labia superioris) of the infraorbital nerve are responsible for the superior labial skin and mucosa and the mentum (they emerge from the mental foramen below the second inferior premolar) through the skin and the inferior labia mucosa and the chin region. The mandibular branch has sensitive (sensorial branch) and motor (motor branch) functions. The mucosa, the inferior lip's skin, the mentum, the anterior portion of the tongue, and the mouth floor are innervated by the mentum and tongue nerve. The buccal mucosa and the skin of the cheeks are innervated by the buccal and auricle temporal nerve.

The superior incisor, maxillary sinus, nasal cavity, and the gingiva are innervated by the alveolar superior medial branch. The inferior alveolar branch innervates the molar tooth, the gingiva of

the superior molar area, the buccal mucosa, and the maxilla sinus. The inferior alveolar nerve originates from the mandible nerve and continues next to the deep layer of the lateral pterygoid muscle than between the medial and lateral pterygoid muscle, directs inferiorly through the medial face of the mandible branch penetrating the mandible foramen, crosses the mandible canal, and emits dental branches to the molars and inferior premolars. At the mental level, it originates the mental nerve (Fig. 11) (innervates the soft tissue of the mentum, the mandible, the inferior labia, vestibular gingiva of the incisors, canines, and inferior premolars) and the incisor nerve (innervates the incisors, canines, and their respective periodontium). It directs anteriorly, inferiorly, and medially to the inferior alveolar nerve and its fibers go with the tongue nerve and distribute with it. It provides afferent fibers to the taste buds at the anterior two-thirds of the tongue and efferent visceral parasympathetic fibers to the submandibular, sublingual, and tongue glands.

The tongue nerve originates from the mandible nerve, locates anterior and medial to the inferior alveolar nerve, and crosses between the medial and lateral pterygoid. At the posterior extremity of the milo-hyoid line, the tongue nerve directs to the oral cavity. This nerve is responsible for the general sensibility of the anterior two-thirds of the tongue, sublingual mucosa, and lingual gingiva of the inferior teeth of the submandible and sublingual glands.

Motor Innervation (Facial Nerve)

The origin of the motor nerves of the face is the facial nerve and its branches. When we inject fillers at the pretragus area, it is important to remember that at the deep layer of the subcutaneous, the injection must be very delicate and slow, avoiding inserting the needle numerous times at the same place. In addition, we must prevent high local volume injection to avoid pressure paresthesia.

The temporal nerve (Fig. 27) leaves the parotid and crosses the zygomaticus arch (intermediate portion) where it becomes superficial and susceptible to trauma or irreversible lesions in minimally invasive procedures. It does innervate the eyebrows, the frontal area, the eyelid, anterior and superior auricular muscle, and the frontal venter of the epicranius muscle. The safest layer for dissection or invasive procedures is at the subcutaneous or deep temporal fascia. The anterior and posterior temporal nerve are responsible for the motor innervation of the temporal and the posterior muscle captures the proprioception or the temporomandibular capsule of its joint.

The frontal branches of the facial nerve are localized in the temporoparietal fascia, at the medium portion of the zygomaticus arch. It is responsible for the motor innervation of the frontalis, corrugators, procerus, and the cephalic portion of the orbicularis oculi muscles.

The infratemporal area nerves are the masseteric, the deep temporal, the buccal, the inferior alveolar, the lingual, the auricle-temporal, the tympanic chord, and the optic ganglion. The mandibular nerve originates the buccal, and it directs laterally between the lateral pterygoid muscle fibers and continues anther-posteriorly and medially to the deep temporal muscle fibers. It runs across the adipose body of the cheek and distributes its fibers to the skin and mucosa of the cheek and the vestibular gingiva of the inferior molars (sometimes of the superior molars). The inferior alveolar nerve goes down passing near the deep area of the lateral pterygoid muscle and then between the medial and lateral muscles. It directs inferiorly through the medial region of the mandible branch, enters into the mandible foramen, crosses the mandible channel, and subdivides in dental branch for the molars and inferior premolars. When overcoming the mental foramen, it originates the mental nerve (innervates the soft tissues of the chin and the inferior lips, vestibular gingiva of the incisors, canines, and inferior premolars) and the incisor nerve (innervates the incisors, canines, and their respective periodontium) (Altruda Filho et al. 2005).

The zygomaticus and buccal branches of the facial nerve are localized at the medial and most superficial part of the cheek. The zygomaticus

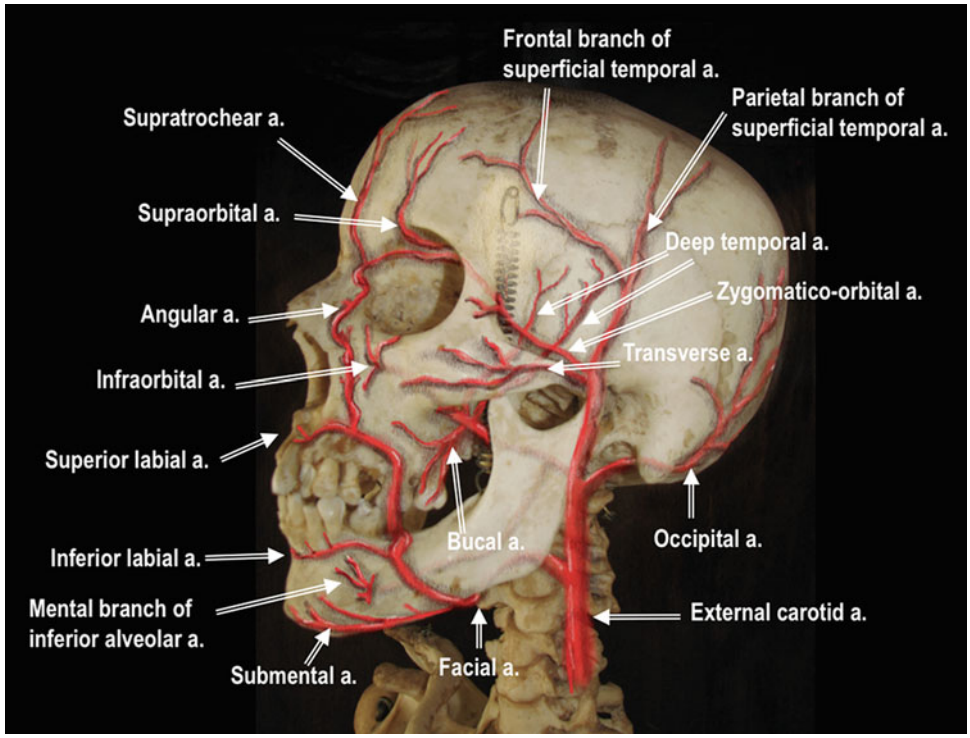

Fig. 28 Vascularization of the temporal, zygomaticus, and mandibular area

innervates the inferior bundle of the orbicularis oculi and the buccal nerve (Fig. 28), and is responsible for the nasal area through the levator labia superioris and the nasal, procerus, risorius, bucinator, superior portion of the mouth orbicularis, and the nasal pars alar and transversal muscle. This nerve passes more superficially at the zygomaticus arch and we need to inject fillers very delicately and every time we inject a greater amount. We need to observe and take into account paresthesia complaints to avoid complications.

The motor nerves at the parotideomasseteric area are the terminal branch of the facial nerve and are originated from the intra parotid plexus (temporal, zygomaticus, buccal, mandible marginal, and cervical branch); the posterior auricular nerve innerves the occipital venter of the occipital-frontal and auricular posterior branch, the stylohyoid innervates the stylohyoid muscle, and finally the digastric branch innervates the posterior venter of the digastric muscle.

The pterygopalatine nerves that should be remembered are the infraorbital, the zygomaticus, posterior superior alveolar, pterygopalatine, nasopalatine, and the pterygopalatine ganglion. The buccal branch is the motor nerve for the superior lip and the marginal of the mandible for the inferior lips and are considered to be at high risk for traumas and complications in slim patients. The sensitive innervation of the superior lip depends upon the infraorbital nerve and the inferior lip on the mental nerve, emerging from the infraorbital and mental foramen. The buccal branch is responsible for the motor innervation of the mouth orbicularis, and the muscle that acts around the mouth is innervated by the buccal branch and the marginal of the mandible (Figs. 27 and 28). Therefore, we need to be careful and delicate when products are injected around 2 cm lateral to the buccal angle where the nerve becomes a little superficial, exposed, and is susceptible to traumas (Gardner et al. 1978).

The mandible marginal nerve (origin of the facial nerve) is responsible for the motor innervation of this area and crosses the parotideomasseteric and the cheek area. The superficial

mandible marginal nerve is deeper to the platysma and is located around 1–2 or 4 cm below the inferior border of the mandible, but as it reaches the mouth, directs superficially and enters at the depressor muscle. This muscle trauma leads to incapability to depress the mouth, the buccal branch until the bucinator muscle, and the damage of the branch that ends at the orbicularis muscle leads to incapability to elevate the mouth angle.

Facial Vasculature (Altruda Filho et al. 2005; Gardner et al. 1978; Tamura 2010a, b)

The external carotid is responsible for facial irrigation, and its main branches are the thyroid, lingual, facial, occipital, posterior auricular artery, maxilla, and superficial temporal artery (Fig. 29).

From these, the one that we study mostly is the facial artery and its branches but the most important issue will be discussed below. The trajectory of this artery extends from the external mandible surface under the platysma until the medial angle of the eye. The facial artery crosses the bucinator and maxilla muscle, deeply to the zygomaticus major and the levator labia superioris. The facial artery divides into lips and lateral side of the nostrils branches. The angular artery is part of the facial artery that runs along the nose until the medial angle of the eye to irrigate the lids.

The largest branch of the external carotid is the maxilla artery that divides into three branches: the deep auricular with branches for the external acoustic meatus; the tympanic for the tympanic membrane; and the meningea alveolaris to the gingiva and teeth. The second part with the masseteric, deep temporal, pterygoid, and buccal branches. The branches for the third part are the superior-posterior; superior media alveolar arteries; infraorbital; descendant palatine; pterygoid channel; and pharyngeal and sphenopalatine arteries.

The superficial temporal artery is a terminal branch of the external carotid and originates

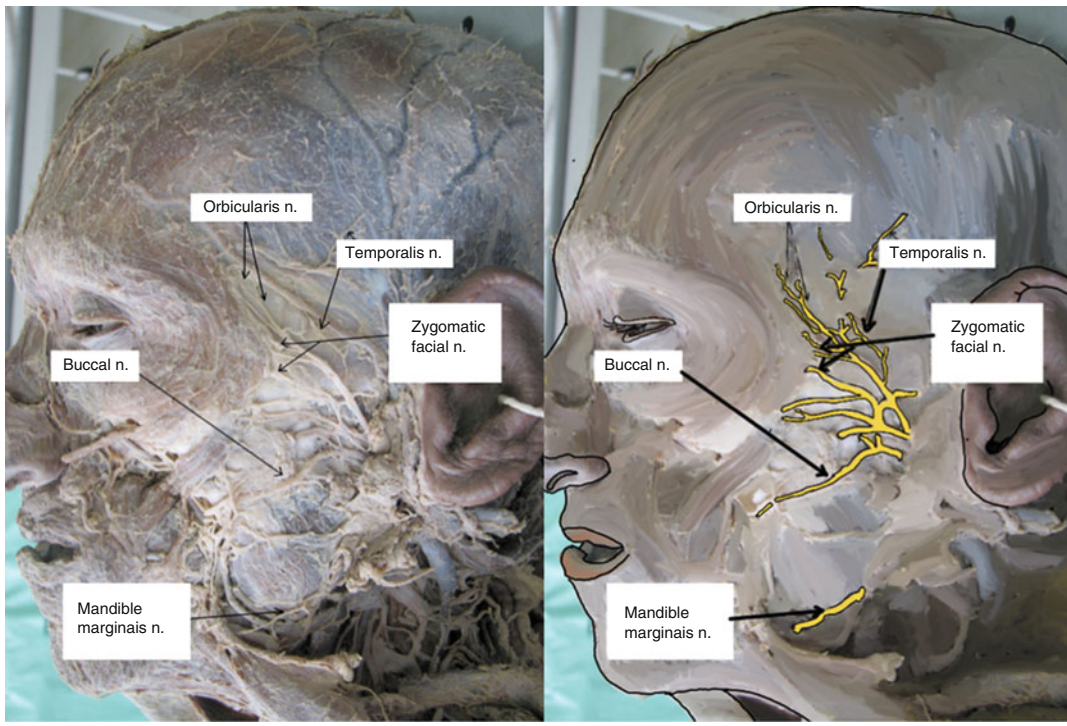

Fig. 29 Branches of facial nerve

at the parotid gland, runs up to a superficial layer to the posterior part of the zygomaticus process of the temporalis bone until the mandible cleavage. It continues upward and crosses anteriorly to the external acoustic pore 2–3 cm above the zygomaticus arch. It irrigates the temporal, frontal, parietal, the duct, and the parotid gland through the branches with the same name, respectively. At the temporal area, the main vein is the superficial temporalis that drains the temporal, frontal, and parietal areas. The lateral and medial pterygoids muscles are nourished by the pterygoid branches of the posterior deep temporalis. The main vein of this region is the retromandibular (maxilla and superficial temporalis vein) that are located near the mandible cleavage going downward into the parotid gland. At the temporal zone, the veins are a tributary of the pterygoid plexus.

The infratemporal area is irrigated by the following arteries: middle meningeal; deep anterior and posterior temporalis; superior, posterior, and inferior alveolar; infraorbital; masseteric; mylohyoid; buccal and lingual arteries. The middle meningeal irrigates the dura mater and the adjacent bone and the superior posterior alveolar artery penetrates into the tuber of the maxilla through the alveolar foramen; it irrigates the molars and superior premolars teeth through the dental branches and the alveolar process, periodontium, and vestibular gingiva through the periodontal branches. The inferior originates from the same region of the middle meningeal artery but directs to the mandibular foramen and before penetrating into the mandible channel ramifies in mylohyoid artery that irrigates the mylohyoid muscles and the anterior venter of the digastric muscle. The infraorbital artery originates from the pterygoid maxilla cleft (near the maxilla tuber) penetrating the orbit toward the face through the infraorbital foramen and the terminal branches irrigate the soft tissue of the medium third of the face (inferior lid); the external nose and the superior lid. The masseteric artery originates from the lateral pterygoid muscle area passing laterally through the mandibular notch irrigating the masseteric muscle and the capsule of the temporomandibular joint.

The buccal artery originates near the deep temporal anterior artery, follows a lateral inferior direction to the jugal area, irrigating the cheek and the bucinator muscle. The lingual artery (originates from the external carotid) directs to the hyoglossus muscle to ramify and irrigate the tongue muscles, the post sulcus part of the dorsum of the tongue, the floor of the mouth, and the sublingual gland. The veins of the infratemporal area form the pterygoid venous plexus that receive the blood from the deep face draining to the maxillary veins.

The supraorbital artery (Fig. 30) is a terminal branch of the ophthalmic artery that originates from the internal carotid artery. At the infraorbital, zygomatic, and cheek the lacrimal artery exteriorizes at the lateral region of the orbit and anastomoses with the transversal facial artery (first branch of the superficial temporal artery). The transversal facial artery originates from the superficial temporal before emerging from the parotid gland and crosses the face superficially to the masseter muscle and divides into several branches that irrigate the parotid gland, its duct, the masseter duct, and the facial skin. There are also terminal branches of the infraorbital artery (inferior palpebral, superior labial, and nasal) that originates from the infraorbital foramen. The branches of the facial, buccal, and alveolar superior and posterior are also important for the irrigation of this area. The tributary veins of the facial, superficial temporal and pterygoid, and the superior-external part of the maxilla area have a deep venous complex that must be avoided when the patient is treated with fillers.

At the parotideomasseteric area, the main artery is the external carotid that directs upward between the styloglossus and the stylohyoid muscles and penetrates in the parotid gland. Its terminal branch is the temporal artery penetrating at the parotid gland.

The facial artery is basically the main artery that irrigates the labial and nasal area. The facial arteries are extremely tortuous and the techniques for injecting fillers in various layers and directions to get natural lips volume leads to a predicable arterial perforation with much more hematomas and ecchymosis as adverse events. The angular

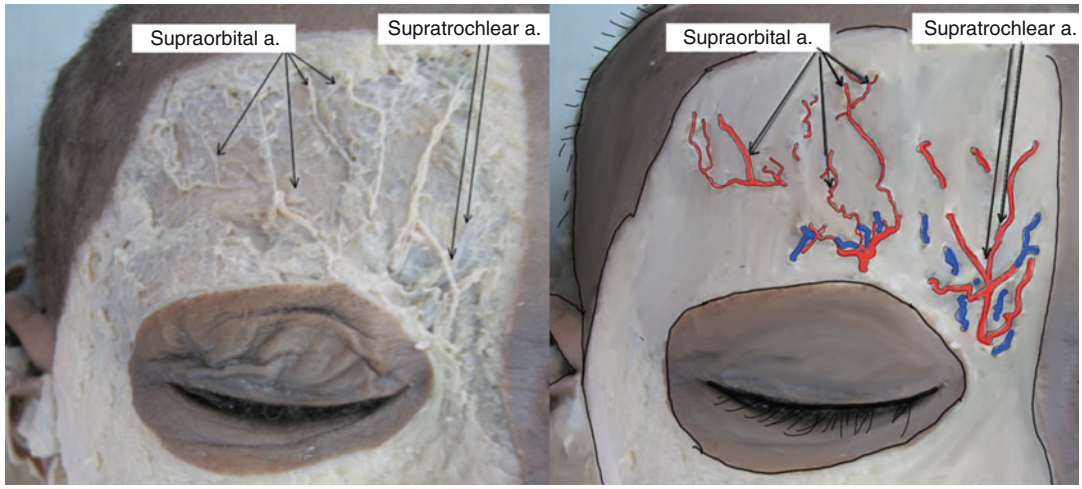

Fig. 30 Vascularization of the frontal area

artery is a terminal branch of the facial artery that irrigates the lateral area of the dorsum near the radix of the nose crossing the levator labii superioris and the nostrils, and because of the characteristics and extension of the nourished area, it has importance when we consider the consequences of its occlusion due to injection, spasms, or compression leading to necrosis and ischemia. The branch of the columella and the nasal lateral branch irrigate the nostril, the dorsum, and the apex of the nose (tip of the nose). The dorsal nasal artery (irrigates the radix and nasal nostrils, and one of its branches that unites with the angular artery at the nasal radix and the other goes down for the external nasal anastomosis) is the branch of the infraorbital branch. The nasal lateral veins are at 2–3 mm over the alar sulcus, and with the columella artery emerge deeply at the nasal basis and end at the tip of the sub dermic plexus. They are tributaries of the angular vein that drains the external nose.

The arteries that irrigate the lips are the superior and inferior labia artery (branches of the facial artery), and they anastomose with the opposite side forming an arterial circle around the buccal rim.

At the mental area, the most important arteries are the submental and the mental. The submental originates at the facial artery at the submandibular area; passes through the mandible basis until the chin; and irrigates the mylohyoid muscle, the anterior venter of the digastric artery and the adjacent structures. The chin is also irrigated by the mental artery that is a branch of the inferior alveolar artery that emerges through the mental foramen. The venous drainage corresponds to the arterial supply. The mandible is irrigated by the facial and alveolar inferior artery (Sykes 2015).

About the Retinal Blood Supply

The central retina artery is a branch of the ophthalmic artery, and the major origin is the internal carotid artery. The central artery passes through the optical nerve and disc dividing into temporal superior and inferior branch and nasal superior and inferior branch. Although having anastomoses between the ciliary arteries, the branches described anteriorly should not have anastomoses between them or other arteries; thus, are considered terminal arteries (without any anastomoses between arterioles and venules) and connection between them occurs only through the capillary system, and the central artery occlusion results in amaurosis. The retina veins run with the arteries and drain at the cavernous sinus (Figs. 31 and 32). Some interesting reports try to explain the central artery occlusion's etiopathogeny after fillers injections in the glabellar area, and there are several reports of amaurosis after fillers injections due to the reversal

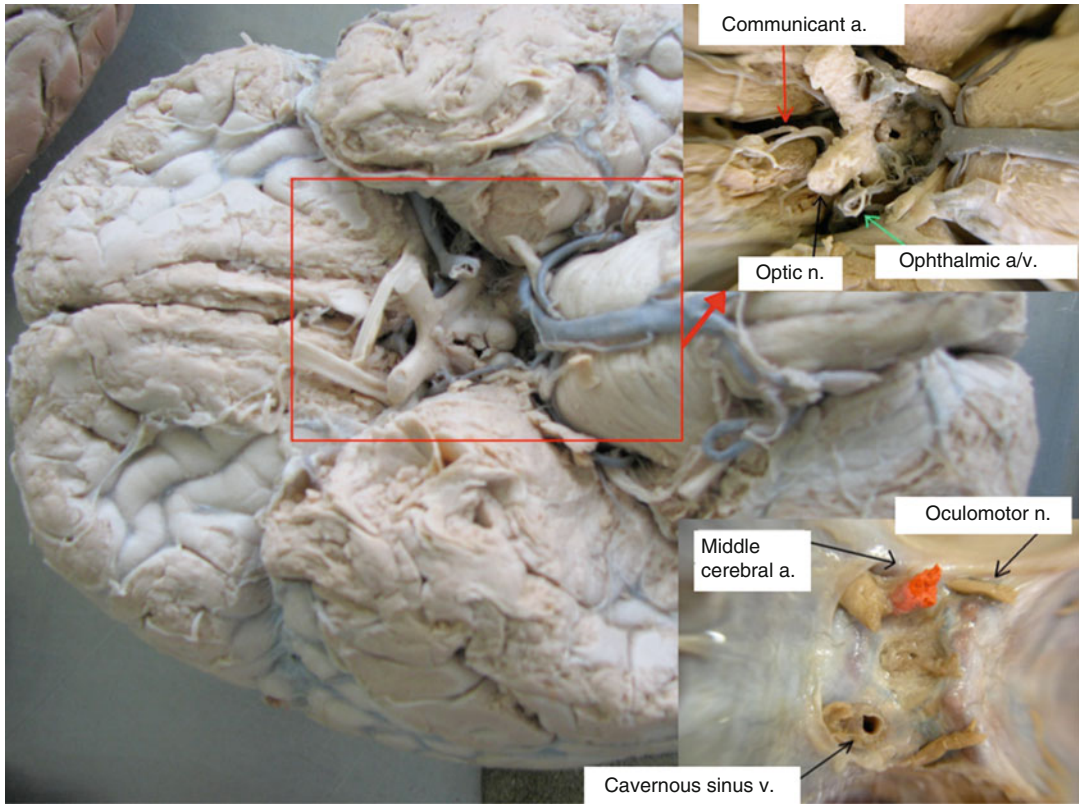

Fig. 31 Intimal relationship from the ophthalmic and the middle cerebral artery

influx, and anastomosis between internal and external carotid arteries supporting this terrible complication. According to Arletti and Trotter (2008), we could understand that fillers injection technique must be reviewed and it justifies the reason for so many reports of vascular occlusion and necrosis. Fig. 33 shows that the 27G needle is far thicker than the dermis between the cheek and the nostril. It is crucial to understand that the dermis thickness varies between patients and also different areas of the face. Fig. 34 shows the frontal dermis thickness of one patient that can also vary depending upon the age, photodamage, and ethnicity, and we must be aware of this to improve our techniques and minimize arterial occlusion risk.

The retina central artery is a branch of the internal carotid artery and any thrombi might lead to blindness after an intra-arterial fillers injection at the periocular area. The palpebral veins drain to the angular (Fig. 34), ophthalmic, and superficial temporal veins. The angular and ophthalmic veins anastomosis drains the blood from the medial palpebral area skin and lateral nasal to the cavernous sinus where intracranial infection might occur (Alam and Dover 2007; Alam et al. 2008; Glogau and Kane 2008; Goldberg 2009; Hirsch and Stier 2008).

There are also reports about possible anastomoses between the internal and external carotid at the intranasal area leading to amaurosis, for example, the ophthalmic area, but there are still issues to be understood about the vascular irrigation of the face and occlusion after implant injections.

Lymphatic System

The lymphatic drainage of the face occurs in a posterior and inferior direction. The medial area (including the upper and lower lips) drains to the facial, submental (including central area of

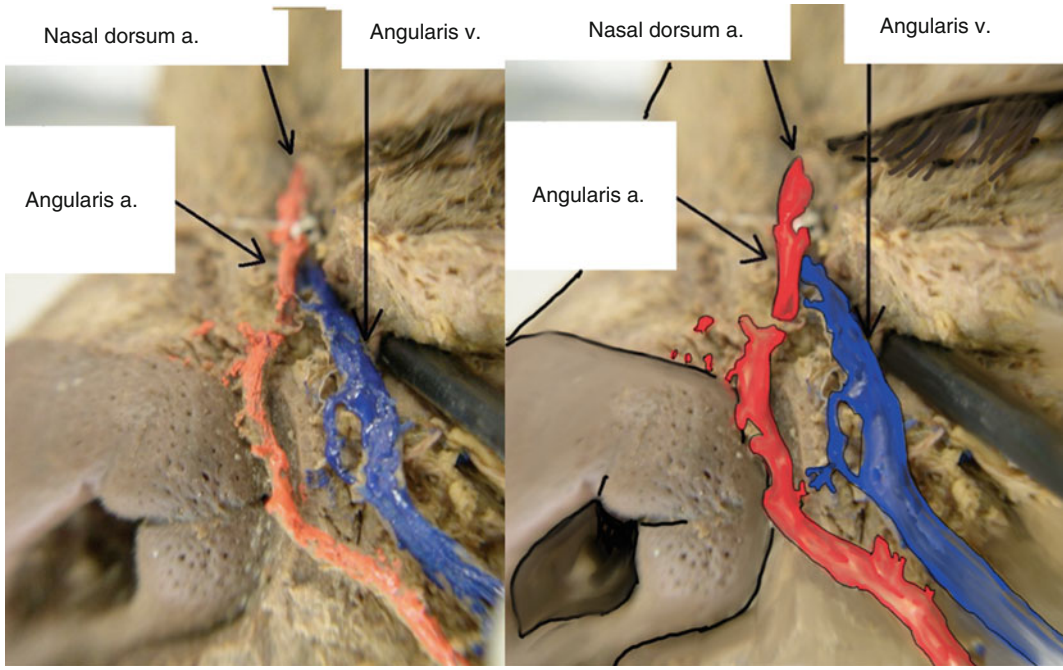

Fig. 32 Angular artery and vein and the nasal dorsum artery

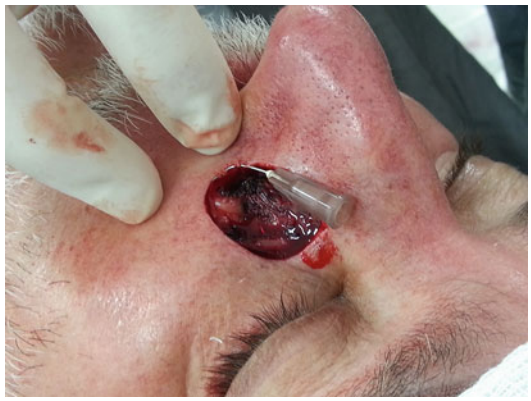

Fig. 33 27G needle is thicker than the dermis itself located between the cheek and the nostril

the lower lip), and submandible lymph nodes; the lateral area of the face, frontal area, and the scalp to a diagonal line (infraorbital, zygomatic and cheeks areas) to the parotid lymph nodes.

In our practice, the periocular area frequently leads to a drainage complication. Botulinum injections with too many units or advanced extra injections might lead to a "puffy" eyes. If we add fillers, sometimes with excessive volume to correct the upper lid hollow or the inner (and/or lateral) palpebral malar sulcus might evolve into not only puffy eyes but long-term edema of the eyelids. Combining both, botulinum toxin and fillers, this adverse event might be frequent, as the palpebral lymphatic system is very delicate and not prepared to undergo trauma or procedures. The muscular contraction at this area is key for a proper local drainage and an excessive relaxation of the orbicularis oculi muscle surely leads to its deficiency. The implant pressure at the palpebral sulcus also presses or occludes the palpebral, very sensitive and delicate lymph ductal system. Although the lymphatic drainage is usually described as the ocular region as a whole, it should be divided into a medial and a lateral direction outflow. To do an efficient manual drainage with the aim of minimizing the local edema, we should strum the infraorbital area from the medial to the nasal direction and from the lateral to the preauricular area.

The lymphatic vessels of the infratemporal area drain to the deep superior cervical lymph nodes. The parietal and occipital area of the scalp drain into the parotid lymph nodes anteriorly

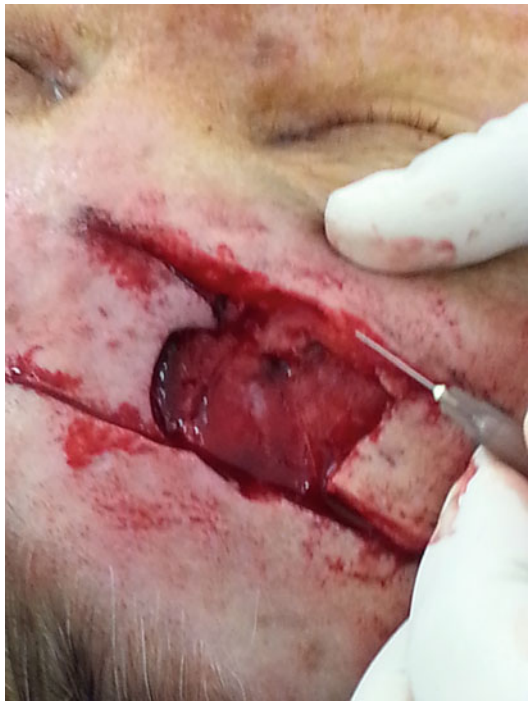

Fig. 34 This photo shows the frontal dermis thickness of a patient that might vary drastically between patients

and retroauricular lymph nodes posteriorly. The occipital area drains into the occipital area lymph nodes and the cervical nodes filters the lymph node between the face and neck, scalp, and mucosa. At the pterygopalatine area, lymphatic drainage occurs basically in the retropharyngeal and deep-superior cervical lymph nodes.

Take Home Messages

- The vessels, especially at glabellar, ocular, nasal areas, and the terminal arteries, must be avoided due to various reports of arterial occlusion, ischemia, and even embolus, leading to severe complications.
- The thickness of the dermis at the nasolabial fold is below 2 mm, and taking into account the bevel and the diameter of the needle, we could understand that fillers injection technique must be reviewed.
- Most of the fillers are injected below the dermis and not intradermally, at the level of the artery, justifying the onset of the many vascular occlusions and necrosis reported in the literature.
- The facial arteries are extremely tortuous, and the techniques for injecting fillers in various layers and directions to get natural lips volume leads to a predictable arterial perforation with much more chances of resulting in hematomas and ecchymosis.
- The angular artery is a terminal branch of the facial artery that irrigates the lateral area of the dorsum near the radix of the nose crossing the levator labii superioris and the nostril muscle of the nose. Because of the angular artery characteristics and extension of the nourished area, we need to consider the terrible consequences of its occlusion due to injection leading to necrosis, ischemia, and scars.
- Botulinum injections with too many units or advanced extra injections might lead to "puffy" eyes. Sometimes, when we add fillers with excessive volume to correct the upper lid hollow or the inner (and/or lateral) palpebral malar sulcus, it might result in not only puffy eyes but long-term edema of the eyelids.

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Facial Nerve-Block Anesthesia in Cosmetic Dermatology

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_17

Abstract

Sensory neural blockade of the face with local anesthetics is an important part of the management of cosmetic procedures, but it is not usually considered a simple approach. The facial sensory innervation is provided mainly by the trigeminal nerve, the largest and the most complex cranial nerve. The peripheral branches of the trigeminal nerve that may be accessible through percutaneous needle techniques are the supraorbital, supratrochlear, nasociliary, infraorbital, and mental branches. In addition to indications for general surgical anesthesia and treatment of painful clinical conditions, the local anesthetic blockade of the trigeminal nerve branches can be used to produce more patient tolerance on painful esthetics procedures, such as facial deep chemical *peelings*, laser, fillers, microneedling, and dermabrasion.

The main purpose of this chapter is to describe the techniques of blockade of the trigeminal nerve branches with local anesthetics by means of practical approaches, including relevant anatomical landmarks, possible complications and unwanted side effects.

Keywords

Neural blockade of the face · Trigeminal nerve · Trigeminal nerve branches block · Supraorbital nerve · Supraorbital nerve block · Supratrochlear nerve · Supratrochlear nerve block · Infraorbital nerve · Infraorbital nerve block · Nasociliary nerve · Nasociliary nerve block · Infratrochlear nerve · Infratrochlear nerve block · Mental nerve · Mental nerve block

Introduction

The local blockade of the trigeminal nerve branches is widely used for surgical procedures, such as excision of malignant skin tumors and blepharoplasty. Furthermore, it can be used clinically, for example, for the treatment of trigeminal neuralgia, cluster headache, and acute cancer pain (Waldman 2015).

With the advancement in cosmetic dermatology, anesthetic blockade of the trigeminal nerve branches became an interesting tool on the management of painful comestical procedures, such as facial deep chemical *peelings*, ablative laser, fillers, microneedling, and dermabrasion.

Depending on the area of the face involved in the cosmetic procedure, we need to block one or more branches of the trigeminal nerve. Thus, procedures in the forehead require blockade of the supraorbital and supratrochlear nerves. Approaches only in the nasal region, such as *peelings*, need blockade of the nasociliary and infraorbital nerves. Procedures involving the periorbital and nasal regions need blockade of the supraorbital, supratrochlear, nasociliary, and infraorbital branches. Approaches only in the perioral region require blockade of the infraorbital and mental nerves.

In behalf of the safety of the procedure, an inquest should be performed, focusing on identifying coagulation disorders and allergies, as well as a minute physical examination of the face. The contraindications to the anesthetic blockade of the face are local infection, vascular tumors, or malignant skin tumors at the local of the injection and important behavioral abnormalities. Coagulopathy is a relative contraindication. Drugs, such as acetylsalicylic acid and warfarin, shouldn't be suspended, but they require a careful local compression after the procedure to avoid hematoma and ecchymosis (Waldman 2015).

Facial Sensory Innervation and Anatomical Landmarks

The sensory innervation of the face is determined mainly by the trigeminal nerve (cranial nerve V), the largest and the most complex cranial nerve. It contains motor and sensory fibers. The nerve carries somatic afferent impulses of touch, pain, thermal sensation, and proprioception from the skin of the face, scalp, oral and nasal mucosa, teeth, paranasal sinuses, muscles of mastication, and temporomandibular joint. Furthermore, visceral efferent fibers reach a variety of muscles of facial expression, some muscles of mastication, and the tensor tympani. The trigeminal nerve also

establishes communication with the autonomic nervous system, including the optic, sphenopalatine, ciliary, and submaxillary ganglia and the facial, oculomotor, and glossopharyngeal nerves. Because of the complex structure of the trigeminal nerve, a good understanding of the clinically anatomical landmarks is important to obtaining satisfactory results of neural blockade (Larrabee et al. 2004; Waldman 2015).

The trigeminal nerve binds to the lateral side of the pons by motor and sensory roots in an area called cerebellopontine angle. The sensory root expands into the trigeminal ganglion (also called gasserian ganglion, or semilunar ganglion, or Gasser's ganglion) which gives rise to three major divisions of the trigeminal nerve: ophthalmic division (V1), maxillary division (V2), and mandibular division (V3). Each division of the trigeminal nerve corresponds approximately to the three embryologic processes of the face: the frontonasal, the maxillary, and the mandibular processes. The motor root also contains afferent fibers of the muscles of mastication, joins the mandibular division. These roots cross the posterior cranial fossa in a forward and lateral direction, passing by the border of the petrous temporal bone, and reach a recess called Meckel's cave, which is formed by an invagination of the surrounding dura mater into the middle cranial fossa (Gardner et al. 1988; Waldman 2015).

The ophthalmic division of the trigeminal nerve (V1) is divided, nearby the superior orbital fissure, into three nerves: frontal nerve, nasociliary nerve, and lacrimal nerve. These three nerves enter the orbit via the superior orbital fissure where originate its branches. The frontal nerve enters the orbit passing ventrally under the periosteum of the roof of the orbit, and, at an extremely variable point inside the orbit, originates two branches, the supraorbital and the supratrochlear nerves. The supraorbital nerve, laterally situated in relation to the supratrochlear nerve, exits the orbital cavity anteriorly via superior orbital foramen and supplies sensation to the upper eyelid, the forehead, the anterior scalp, and frontal sinus. The supratrochlear nerve, so minor branch, leaves the orbit at a medial extremity of the supraorbital border and aides the innervation of the forehead (inferomedial section) and medial portion of the upper eyelid. The lacrimal nerve provides innervation to the lacrimal gland and the portion of the skin and the conjunctiva of the upper eyelid. At last, the nasociliary nerve is the sensory nerve of the eye. Furthermore, the terminal branches of the nasociliary nerve consist of the infratrochlear nerve and external nasal branches of the anterior ethmoidal nerve. The external nasal branches of the anterior ethmoidal nerve provide cutaneous and mucosal innervation to the apex and ala of the nose and anterior nasal cavity, and the infratrochlear nerve supplies the root of the nose (Gardner et al. 1988; Larrabee et al. 2004; Waldman 2015).

The maxillary division of the trigeminal nerve (V2) passes through the foramen rotundum and enters the pterygopalatine fossa. Crossing the inferior orbital fissure, it enters the orbit, passing along the floor of that structure in the infraorbital groove, and arrives at the face, as the infraorbital nerve, via the infraorbital foramen. Therefore, the infraorbital nerve is considered an extension of the maxillary nerve. When arrives at the face, it originates various branches: the inferior palpebral branch, which innervates the conjunctiva and skin of the lower eyelid; the external nasal branch, which supplies the nasal sidewall; the superior labial branch, which supplies the skin of the cheek and part of the upper lip and oral mucosa; and the anterior superior, middle superior, and posterior superior alveolar nerves, which supply the superior dental arcade as well as the mucosa of the anterior maxillary sinus, the nasal cavity, and the buccal and gingival mucosas. Furthermore, before the maxillary nerve enters the orbit, it originates the zygomatic nerve. The zygomatic nerve crosses the inferior orbital fissure and is divided into two branches: the zygomaticotemporal and zygomaticofacial nerves. These nerves perforate the zygomatic bone and provide sensory innervation to the skin of the temporal and lateral zygomatic regions (Gardner et al. 1988; Waldman 2015).

The mandibular division of the trigeminal nerve (V3) passes through the foramen ovale and arrives at the infratemporal fossa. When the mandibular nerve crosses the skull base, it joins to the motor root of the trigeminal nerve. This combined

trunk gives off two divisions, anterior and posterior, and, consequently, originates various branches. The posterior division is mainly sensitive and gives off the auriculotemporal nerve, the lingual nerve, and the inferior alveolar nerve. The auriculotemporal nerve provides innervation to the skin of the external ear (tragus and helix) and temporal region. The lingual nerve supplies sensation to the tongue and buccal mucosa. The inferior alveolar nerve provides sensory innervation to the lower teeth, gingival mucosa, and mandible. The terminal branch of the inferior alveolar nerve, the mental nerve, exits the mandible via the mental foramen at the level of the second molar tooth and provides sensory innervation to the skin of the chin and lower lip as well as to the mucous membrane of the lower lip (Gardner et al. 1988; Waldman 2015).

Patient Preparation

The patient is placed supine with the head in neutral position. In this moment, the vital signs should be measured.

Conventional antiseptics, such as 70% ethanol, iodinated compounds, and chlorhexidine can be used to prepare the site, with care taken to avoid spilling solution into the eye. Aqueous solution of chlorhexidine can be applied to the oral mucosa in the neural blockade with intraoral approach.

Anesthesia

Local anesthesia generates a reversible loss of sensation in a portion of the body. Its mechanism of action is to block impulse conduction along nerve axons, decreasing reversibly the rate of depolarization and repolarization of excitable membranes. The local anesthetics act principally by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane (especially voltage-gated sodium channels). Once the influx of sodium is suspended, an action potential can't be accomplished and so the signal conduction is inhibited (Davies et al. 2014).

The local anesthetic most commonly used is lidocaine. Given its vasodilating action, a small amount of epinephrine can be added to cause vasoconstriction, reducing the bleeding and risk of hematoma and prolonging the anesthesia. In general, about 2–3 mL of the anesthetic solution with 2% lidocaine with or without epinephrine (generally at a dilution 1:200,000–1:400,000) is sufficient for each neural blockade. For patient comfort, use delicate needle (25G–30G). For prolonged analgesia (4–6 h), bupivacaine or ropivacaine, anesthetic drugs of later elimination, can be used (Davies et al. 2014).

Topical anesthesia of the skin with 4% lidocaine, 2.5% lidocaine/2.5% prilocaine or 7% lidocaine/7% tetracaine creams or precooling agents can be used in individuals sensitive to pain, with blenophobia (fear of needles) or psychologically unstable, reducing pain and anxiety produced by administration of local injectable anesthetics. Already in the mucosa, cotton ball soaked with 2% viscous lidocaine or 10% cocaine solution, 4% lidocaine ointment, 20% benzocaine gel, 5% lidocaine patch or cryoanesthesia can be applied (Alster and Lupton 2002; Lathwal et al. 2015).

Finally, after the introduction of the needle and just before the infiltration, it is advisable to pull back the syringe plunger (aspiration) to avoid intravascular injection.

Technique of Blockade of the Supraorbital Nerve

The supraorbital nerve exits the orbital cavity via the superior orbital fissure, along the orbital roof, to emerge through the supraorbital foramen (or superior orbital foramen). It supplies sensation to the upper eyelid, the forehead (supraorbital portion), part of anterior scalp and frontal sinus. The anatomical reference is the superior orbital rim, in the junction of its two thirds lateral and medial third, about 2.5 cm from the midline, where the foramen is easily identified by palpation (Fig. 1). The supraorbital foramen is also named as supraorbital notch, situating on an imaginary

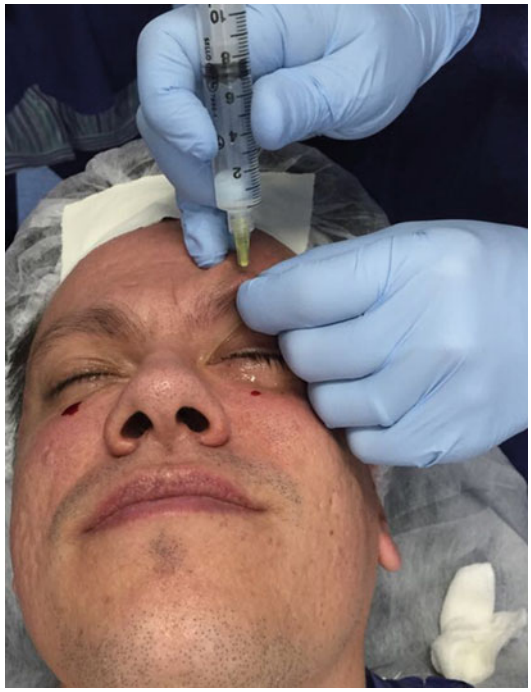

Fig. 1 Supraorbital nerve block

line passing through the pupil when the eye is in the primary position.

The syringe needle is inserted perpendicularly to the skin at the level of the supraorbital notch. It is important to avoid passing through the foramen, which could pin the nerve against the periosteum and cause compressive neuropathy. It is safer to slide the needle medially when the periosteum is contacted and it reaches the foramen, such that its tip abuts the rim of the foramen. To anesthetize the peripheral branches of the nerve, 2–3 mL of local anesthetic (e.g., 2% lidocaine with or without epinephrine) are injected at the reference point. There may be bleeding from the supraorbital artery that accompanies the nerve. After infiltration, a local gentle compression with gauze or cotton should be performed for preventing periorbital hematoma or ecchymosis (Larrabee et al. 2004; Salam 2004; Tomaszewska et al. 2012; Ilhan Alp and Alp 2013; Candido and Day 2014; Davies et al. 2014; Latham and Martin 2014; Waldman 2015).

Technique of Blockade of the Supratrochlear Nerve

The supratrochlear nerve leaves the orbit at a medial extremity of the supraorbital border and aides the innervation of the forehead (inferomedial section) and medial portion of the upper eyelid. The nerve exits the orbit between the trochlea and supraorbital foramen. To block the supratrochlear nerve, the needle is directed medially from the supraorbital notch toward the apex of the nose. The needle is inserted just lateral to the junction of the bridge of the nose and the supraorbital ridge and it is advanced medially into the subcutaneous tissue. It is used to block 1–2 mL of anesthetic with or without vasoconstrictor under the superomedial orbital rim. Adequate compression with gauze or cotton must be applied at the injection site because of the loose alveolar tissue of the eyelid, preventing periorbital hematoma and ecchymosis (Larrabee et al. 2004; Salam 2004; Latham and Martin 2014; Waldman 2015).

Technique of Blockade of the Nasociliary Nerve

The terminal branches of the nasociliary nerve consist of the infratrochlear nerve and external nasal branches of the anterior ethmoidal nerve. The external nasal branches of the anterior ethmoidal nerve provide cutaneous and mucosal innervation to the apex and ala of the nose and anterior nasal cavity, and the infratrochlear nerve supplies the root of the nose.

The infratrochlear nerve and external nasal branches of the anterior ethmoidal nerve are blocked below the trochlea and about 1 cm above the medial palpebral ligament (or medial canthal tendon) along the medial wall of the orbit. The needle should be inserted to a depth of 1–1.5 cm, where is the anterior ethmoidal foramen, injecting about 1–2 mL of the anesthetic solution. Terminal branches of the ophthalmic artery and small tributaries of the superior ophthalmic vein can be reached during blockade of

the infratrochlear nerve, which may cause retrobulbar hematoma. It is important highlight that the blockade should be accomplished without adrenaline to eliminate any risk of retinal artery spasm (Molliex et al. 1996; Larrabee et al. 2004).

Technique of Blockade of the Infraorbital Nerve

The infraorbital nerve is considered an extension of the maxillary nerve, arriving at the face via the infraorbital foramen. It originates various branches: the inferior palpebral branch, which innervates the conjunctiva and skin of the lower eyelid; the external nasal branch, which supplies the nasal sidewall; the superior labial branch, which supplies the skin of the cheek and part of the upper lip and oral mucosa; and the anterior superior, middle superior, and posterior superior alveolar nerves, which supply the superior dental arcade as well as mucosa of the anterior maxillary sinus, the nasal cavity, and the buccal and gingival mucosas.

There are two techniques for blockade of the infraorbital nerve: intraoral and extraoral approaches.

Intraoral Approach

The infraorbital foramen is palpable as a small depression about 1.5 cm below the inferior orbital rim and approximately 2.5 cm from the midline of the face, being in an imaginary line through the pupil (Fig. 2). Thereby, the foramen is located by the index finger and the upper lip is lifted by the thumb of the same hand. A fine needle is introduced superiorly by the alveolar ridge of the mucosa, just inferior to the infraorbital foramen, and toward the index finger already placed. For patient comfort, topical anesthesia can be performed in the alveolar ridge before infiltration. After careful aspiration, about 2–3 mL of local anesthetic are injected. An adequate pressure over the inferior orbital rim limits dissection of the local anesthetic superiorly into the periorbital region, avoiding hematoma and ecchymosis

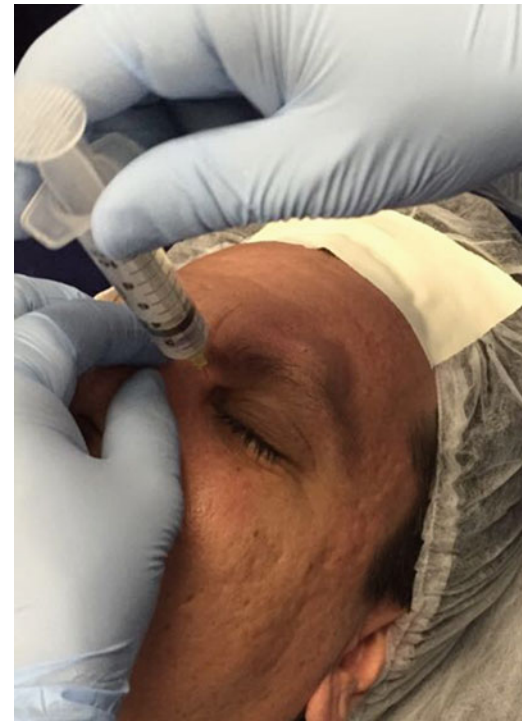

Fig. 2 Supratroclear nerve block

(Ilhan Alp and Alp 2013; Candido and Day 2014; Davies et al. 2014; Latham and Martin 2014; Waldman 2015).

Extraoral Approach

As mentioned previously, the infraorbital foramen is in an imaginary line through the pupil. It is palpable as a small depression in the infraorbital ridge of the maxillary bone, about 1.5 cm below the inferior orbital rim (Fig. 3). A fine needle is advanced toward the foramen. Once the needle reaches the foramen and the periosteum is contacted, the needle should be slid slightly medially. This maneuver prevents the pinning of the nerve against periosteum and compressive neuropathy. If the needle enters the infraorbital foramen, it should be withdrawn to avoid potentially nerve injury. After careful aspiration, about 2–3 mL of the anesthetic solution is injected into the outer opening of the foramen. Similar to the intraoral approach, gentle compression with

Fig. 3 Infraorbital nerve block: extraoral approach

gauze or cotton should be performed at the injection site, avoiding dissection of local anesthetic and preventing periorbital hematoma and ecchymosis (Larrabee et al. 2004; Salam 2004; Candido and Day 2014; Latham and Martin 2014; Waldman 2015).

Technique of Blockade of the Zygomatic Nerve

Before the maxillary nerve enters the orbit, it originates the zygomatic nerve. The zygomatic nerve crosses the inferior orbital fissure and is divided into two branches: the zygomaticotemporal and zygomaticofacial nerves. These nerves perforate the zygomatic bone and provide sensory innervation to the skin of the temporal and lateral zygomatic regions. The zygomaticotemporal and zygomaticofacial branches arrive at the face via a small foramen in the zygomatic bone at the junction of the lateral and inferior orbital rim. Infiltrative anesthesia at this site will block these nerves. After gentle aspiration, about 2–3 mL of local anesthetic is injected. An adequate pressure over the lateral and inferior orbital rim limits dissection of the local anesthetic

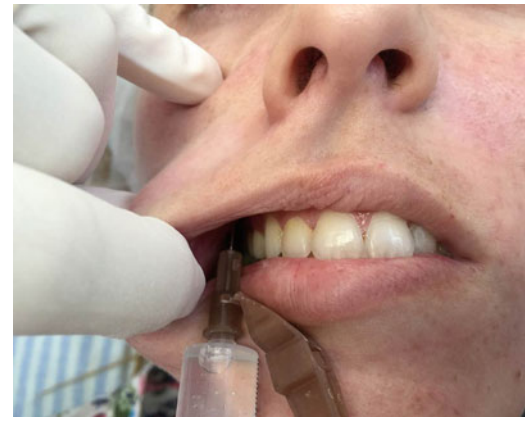

Fig. 4 Infraorbital nerve block: intraoral approach

superiorly into the periorbital region, avoiding hematoma and ecchymosis (Larrabee et al. 2004; Davies et al. 2014).

Technique of Blockade of the Mental Nerve

The terminal branch of the inferior alveolar nerve, the mental nerve, exits the mandible via the mental foramen and provides sensory innervation to the skin of the chin and lower lip as well as to the mucous membrane of the lower lip.

As in the infraorbital nerve block technique, there are two techniques for blocking the mental nerve: intraoral (Fig. 4) and extraoral (Fig. 5) approaches.

Intraoral Approach

The mental foramen is located in an area approximately 2 cm from the midline in a plane parallel with the supraorbital and infraorbital foramina and between the superior and inferior borders of mandible. Careful palpation of the jaw allows its location and generates a "sensation of shock" after a little nerve compression in the mental foramen area. The lower lip is pulled downward and a fine needle is advanced perpendicularly in the alveolar ridge of the mucosa, just superior to the mental foramen. For patient comfort, topical anesthesia

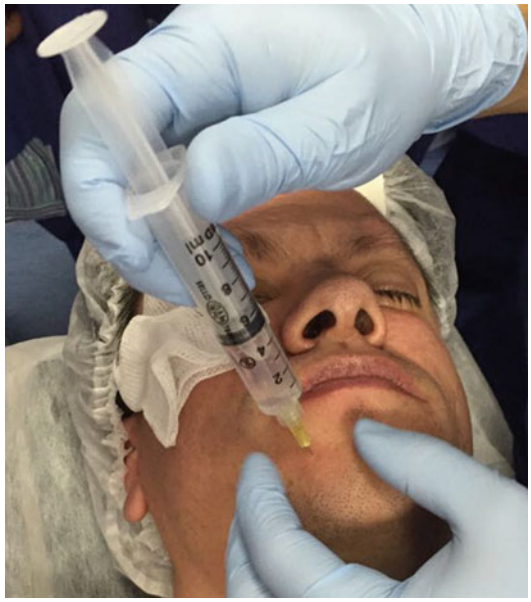

Fig. 5 Mental nerve block: extraoral approach

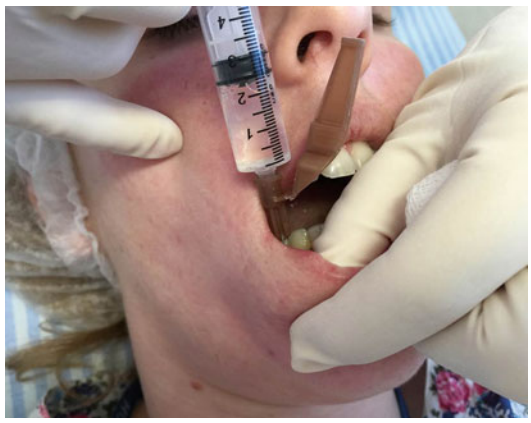

Fig. 6 Mental nerve block: intraoral approach

can be applied in the alveolar ridge before infiltration (Fig. 6). After careful aspiration, about 2–3 mL of anesthetic solution are injected (Candido and Day 2014; Davies et al. 2014; Latham and Martin 2014; Waldman 2015).

Extraoral Approach

The mental foramen is located in a plane parallel with the supraorbital and infraorbital foramina, in about 2 cm from the midline. Because of the acute angle at which the mental nerve exits the mental foramen, the local palpation generates a "sensation of shock" after a little nerve compression in the mental foramen area. A fine needle is advanced toward the mental foramen using a slight medial approach, as noted earlier for supraorbital and infraorbital nerve blocks, and about 2–3 mL of anesthetic solution are injected after preventive aspiration. As the nerve is susceptible to compression, it isn't advisable to enter the needle into the mandibular canal in order to avoid neuropathy by pinning the nerve against periosteum or increment of pressure during injection (Candido and Day 2014; Salam 2004; Latham and Martin 2014; Waldman 2015).

Complications and Unwanted Side Effects

Complications and unwanted side effects are rare but can include local bacterial infection, postprocedure dysesthesias, facial asymmetry, activation of herpes simplex and herpes zoster, retinal artery spasm, ecchymosis or hematomas, local anesthetic toxicity, and injection-induced compressive neuropathy. Although generally not harmful, they are quite upsetting to the patient. Therefore, the patient must be forewarned of these possible consequences before the procedure (Davies et al. 2014; Waldman 2015).

Conclusion

With recent trends focusing on less aggressive cosmetic procedures, advances in anesthesia are required to avoid the need for local injectable anesthetics and intravenous sedation. Although there are several topical anesthetic agents that are effective in reducing the pain associated with moderately painful cutaneous procedures, most are limited by a necessarily prolonged preoperative application time in order to

achieve deep dermal anesthesia. Continuing advances in the understanding of the physiology of pain will produce new topical anesthetics with rapid onset, prolonged duration, and minimal side effects so that improve consequently the management of these patients.

Take Home Messages

- The sensory innervation of the face is determined mainly by the trigeminal nerve (cranial nerve V), the largest cranial nerve.
- Depending on the area of the face involved in the cosmetic procedure, we need to block one or more branches of the trigeminal nerve.
- The imaginary line passing through the pupil when the eye is in the primary position is an important anatomical reference for the blockade of the trigeminal nerve branches.
- The neural blockade of the face is a safe, effective, and simple approach. Although the complications and unwanted side effects are rare, they are quite upsetting to the patient and therefore the patient should be forewarned of them.
- Recent trends focusing on less aggressive cosmetic procedures, advances in anesthesia are required to avoid the need for local injectable anesthetics and intravenous sedation.
- Continuing advances in the understanding of the physiology of pain will produce new topical anesthetics with rapid onset.

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Hyaluronic Acid Dermal Filler: Physical Properties and Its Indications

Marcelo Neira Ave and Maria Claudia Almeida Issa

Contents

Abstract

In the other chapters of this volume, authors are describing injection techniques and general handling of hyaluronic acid gels. This class of dermal fillers is the mainstay of modern dermal filling practice around the world for the past 20 years. The practicing doctor, while studying the subject further in the medical literature, will most certainly face some debates on the physical properties of hyaluronic acid gels. In this chapter, we summarize and explain the main concepts of hyaluronic acid gel rheology. With this information, doctors should be able to see past commercial and marketing claims and make an educated choice on which products he should employ and what results he should expect.

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_39

Keywords
Hyaluronic acid gel · Viscoelasticity · Lifting capacity · Rheology · Complex modulus · Loss modulus · Storage modulus · Tan δ

Introduction

As our knowledge of facial aging evolved, it has become clear that volume loss from facial fat and cranial bone remodeling are strongly associated with the resultant facial cosmetic appearance. This new paradigm has assured the increasing application of hyaluronic acid (HA) as the most widely used agent for dermal filling. As a class of fillers, HA gels stand out for their properties: they require a relatively simple technique, they have low adverse reaction profile, are not immunogenic, give predictable, reproducible, durable, and reversible results. Hence, it is not surprising, according to data published by the American Society of Plastic Surgeons (ASPS), that a total of 2,012,672 HA gel filling procedures were performed in the US in 2016. This figure represents 13% of all minimally invasive aesthetic procedures and nearly 77% of overall dermal filler procedures performed in that country in the same year (American Society of Plastic Surgeons 2016; Borrell 2011).

There is no such thing as an ideal filler, that is, a long-lasting nonallergenic filler with minimal side effects, painless upon injection, and cost effective. Many modifications on hyaluronic acid filler manufacturing have given rise to a new generation of products different in both physical properties and biological interaction with tissue host (Dover 2006; Tezel and Fredrickson 2008). No ideal filler exists so far; they vary in their physical properties and therefore the physician must understand the differences among the available products on the market.

By understanding these physical properties, one can grasp a better application of these gels in the esthetic enhancement of patients. The physician shall become able to better select the proper filler for the right job. Rheology is the field of physics responsible for the study of fluid motion and behavior of liquids and semisolids. On this chapter, we will focus on the rheological aspects surrounding hyaluronic acid dermal fillers. It is a maxim of hyaluronic acid filling that the gel should have similar consistency as the surrounding tissue to be injected, in order to achieve a more natural look and feel to the touch. Besides that, hyaluronic acid gel (HAG) must sustain its shape and physical integrity against constant physical strain caused by muscle contraction and weight load forces over the face, if it is to last long after injection. Softer gels indicated to fill superficial wrinkles are not usually indicated to perform lifting work over juxtaperiosteal levels, or even volumizing entire areas of the face. The latter require more robust, stiffer gels. We will start by understanding further the chemical nature of hyaluronic acid.

Hyaluronic Acid Physicochemical Properties

Chemical Structure

Most commercial hyaluronic acid today are synthesized in laboratories by bacterial fermentation.

Hyaluronic acid is a glycosaminoglycan disaccharide polymer composed of monomers of D-glucuronic acid and *N*-acetyl-D-glucosamine (Fig. 1).

Each disaccharide monomer weights 401 Da. A hyaluronic acid molecule can comprise thousands of such monomers. Whenever a commercial product alludes its molecular weight, it can only refer to a mean molecular weight, for such preparations are actually composed of a large number of

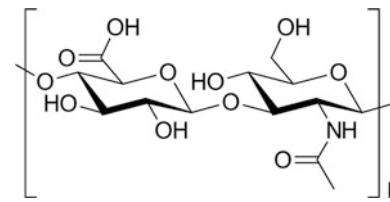

Fig. 1 D-Glucuronic acid and *N*-acetyl-D-glucosamine

molecules with molecular weights varying within a well-distributed range. In fact, such declarations are quite misinformative since cross-linked hyaluronic acid (the true commercial form) is a macromolecule composed of many hyaluronic acid chains and thus bear an enormous molecular weight (Kablik et al. 2009; Kogan et al. 2007).

Hyaluronic Acid Human Metabolism

Hyaluronic acid is naturally found in the dermis, synovial fluids, vitreous fluid, and cartilage. It mechanically functions as a scaffolding and cushioning filling for these tissues. Hyaluronic acid turnover in human tissues is surprisingly high. Every single day, one-third of its total amount in the body is degraded (Kablik et al. 2009). This fact is one of the reasons why injectable hyaluronic acid is chemically altered to last longer. Nearly half of total hyaluronic acid of the human body resides in the skin (totaling 7–8 g per average human adult) (Kablik et al. 2009).

Hyaluronic acid is a major component of the extracellular matrix and its molecular structure has been left mostly unaltered in the evolutionary process. This fact allows the employment of hyaluronic acid from nonhuman sources for human injection with little concern for allergic or graft reactions. The degradation paths of hyaluronic acid are very well understood. HAG suffers degradation from both enzymatic (e.g., hyaluronidase) and oxidative (as in reactive oxygen species) pathways. Current evidence accumulated over 20 years of preclinical, clinical, and postmarketing experience points to the fact that these pathways not only are minimally affected but even commercial cross-linked HAGs do not present any significant deviation or risk to humans. Even with all this evidence, certain late-phase chronic reactive adverse events due to HAG injections leave it unexplained whether extensively modified HAG or its degradation byproducts could be recognized by the human immune system and elicit immune reactions (Artzi et al. 2016; De Boulle et al. 2013).

Manufacturing Process

Each manufacturing process results in products with different characteristics. Hyaluronic acid in its most natural form is a viscous gel with great fluidity and bears no resistance to physical deformation as well as little resistance to enzymatic degradation by tissular hyaluronidase (Tezel and Fredrickson 2008). If injected unaltered, hyaluronic acid will last for 1–2 days in the host tissue (as discussed earlier about turnover). For this reason, almost 20 years ago, a technique using cross-linking molecules was firstly employed to increase hyaluronic acid physical resistance to deformation and to enzymatic degradation thus stretching its duration in a human host for months. The cross-linking agent is usually BDDE (1,4-butanediol diglycidyl ether, see Fig. 2), a linear carbon-based molecule that bridges distant branches of the hyaluronic acid molecule via ligation (see Fig. 3) by its reactive epoxide terminals (this reaction is usually catalyzed by a base) NaOH (Tezel and Fredrickson 2008; Sundaram and Fagien 2015; Khunmanee et al. 2017). Another possible, though rarer cross-linker, is divinyl sulfone (DVS, see Fig. 4). The cross-linking reaction creates a mesh-like structure of hyaluronic acid, thus altering its mechanical properties. The more cross-linking density a gel has, the firmer the gel and the more resilient to physical deformation and enzymatic degradation it becomes (Sundaram and Fagien 2015). After the cross-linking reaction step, the gel becomes firm and adopts the shape of the vessel it occupies, effectively turning into a single solid block of gel (Tezel and Fredrickson 2008; Falcone and Berg 2008; Pierre et al. 2015). To make it possible to insert HAG under the skin without an incision, a second stage in the manufacturing process of hyaluronic acid called *sieving* is required (Segura et al. 2012). As the name implies, the block of hyaluronic acid is pressed against a sieve, thus causing the breakage (or calibration) of the block into extremely tiny particles (Segura et al. 2012). These particles are able to be injected through a hypodermic needle, thus solving the insertion problem.

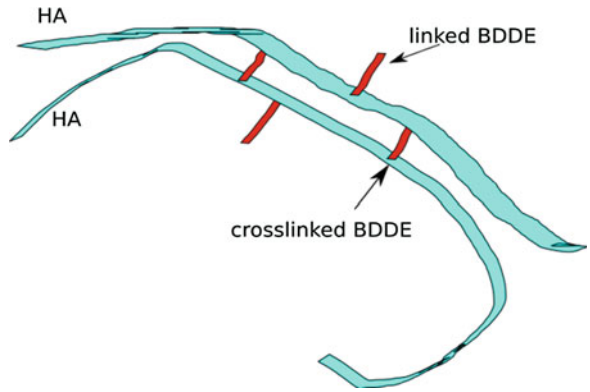

Fig. 2 Molecular structure of 1,4-butanediol diglycidyl ether with its epoxyde terminals

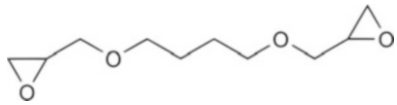

Fig. 3 BDDE binds to HA structure to form cross-links (Note that some of the BDDE only binds at one end, not forming a cross-link)

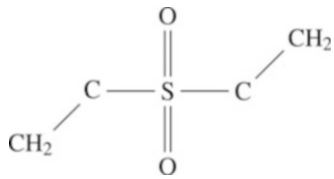

Fig. 4 Molecular structure of divinyl sulfone

The physical properties of cross-linked HAGs are influenced by particle size and the amount of polymer per unit of volume (HA concentration) (Segura et al. 2012). A larger particle sized cross-linked HAG requires a larger gauge needle than noncross-linked HA. Most products in the market have a concentration range from 5 to 24 mg/ml. Above 25 mg/ml, the HA gel becomes too stiff to be injected (remember G′ is also determined by HA concentration). (Kablik et al. 2009)

The HA gels can have a granular or a smooth appearance. NASHA (an acronym for non-animal stabilized hyaluronic acid) technology gels usually assume granular appearance, whereas other manufacturing processes usually produce smooth gels (e.g., OBT and Hylacross gels) (Kablik et al. 2009; Belmontesi et al. 2018; Edsman et al. 2012).

On Exogenous Hyaluronidase

Hyaluronidase has been successfully utilized in cosmetic dermatology for its capacity to decomplex hyaluronic acid. This particular use of hyaluronidase is off-label and yet considered a gold standard for the management of injected HAG complications such as overcorrection and, most importantly, the reversion of arterial occlusion (Buhren et al. 2016). The enzymatic degradation rate by exogenous hyaluronidase varies among different HA products. There are some products that are really or nearly impossible to suffer complete degradation and that in part is due to a high-modified HA with a high-cross-linking density (Sundaram and Fagien 2015; Buhren et al. 2016). If hyaluronidase has difficulty coupling and recognizing the HA structure, so could other proteins of the immune system.

In one study, the NASHA product family showed the fastest rate of degradation. This may be seen as an advantage not only for these NASHA products being perceived as self and not eliciting any immune reaction but also bears for its easy reversibility in cases of overcorrection or worse: a vascular embolism event. Overall, NASHA products seem to have a better safety

profile (Sundaram and Fagien 2015; Buhren et al. 2016; Juhász et al. 2017).

Assessment of Degrees of Cross-Linking

A cross-linking agent such as BDDE (Fig. 2) can create a strong covalent bond at both ends (creating an actual cross-link) or only at one end. The latter does not constitute a cross-link and does not contribute to form the mesh-like structure and its corresponding physical properties. (Edsman et al. 2012). The pendant end of the molecule usually reacts with water during a washout step (epoxide is reactive due to their high-ring strain) rendering in this end a more stable nonreactive glycol (Kablik et al. 2009; Edsman et al. 2012). The efficiency of a cross-linking manufacturing step relies on using the less possible amount of BDDE to create more functioning cross-links and the less amount of pendant BDDE possible. (Edsman et al. 2012). While performing biochemical analysis of the gels, many ratios can be used to assess modifications to the HA gels. Below are some equations cited in the literature to calculate and quantify the amount of cross-linker added, the relative modification to HA structure and finally gain perspective on how effective the cross-linker added was in turning the gel more robust. All these ratios can be determined following specific protocols, such as those described by Edsman et al. (Kablik et al. 2009; Edsman et al. 2012). Modification efficiency is a measure of the gel strength gained for each BDDE molecule added. The higher the modification efficiency ratio, the more efficient the process. The modification efficiency is particularly interesting and uses C_{min} as the numerator and we will explain it further (Kablik et al. 2009; Edsman et al. 2012).

Minimum Concentration: C_{min}

The more cross-linked a gel is, the less it expands while absorbing water. This makes sense since the mesh-like structure is more intricate and stiff for greater cross-linking. It is less deformable. After becoming saturated with water, the HA gel no longer expands and a thin layer of free water forms over the gel. If we measure the HA concentration at this state, we will have an indirect measure of gel strength. The more expanded and less cross-linked a gel is, the less HA concentration we will find in a water saturated state. The inverse is obviously true as well. The more concentrated the HA at water saturated state, the stiffer the gel. That being explained, high cross-linking gels tend to swell less (Edsman et al. 2012) Therefore, C_{min} is a surrogate measure to the complex modulus and is applied in the calculation of the modification efficiency in such a way that a high-stiffness gel that requires less BDDE cross-linking is considered a highly efficient gel.

HAGs Modification Indexes

$$\text{Degree of modification} = \frac{\text{Moles of linked BDDE}}{\text{Moles of HA dissacharides}}$$

$$\text{Crosslinking ratio} = \frac{\text{Moles of crosslinked BDDE}}{\text{Moles of linked BDDE}}$$

$$\text{Degree of crosslinking} = \frac{\text{Moles of crosslinked BDDE}}{\text{Moles of HA dissacharides}}$$

$$\text{Modification efficiency} = \frac{C_{\text{min}}}{\text{Degree of modification}}$$

Unbound HA fragments diffuse in water thus not contributing to C_{min} measurement, unlike G^*. HA concentration is also a tricky measurement, for the same reason, and unbound HA does not contribute to volumizing or lifting capacity of the gel. C_{min} is also unaffected by HA concentration, but solely dependent on cross-linking density. Notice that the C_{min} assessment protocol simulates what truly happens to a gel *after* it is injected in a human host, effectively simulating the final stage of any HA gel after injection. This explanation is the very reason why biphasic and monophasic gel classification are not used any longer. After being injected in human tissue, all biphasic gels become monophasic just after all unbound fragments of HA disperse leaving only the mesh-like structures in place (Edsman et al. 2012).

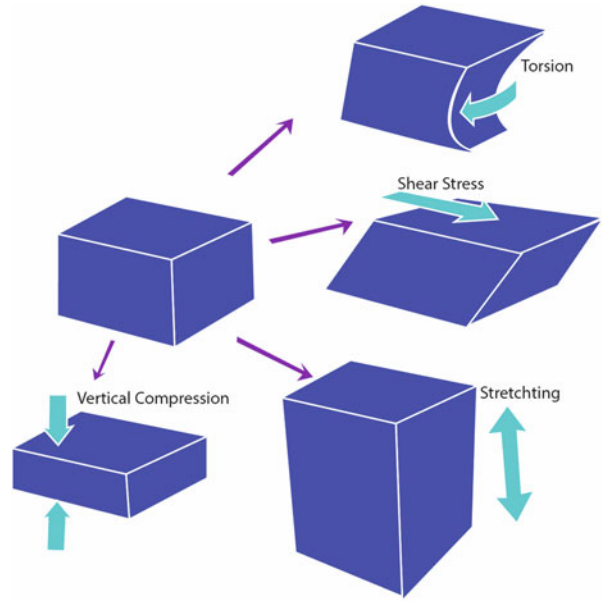

Fig. 5 There are many models of gel-like deformation but shear deformation is the most used in the analysis of HAGs physical properties

Across various comparison studies, the NASHA family of products usually present higher G′ or G^* (meaning they are more resistant to deformation) than HA products from other families such as Vycross (Edsman et al. 2012). The NASHA family of products employs a very low synthetic cross-linking density (usually less than 2%). Its higher G^* is due to a long HA chain that folds onto itself forming natural nonmeasurable cross-linking (also called entanglements). NASHA product family also have higher C_{min} than other family products. Edsman et al. have reported some direct correlation between C_{min} and G^* along a long list of tested products from a myriad of manufacturers, despite the fact that these two measurements suffer influence from a different list of factors. By examining the modification efficiency formula, one can verify a high C_{min} in the numerator along with a low degree of modification (low quantity of linked BDDE) in the denominator revealing the NASHA method to be the most efficient method for HA modification. It means it gets great gel strength with minimal chemical modification (Edsman et al. 2012).

Lifting Capacity

It is generally agreed that the lifting capacity of a gel is its ability to lift tissue and maintain the new shape, not subsiding to deformation. Although there is no quantifiable unit for lifting capacity yet, it is also agreed that a high-gel strength correlates with a high-lifting capacity. The opposite is true and it is not expected to a very fluid or weaker gel to sustain tissues lifted.

Forces That Apply to Filler Material on the Face

Shear stress refers to the force that is applied parallel over a surface area causing deformation of material (lateral shear or torsion, See Fig. 5). Compression forces (also called normal stress) refer to force vectors applied perpendicularly to the surface of the gel. It causes stretching, compression, and spread of an HAG (See Fig. 5). Both shear stress and compression can result from facial muscle contractions, external compression, or external shear stress over the face (e.g., the compression of a pillow or mattress over the

zygomatic bone). Each facial area must have distinctive acting forces, but these have not been fully studied under the subject of HA fillers. The complex modulus, G^*, is usually measured by applying shear stress to a gel sample. Some articles suggest cohesivity as a way to evaluate resistance to compression, but cohesivity is still a much debated aspect in its measurement methods.

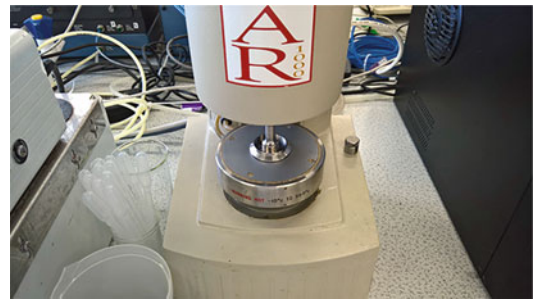

Fig. 6 A rheometer can directly assess G^*, tan δ, and frequency. Other parameters such as G' and G'' are calculated from those first three (Source: Wikipedia Commons)

On Viscoelasticity

All HA gels have viscoelastic properties, in other words they can act as both a viscous material (a material that deforms as long as sheer stress is applied and does not recover its original form, e.g., a liquid) and an elastic material (that is, it deforms under shear stress but can go back to its original shape once the force dissipates).

No gel can be fully elastic and viscous at the same time. Its rheologic properties usually fluctuate between these two aspects. A more viscous gel has a more "fluidic" nature whether a more elastic gel act a bit more "solid and robust." As a practical example, water would be a purely viscous material (also called a Newtonian fluid), honey would be more viscous than elastic, a block of gelatin would be more elastic than viscous, and a brick would be considered totally elastic with no viscosity whatsoever. Generally, all HA fillers are more elastic than viscous, but they must retain both characteristics to function properly. This viscous/elastic duality is best represented by physical measurements, namely G^*, G', and G'' and a fourth rheological parameter known as tan δ. These physical measurements can be assessed using a method called *dynamic mechanical analysis*, usually performed by an equipment called a *rheometer* (see Figs. 6 and 7). Usually, a small amount of gel is placed between two sensor plates. One of the plates partially spins back and forth at a specific frequency, and the relative movement from the upper and lower gel surfaces are measured against the amount of shear stress applied. All these measurements (G^*, G' and G'') are dynamic and change with frequency of force applied, temperature, pressure, etc. This becomes

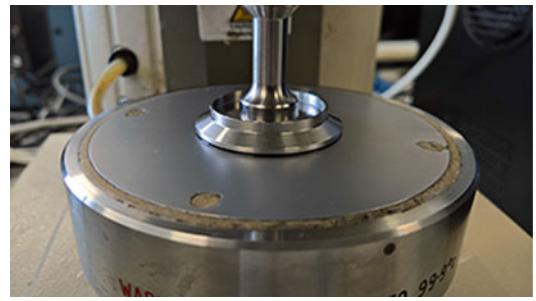

Fig. 7 Detail on the plate-to-plate sensor of the rheometer. HAG is placed between these two plates. The upper plate begins an oscillatory movement with a frequency causing shear stress. The displacement of gel in the lower layer is detected and compared with displacement in the upper layer (Source: Wikipedia Commons)

important when comparing HAG properties; all physical parameters must be comparable if test conditions are all the same. As an example of pressure influence on G', whenever a HAG syringe bottom is pressed in order to inject, the HAG's G' decreases allowing the gel to deform in order to pass through the needle lumen. Once this pressure ceases, the recently implanted HA gel resumes much of its former G' and again becomes more rigid and resistant to deformation. This is the very reason why viscoelasticity of HA gels is so important for them to function as a cosmetic implant. Some conditions such as temperature appear to have little impact on HAG's G^* when considering a range between 25 °C and 37 °C, as demonstrated by Lorenc et al. in their article (Paul Lorenc et al. 2017).

Fig. 8 Formulas correlating complex modulus, storage modulus, and loss modulus

$$|G^*| = \sqrt{(G')^2 + (G")^2}$$
$$|G^*| = G' + G"i$$
$$G^{*2} = G'^2 + G"^2$$

Complex Modulus: G*

The complex modulus, also known as G* (the name derives for its mathematical notation as a complex number), represents the total hardness of a gel, the amount of energy needed to deform the gel using shear stress. The complex modulus derives into other two values, G′ and G″ (see Fig. 8). The elastic or storage modulus also known as G′ (it is read G *prime*), represents the energy stored by the gel during deformation. After the shear stress is terminated, this energy is released to get the gel back to its original shape. It represents the elastic facet of the gel in such a way the higher the G′, the more the gel behaves as a solid. The loss or viscous modulus, also known as G″ (it is read G *double prime*), represents the amount of energy lost during deformation of the gel and represents the conversion of shear stress into heat energy through attrition of the gel layers. This energy is lost and cannot regain the gel its original shape, remaining deformed. This modulus represents the viscous facet of the gel, in such a way that the higher the G″, the more the gel behaves as a liquid. In practice, all HAGs have a very high G′ and a very low G″, meaning HAGs, in clinical practice, have great elastic and low viscous properties. Therefore, while concerning HAGs, G* is mostly composed by the G′ in such a way that is practical to state that $G^* \approx G'$. The formulas below, show the relationship between G*, G′ and G″. Be warned that the three equations are one and the same (they are just different mathematical notations of the same formula). Commercially available HAGs usually bear a G* from 10 to 1000 Pa at 0.1 Hz. This range is a result from the combination of HA concentration, cross-linking density, and the presence of HA fragments free from the mesh-like structure, and this is the very reason it is not advisable to further dilute in the office an HAG for it not only tampers G* and G′, but also because the resultant gel would not be homogenous in structure, texture, and concentration giving rise to lower results and lesser duration after injection.

Tan δ

Tan δ is a ratio to the viscous and elastic modulus, G′ and G″ (tan $\delta = \frac{G''}{G'}$). Tan δ measure the domineering behavior of a viscoelastic gel (either a viscous or elastic tendency). If tan $\delta > 1$, the gel behaves more like a liquid, and if tan $\delta < 1$ the elastic properties dominate and the gel shows a more elastic nature (Fig. 9).

Because HA gels tend to have high G′ over low G″, we expect tan δ to be low. Tan δ is directly measured in a dynamic mechanical analysis as well G* (Table 1).

On Cohesivity

Cohesivity is a more tricky subject. After searching the main biological and health databases, one finds the terms "cohesive", "cohesivity," and "cohesiveness" mainly associated to articles on HA fillers.

In the published articles, cohesivity is described as a function of molecular attraction among cross-linked HA molecules resulting in a gel that is not easily "breaked" apart. If G′ and G* are related to shear stress, articles defending cohesivity argue that it is a measurement of resistance against vertical compression (Sundaram et al. 2015).

Many authors agree that other rheological properties such as G* and G′ are related to clinical effects such as lifting capacity, but cohesivity still lacks a proper consensus. Falcone et al. also claim there is no advantage in cohesivity for fillers (Falcone and Berg 2008), whereas other authors state it contributes to lifting capacity (Borrell 2011; Pierre et al. 2015). Falcone et al. explicitly states that highly cohesive materials usually are dilute solutions of noncross-linked HA with low elasticity and short duration (Falcone and Berg 2008). Flynn and Tran have studied tissue

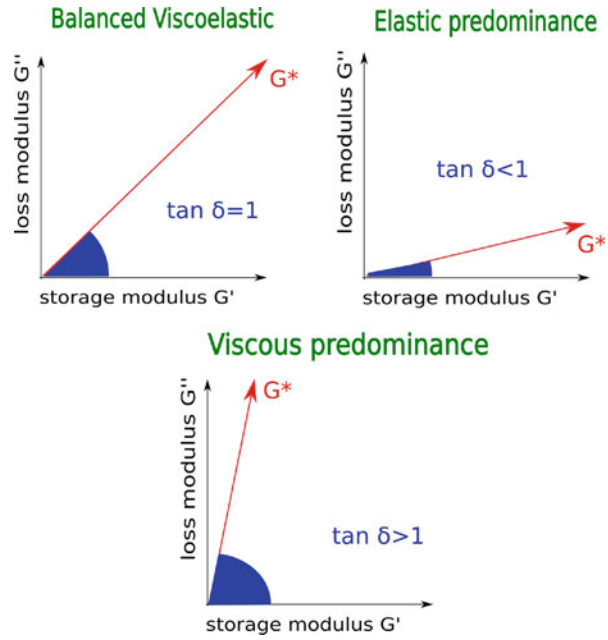

Fig. 9 G^* vector can be decomposed in the storage modulus and loss modulus vectors. Note the predominant viscoelastic behavior according to G' and G''

Table 1 Comparative rheological parameters among a limited selection of commercially available hyaluronic acid gels (Data was recovered from Pierre et al. (2015) and Segura et al. (2012))

HA filler	G'	G''	tan δ
Restylane Fynesse	34.5	18.6	0.54
Restylane Refyne	67.7	20.3	0.31
Belotero balance	128	82	0.64
Restylane Volyme	131.6	20.3	0.15
Restylane Kysse	151.1	19.9	0.13
Juvéderm ultra XC	207	80	0.39
Restylane Defyne	213.8	23.3	0.11
Juvéderm ultra plus XC	263	79	0.30
Juvéderm Volbella with lidocaine	271	39	0.14
Juvéderm Volift with lidocaine	340	46	0.14
Juvéderm Voluma XC	398	41	0.10
Restylane	864	185	0.21
Restylane Lyft	977	198	0.20

integration of HA gels and have concluded that high-cohesivity gels have better tissue integration (Flynn et al. 2011; Tran et al. 2014). Pierre et al. in their work hypothesize that low cohesive HA gels will eventually spread and flatten when injected in the subcutaneous layer (Pierre et al. 2015). Sundaram et al. have published a method to measure cohesivity of HA gels using the dispersion time of dyed gel when injected in water under centrifugation (Sundaram et al. 2015). Edsman in her work has proven that both the dispersion-time method and the compression force method (another method to measure cohesivity) do not correlate well with human perceived cohesivity. She proposed and devised a new method based on IUPACs' Golden Book definition for cohesivity. The method is called the *drop-weight test method* and correlates well with human-perceived cohesiveness. She also reports an inverse correlation between cohesivity and the elastic modulus G', supporting Falcone's statement further suggesting there should be no need to pursue methods to measure a second rheologic parameter other than the elastic modulus to

stipulate an HA gel performance (Edsman et al. 2015).

Besides it is suggested that unbound HA would decrease gel cohesivity and dissipate after injected into tissue, and that the remainder injected gel would acquire lower cohesivity after that. So what is the value to measure cohesivity in vitro? (ke Öhrlund and Edsman 2015).

Falcone et al. (Falcone and Berg 2008) in his work has compared the rheological properties of many market HAGs using a rheometer. He concluded that market dermal HA gels have quite variable rheological properties with respect to magnitude of complex modulus, complex viscosity and percent elasticity. He concluded the storage modulus G′ for the Juvederm family of products has lower magnitude than the Restylane family of products. He cites clinical data that indicates the persistence of the product correlates with HA concentration, but when concentrations are the same, persistence is mostly influenced by elasticity. Hence, he declares that persistence of the product is a function of the product of both HA concentration and elasticity (Falcone and Berg 2008).

Conclusion

Rheology is an important discipline to understand the physical behavior of different hyaluronic acid gel compositions. G^* is considered the most important factor capable of predicting the lifting capacity of a HAG and it is reliably measured and can easily be used to compare different commercial HAG presentations. Deep and bony areas of the face (as in malar restructuring techniques) should employ higher G^* materials while softer gels are best suited to treat superficial, more soft tissue (as is the case of wrinkle filling, lip contouring, etc.). Current evidence confirms HAGs are safe products with no mutagenic, irritant, or chronic inflammatory properties, thus reassuring its continuous use for many years to come. Yet, there are few adverse events that require further study. Many new varieties of cross-linked HAGs can be expected in the future, and the doctors that fully understand rheological properties of HAGs will become better at making decisions for their cosmetic practices.

Take Home Messages

- Rheology is the field of physics responsible for the study of fluid motion and behavior of liquids and semisolids.
- Hyaluronic acid is a major component of the extracellular matrix and its molecular structure has been left mostly unaltered in the evolutionary process, allowing nonhuman HAG to be injected in humans with little concern for allergic or graft reactions.
- HAG suffers degradation from both enzymatic (e.g., hyaluronidase) and oxidative (as in reactive oxygen species) pathways.
- Hyaluronic acid in its most natural form is a viscous gel with great fluidity and bears no resistance to physical deformation as well as little resistance to enzymatic degradation by tissular hyaluronidase.
- A technique using cross-linking molecules was firstly employed to increase hyaluronic acid physical resistance to deformation and to enzymatic degradation.
- The cross-linking agent is usually BDDE (1,4-butanediol diglycidyl ether).
- The physical properties of a HAG can be assessed using a method called *dynamic mechanical analysis*, usually performed by an equipment called a *rheometer.*
- The complex modulus (G^*) represents the total hardness of a gel. The complex modulus derives into other two values, G′ and G″. The storage modulus (G′) represents the energy stored by the gel during deformation and represents the elastic facet of the gel in such a way the higher the G′, the more the gel behaves as a solid. The loss modulus (G″) represents the amount of energy lost during deformation of the gel and represents the viscous facet of the gel (the conversion of shear stress into heat energy through attrition of the gel layers).

- In practice, all HAGs have a very high G′ and a very low G″, meaning HAGs, in clinical practice, have great elastic and low viscous properties. Therefore, while concerning HAGs, G^* is mostly composed by the G′ in such a way that is practical to state that $G^* \approx G'$.
- Tan δ is a ratio to the viscous and elastic modulus, G′ and G″ (tan $\delta = \frac{G''}{G'}$). Tan δ measure the domineering behavior of a viscoelastic gel (either a viscous or elastic tendency).

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Three-Dimensional Approach of Cosmetic Patient: Aging Gracefully

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_40

Abstract

Aging is a complex process that involves intrinsic and extrinsic factors and result in modifications in all tissues of the body. The aging of the face comprise a set of changes in bone support along with atrophy and flexibility of soft tissues such as skin, muscles, fat, and ligaments. Anatomically, the face can be divided in two regions: anterior and lateral. In the anterior part, there is predominance of the structures related to facial expression, while in the lateral region muscles related to mastication stand out. Another way to divide the facial components is related to general stratification in five basic layers joined by a system of facial retention ligaments. To promote the mobility required for facial expression independent of the basic functions of the face, particularly chewing, a number of soft tissue spaces are incorporated into the face architecture. This arrangement, most clearly seen on the scalp, also exists on the rest of the face, although with significant modifications. Understanding the anatomy of the aging process, in other words, the impact of facial skeletal aging and its correlations with soft tissue changes, will lead to an understanding of the current perspective of a three-dimensional approach to injectable procedures that are much more effective in preventing and treating the signs of aging.

Keywords

Aging · Anatomy · Fat compartments · Ligaments · Malar · Rejuvenation · Botulinum toxin · Fillers · Biostimulators

Introduction

The modern concept of rejuvenation is based on a comprehensive approach to the face. The traditional concept of elevation and correction of wrinkles was extended to a new three-dimensional approach. This global approach aims not only to perform relaxation of facial expression muscles with botulinum toxin and correction of folds with fillers but also a replacement of lost volumes and treatment of contours of the face such as the temple, zygoma, mandible, nose, and chin. For those purposes, it is very important to have reliable products that are adaptable to different levels and application plans. The combined use of botulinum toxin, fillers, and collagen neo-stimulation techniques such as injectable biostimulators and noninvasive technologies allows natural results in facial rejuvenation, especially for patients willing to improve their appearance but are not wishing for surgical procedures.

Moreover, through the knowledge of anatomical changes related to the aging face and of individualities between genders and ethnicities, it is possible to diagnose how individuals will tend to age and thus intervene early. It is now possible to perform small corrections even in young patients for beautification, correction of asymmetries, and prevention of aging. This is the key of aging gracefully (Fig. 1).

Regions of the Face

The face can be subdivided into regional, anatomical, topographic, or aesthetic units. These regions are divided according to the anatomical boundaries of areas that share similar characteristics as color, texture, pores, and hair follicles. The regional units of the face are divided into segments such as frontal, temporal, glabellar, nasal, periorbital, malar, labial, mandibular, mental, labial, and periorbicular areas.

Generally the face is divided into thirds: upper, middle, and lower. Each third has also a layered structural arrangement. Despite some exceptions such as temporal and palpebral region, there are five layers that can be dissected in the face (Mendelson 2007) (Fig. 2).

Face layer divisions
Layer 1: skin
Layer 2: subcutaneous layer
Layer 3: superficial musculoaponeurotic system (SMAS)
Layer 4: subaponeurotic, containing ligaments and soft tissue spaces
Layer 5: deep fascia

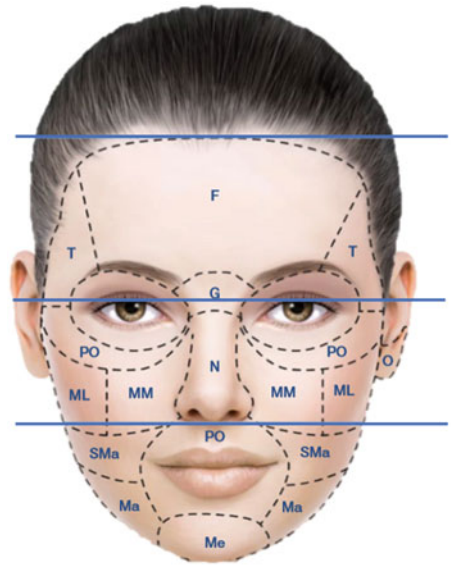

Fig. 1 Regions of the face

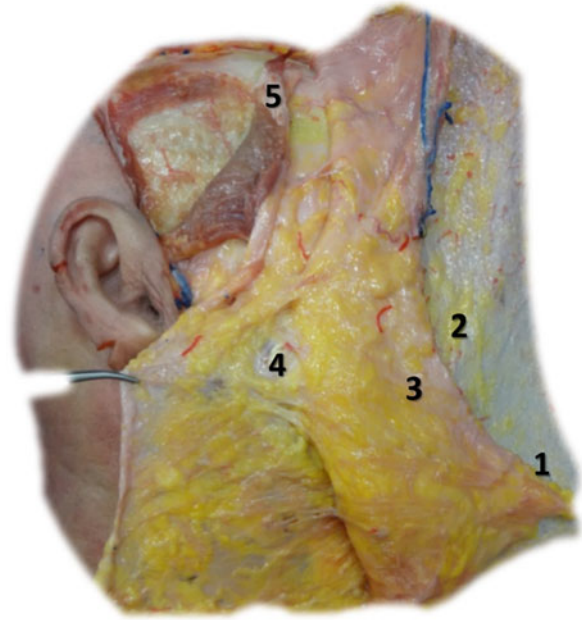

Fig. 2 Face Layers (1) Skin; (2) subcutaneous layer; (3) SMAS; (4) sub aponeurotic, containing ligaments and soft tissue spaces and (5) deep fascia

In the aging process, each layer presents a different behavior, being more or less compromised. Knowing to identify the layers affected in each patient and knowing how to manage the available treatments promotes more satisfactory results.

As briefly mentioned before, a more functional approach would be to separate the face in anterior and lateral regions. In the anterior face predominate the structures related to mimic facial expression, while in the lateral region, we find structures related to mastication as gland, fascia, and muscles. This division occurs through a vertical imaginary line that connects the lateral angle of the orbit to the jaw body. This line marks the position of a series of facial retaining ligaments, such as temporal ligament, lateral orbital retention ligament, and zygomatic, masseteric, and mandibular ligaments (Mendelson and Wong 2012b).

Anatomy of the Face

Layer 1: Skin

The skin diversifies among the different areas of the face regarding to texture, thickness, pigmentation, and type of adherence to deep layers. The thickness of the dermis is related to its function and tends to be inversely proportional to its mobility. The dermis is thicker in the frontal, glabellar region and the nasal tip while in eyelid is thinner (Cotofana et al. 2015).

Also, in the palpebral region the skin is firmly adhered to the orbicularis muscle, without subcutaneous tissue, that promotes a local bluish discoloration related to the transparency of the orbicularis muscle. In the buccal area and in the parotideomasseteric area, the skin is connected by vascular septa to the subcutaneous fat layer and to the mimetic muscles of the nasolabial and labiomental fold. This strong skin adhesion can also be identified between the skin and the muscle and propitiate the formation of local creases (Cotofana et al. 2016; Mendelson and Wong 2012).

Layer 2: Subcutaneous Tissue

The subcutaneous layer of the face is composed of reticular fibers and subcutaneous fat. The fat provides volume and the fibrous retinacular cutis provides support, binding the dermis to the underlying SMAS. The retinacular cutis is the portion of the retaining ligament that passes through the subcutaneous tissues (Rohrich and Pessa 2008).

These connective fibers are named retaining ligaments or fibrous septae depending on the location. Through these tissues, nerves and blood vessels emerge from the depth to the surface and often coincide with facial creases. They also work as a fixation placement for the skin to facial expression muscles. Their structure is similar to a tree: the branches are thicker and smaller in the lower portion and become more numerous and thin on the surface when they reach the dermis. This explains why it is easier to dissect at the subcutaneous level deeper than more superficially closer to the dermis. These fibers in some places become more organized and subdivide the subcutaneous tissue into distinct fat compartments that maintain the stability of the soft tissues in the face. In other places, the connective fibers insert in the dermis delimiting certain regions and attaching the layers of soft tissues to the muscular fascia and to the facial skeleton, constituting true ligaments (Mendelson 2012). The fat pads of the cheek were described in detail by Owsley (1993), Pessa et al. (1998a), Rohrich and Pessa (2007), Gierloff et al. (2012a), and Pilsl et al. (2012).

The adipose tissue of the face can be further subdivided into two compartments, superficial and deep fat. The fat inside each compartment provides volume and stability, thus contributing to the overall appearance of the face.

The superficial subcutaneous fat also varies according to regions of the face: in areas such as eyelids and lips, this layer is scarce, while in other areas, as the nasolabial segment, it is thicker and adhered to the surface.

There are three distinct cheek fat compartments: the medial, middle, and lateral temporal-cheek fat. The lateral temporal-cheek compartment is the most lateral compartment of cheek fat. Three subcutaneous fat compartments exist around the eye (Fig. 3).

The most important area of thickened subcutaneous fat is the malar fat pad. The two central fat compartments (medial and middle) are the main components of the malar fat pad. The malar fat pad is a triangular area of thickened superficial fat with its base placed along the nasolabial fold and its apex over the superolateral malar prominence (Mendelson and Jacobson 2008).

The nasolabial fat extends lateral and parallel to the nasolabial sulcus and is responsible for the formation of the nasolabial fold. The malar fat is located lateral to the nasolabial fat in the zygomatic region where it thickens to form the malar prominence, whose lateral portion extends to the parotid. Jowl fat is the most inferiorly situated and is located laterally to the depressor anguli oris muscle (Fig. 4).

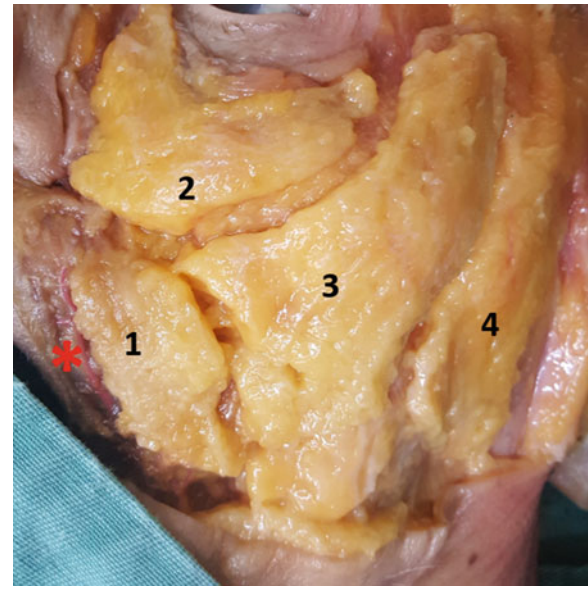

Fig. 3 A fresh-frozen cadaver where subcutaneous fat compartments were exposed and separated. 1: nasolabial subcutaneous fat compartment; 2: medial subcutaneous fat compartment; 3: middle subcutaneous fat compartment and 4: lateral subcutaneous fat compartment. * Facial artery

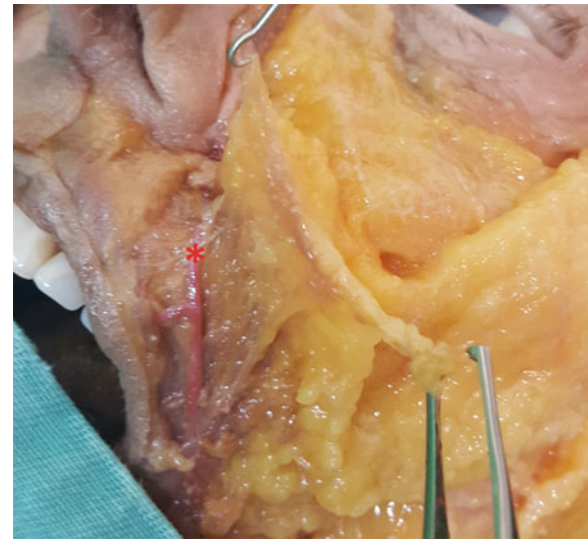

Fig. 4 A fresh-frozen specimen where nasolabial fat compartment where removed showing the facial artery just below the subcutaneous fat

Superficial fat compartments
Temporolateral fat pad
Superior orbital fat pad
Lateral orbital fat pad
Inferior orbital fat pad
Nasolabial fat pad
Medial cheek fat pad
Middle cheek fat pad
Jowl fat pad

Deep fat compartments
Medial suborbicular fat pad (medial SOOF)
Lateral suborbicular fat pad (lateral SOOF)
Deep medial cheek fat pad
Buccal fat pad

Layer 3: Superficial Musculoaponeurotic System (SMAS)

The SMAS was initially described as a fibromuscular layer separating deep facial fat from superficial facial fat (Mitz and Peyronie 1976).

It extends as a single layer from the superficial temporal fascia, passing through the lateral face to the neck where it can be identified as the superficial cervical fascia containing the platysma muscle (Ghassemi et al. 2003; Gladstone et al. 2005).

Despite being a continuous layer throughout the face, in some areas the superficial muscular component predominates, whereas in other areas, devoid of muscle, predominates the aponeurotic element. The SMAS is located on the lateral portion of the face, that is, posteriorly to the anterior margin of the parotid-masseteric region. Therefore, in this region there is only fascia and fat, and in the lower part, there is part of the platysma muscle. Regarding the nomenclature, it is named temporal fascia in the region with the same name and parotideomasseteric fascia that involves both the masseter muscle and the parotid gland. The last is a cranial continuation of the superficial lamina of the cervical fascia. Along the cervical fascia, we have the platysma muscle that usually reaches up to the level of the buccal angle (Mendelson 2009; Stuzin et al. 1992).

Unlike skeletal muscles that are located below the deep fascia in practically all regions of the body, facial expression muscles are located interspersed in the subcutaneous tissue and usually have bone insertion only at one of its extremities, while the other is inserted into the skin, mucosa, or other muscles. In the medial region of the face are more bulky and flat muscles forming a more superficial layer just below the subcutaneous tissue.

The third layer has strong connections with the deep layers through orbicular, zygomatic, masseteric, and mandibular septa and retention ligaments. The retention ligaments are attached to the periosteum and the deep muscles and pass through the layers of the face and the SMAS. The occipitofrontal muscle is fixed by the superior temporal septum. In the medial orbital region between the palpebral and orbital portion of the orbicularis muscle is located the orbital retention ligament. The orbicularis oculi muscle is fixed medially by the orbital retention ligament, and in the lateral portion, it joins the zygomatic ligament composing the "tear trough."

The frontal portion of the occipitofrontal muscle has insertions into the procerus, corrugator supercilii muscle, orbicularis oculi muscle, and into the skin. The platysma muscle at its upper limit has adhesion to the masseteric ligament and the mandibular portion by the mandibular ligament. At the border between the anterior and lateral portions of the face, layer 3 is strongly connected to the buccinator muscle by the masseteric ligaments, which have no direct connection to the masseter muscle itself. In the lateral part of the face, SMAS joins several mimetic muscles during facial expression such as zygomaticus major and minor, orbicularis oculi, depressor anguli oris, depressor labii inferioris, and sometimes the risorius muscle in order to act together as a unit around the oral commissure (Mendelson and Wong 2012).

Layer 4: The Loose Areolar Connective Tissue Layer

Layer 4, the loose areolar connective tissue layer, is located below the SMAS and contains deep fat spaces and compartments, ligaments, deep layers of the intrinsic muscles, and branches of the facial nerve. Functionally, these spaces in layer 4 allow muscular movements independent of muscles of facial expression, over the deep fascia responsible for mastication (Muzaffar et al. 2002).

In the lateral side, immediately in front of the ear, extending 25–30 mm forward of the cartilage to the posterior border of the platysma, there is a diffuse area of ligament attachments, described by Furnas as the platysma auricular fascia (PAF) (Furnas 1989).

The part of the PAF immediately forward and inferior to the tragus was later named the Lore's fascia. Therefore, the entire lateral side of the face, where the PAF and Lore's fascia are located, is the most fixed region of the face, being commonly

used for the fixation of sutures such as those used in facelift and nonpermanent suspension sutures (Moss et al. 2000).

Another important region is delimited in the anterior part of the masseteric ligaments: the zygomaticus major muscle crosses layer 4, and its fibrous fixation in the maxillary bone delimits the lateral and lower portion of the deep medial cheek fat (DMCF). One way to find the bone insertion of the zygomaticus major is to draw a line from the lateral angle of the orbit to the angle of the jaw. This triangular space lies directly in the maxilla and is limited medially and inferiorly by the facial vein and superiorly by the zygomatic ligament and is very important in facial reconstruction procedures with fillers (Cotofana 2015).

The buccal space is located below the medial and lateral part of the DMCF. This compartment is posteriorly separated from the masticatory space (which includes the buccal fat pad or Bichat's fat) by the facial vein and the masseteric ligaments (Cotofana et al. 2015).

Layer 5: Deep Fascia and Periosteum

Located under SMAS, this layer has different names and structures depending on the location on the face or neck. In the region of the scalp we have the periosteum, in the temporal region this layer is called deep temporal fascia and includes the temporal fat pad. In the neck it continues with the cervical fascia, and in the lateral region of the cheek, it is denominated parotideomasseteric fascia (Sykes et al. 2015; Cotofana et al. 2015).

In the lateral portion of the parotid gland and the masseter muscle, SMAS is densely adherent and continues as the parotideomasseteric fascia. It embraces the parotid gland, the parotid duct, and the buccal branches of the facial nerve and the transverse artery of the face. In continuity, it crosses the zygomatic bone and in the temporal region, where it includes superficial temporal fat and is named as superficial lamina of the deep temporal fascia. On the anterior margin of the masseter muscle, this fascia divides into two parts and forms a tent-like space, adhered to the buccinator muscle and to the masseteric ligaments. Within this space, they cross the parotid duct and the facial vein. Superior to this fascia, there is a fibrous ligament widely attached to the zygomaticus major muscle (Cotofana 2015).

The parotid cutaneous ligament is in fact a false retention ligament and lies like a fibrous band along the lower part of the parotid gland, which originates from the parotid fascia and runs to the dermis where it anchors the skin. In contrast to the above area, on the lower half of the masseter muscle, Mendelson et al. (2008) described a space called the pre-masseteric space, which exists between the parotideomasseteric fascia and the platysma SMAS. This space contains no vital structures and can serve as a safe and avascular sub-SMAS dissection plan in surgical and cosmetic procedures (Thomaidis 2014; Mendelson et al. 2008).

The infraorbital foramen is located in the midpupillary line, protected between the insertion of two muscles: the levator labii superioris, superior to the foramen, and the levator anguli oris muscle, whose bony attachment of the can be found close to the infraorbital foramen (see chapters ▶ "Facial Anatomy View for Aesthetic Botulinum Toxin Injection" and ▶ "Facial Anatomy View for Aesthetic Fillers Injections").

Aging Changes in the Face

At first, fillers were based only on dermal and subcutaneous applications. Without the knowledge of three-dimensional anatomy and aging processes, the results were limited. Plastic surgeries were often performed early, and even so, the results were limited to the upper layers, treating only sagging skin and musculature.

Aging is a biological process that results from the gradual reduction of the function of cells and structural components. A young face presents preserved volumes and well-defined contours. As we age, there is an increase in compartmentalization of the regional facial aesthetic units, which become more individualized, mainly due to resorptions in the bone and adipose tissues (Ilankovan 2014).

Some of the changes in aging include skin sagging, decreased elasticity and thickness of skin, accentuation of folds and ridges, and deterioration of the ligaments that support the soft tissues such as the orbitomalar, zygomatic, and masseteric ligaments.

The loss of bone support, as well as redistribution or reduction of volume of fat compartments, is a heterogeneous process. The accentuation of the folds, for example, is most pronounced in some areas like nasolabial fold, labiomandibular fold (marionette line), and malar mound (Weinkle and Susan 2017).

Facial Bones

Bone changes are undoubtedly a major cause of the manifestations of individual differences among humans, whether in ethnicity, gender, or age. It is believed that the facial skeleton expands continuously throughout life. Some facial anthropometric measures of the face progressively increase with age, while certain areas of the facial skeleton reabsorb. Areas with a strong predisposition to reabsorption include the middle face skeleton, particularly the maxilla, superomedial, and inferolateral areas of the orbital border; the piriform region; and the anterior portion of the mandible (Mendelson and Wong 2012a).

Studies such as Hellman (1927), Lambros (2007), Pessa et al. (1998b), and Shaw et al. (2011) highlighted the skeletal changes over time and demonstrated the bone remodeling with aging mainly of the middle face, jaw, and orbit.

The Mendelson Study 2012 was undoubtedly the basis for our current understanding of facial changes during bone aging and guided the modern approach to face fillers and volumizers. In summary the main features are protrusion of the glabella; lateral translation of the orbits; expansion of the supraorbital ridges; increase in length, width, and vertical dimensions of the nose; increase in the depth and lateral expansion of the cheeks; and increase in vertical height in the occlusal region associated with increased chin prominence (Mendelson and Wong 2012a).

A study by Richard et al. (2009) and Kim et al. (2015) demonstrated changes in facial angles and reported that glabellar, orbital, maxillary, and piriform angles decrease with age as well as the maxillary, piriform, and infraorbital borders regress. Other study performed in an Asian population found similar results; however, the orbital and maxillary angles showed fewer changes, and the piriform angle showed more prominent changes compared to studies in Caucasian populations (Richard et al. 2009; Kim et al. 2015).

Facial bones changes
The frontal region becomes more prominent and the supraorbital border undergoes greater bone deposition
The orbital region loses its normal rounded shape and becomes irregular, with resorption in the inferior lateral portion and superior medial portion
Increased pyriform aperture/increased nasal opening
Anterior and inferior maxillary resorption (retrusion of the middle third of the face)
Increased jaw angle
Chin grows forward and oblique
Anterior resorption of the zygomatic bone
Anterior and posterior remodeling of the zygomatic arch, accentuation of the temporal fossa
Anterior and inferior reabsorption of the mandible

Facial Ligaments

The face ligaments in their pathway from their fascial origin to the superficial musculoaponeurotic system (SMAS) are robust and do not undergo significant primary aging changes (Brandt 2012).

The bony skeleton of the face serves as support for soft tissues, musculature ligaments, and fat. Therefore bone changes of the face with aging affect all these structures. It is known that the ligaments of the face such as the orbital retention ligament, mandibular ligament, and the zygomatic ligament, one of the most rigid, have bone insertions, and therefore changes in bone angulation greatly affect the competence of these structures to support the soft tissues.

One of the most common and early examples occurs between the orbital and malar regions: the decrease of the maxillary angle and the expansion of the inferior orbital border directly affect the anterior positioning of the orbital septum, consequently the orbital retention ligament and the

structures contained in the orbit and maxilla. The loss of orbicularis muscle stability and reduced competence of the retaining ligament facilitates a herniation of the eyelid bags and accentuates the nasojugal groove. Orbital aging also affects adjacent areas providing increased prominence of the medial fat pad, elevation of the medial brow, and lengthening of the cheek junction, in addition to the changes in the zygomatic ligament.

One of the questions still unanswered refers to the physiology of aging of the ligaments and septa. A study with knee ligaments in rabbits by Thornton 2015 demonstrated no age-related changes but changes in expression of the lubricin/PRG4 gene. It is therefore speculated that perhaps age-related changes such as alteration in the position of the ligament and its bone, cutaneous adhesion, and other adjacent structures are being affected and therefore can influence the mechanical function (Thornton et al. 2015).

It is also postulated that during aging the ligaments that act as a fixation network to support the fat pads can lose stability and the ability to lift when distended due to soft tissue changes and excessive muscle contraction. Most of the ligament change is in the multiple finer retinacular ligament branches from the SMAS through the subcutaneous layer to the dermis, which are more prone to the being weakened over time by repetitive movement (Brandt et al. 2012).

The attenuation of the retention ligaments occurs mainly in the superficial part next to its insertion in the dermis. This gives the impression of descent of the facial soft tissue contributing to the morphological appearance which can be observed clinically as accentuation of grooves (nasojugal, malar orbital, nasolabial, and labiomandibular), besides the deflation of the cheek tissues and loss of the mandibular contour in the aged individuals (Farkas et al. 2013).

Facial Fat Compartments

In the aging face the fat compartments change differently in volume and position, according to the anatomical region of the face. There are also important differences between genders and among ethnicities (Rohrich and Pessa 2007).

A young face is characterized by a homogeneous and well-balanced distribution of the superficial and deep fat. As people age, subcutaneous fat is lost in some parts, particularly in the periorbital, perioral, forehead, jaw, chin, and in the malar regions. Some adipose compartments tend to decrease earlier, while others, later. Clinical observation shows that the periorbital and malar fat pads tend to be affected first, followed by the lateral, deep malar, and lateral temporal areas (Lee and Yen 2017).

A study by Gosain et al. (2005) with MRI showed relative cheek fat hypertrophy in the older group compared to the younger group (Fig. 5).

Gierloff et al. (2012b) demonstrated an inferior migration of the midfacial fat compartments and an inferior volume shift within the compartments and volume loss of the deep medial cheek fat during aging. The buccal fat pad, the component of the deep layer, has a pronounced reduction, and its descent increases the marionette lines.

The decrease of the malar fat pad and decrease of the region accentuate the nasojugal and nasolabial grooves. Absorption of the periorbital fat accentuates the orbital concavity, while the palpebral fat of the orbital septum become prominent (Cotofana 2016).

Another study by Wan 2014 examined the size of adipocytes from cadaveric specimens with a mean age of 71 years and demonstrated that the adipocyte size in the median deep cheek fat was significantly lower relative to the nasolabial fat located more superficially, supporting the theory that the deep and superficial facial fat pads are morphologically different (Wan et al. 2014).

It is unclear what drives morphological differences, but more recent observations point to a trend suggesting that deep compartments may be more prone to atrophy, while some superficial fat compartments may hypertrophy during aging as the superficial nasolabial fat compartment (Wan et al. 2013).

Approach to Cosmetic Patients

New concepts in aging anatomy, coupled with safe and effective fillers, have revolutionized the approach to cosmetic patients. The addition of volume to the subcutaneous compartments and

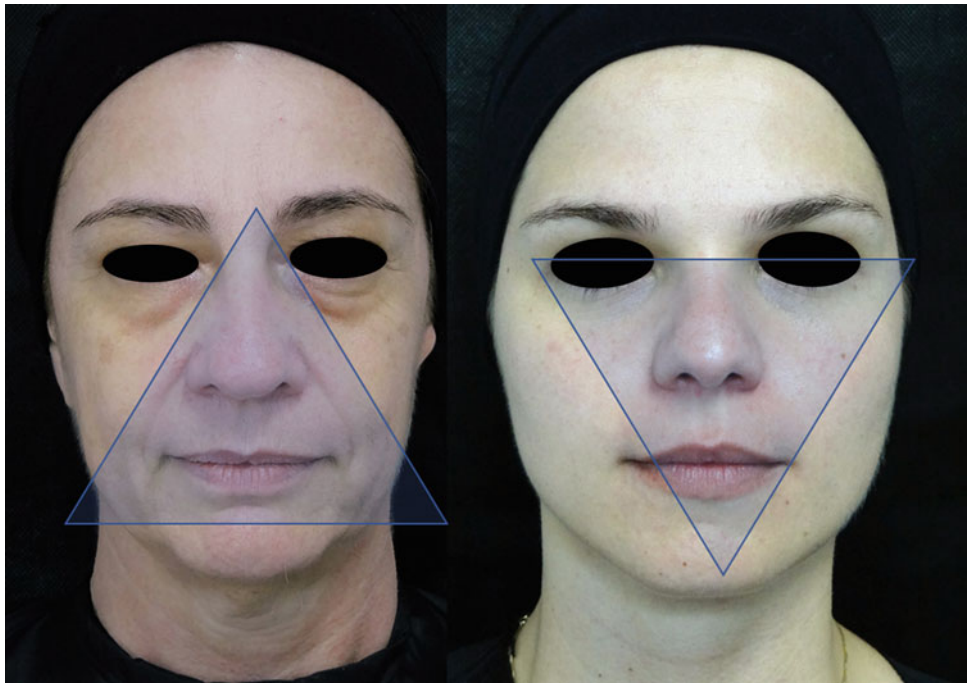

Fig. 5 The combination of features of the aging face include flattening of the cheeks, drooping of the skin over the cheeks, sagging and lack of definition of the jawline and fat accumulating between the neck and chin. All these changes invert the "triangle of youth" into the "pyramid of age"

restoration of the support of the superficial musculoaponeurotic system and adjacent structures associated with biostimulators and biomodulators, such as botulinum toxin, promote true nonsurgical "lifting" (Fig. 6).

However, there is no universal prescription to be repeated for all patients, and this is perhaps the most important aspect of the facial evaluation of these patients. When performing an assessment for the establishment of the aesthetic treatment plan, it is essential to identify the individual characteristics of each face and the possible treatment areas, establishing priorities and planning the sequence of interventions.

Although the application techniques may be similar, each patient has a unique face with its deficiencies and needs an individualized diagnosis. The goal is to restore youthfulness without overdoing it, to maintain the harmony of a face without caricaturize, and to approach male patients without feminizing. It is not only about rejuvenation but about facial beautification and harmonization.

Swift published a literature review study in 2011 and identified seven important facial features impacting on the perception of beauty: facial shape (cheeks and chin), forehead height, eyebrow shape, eye size and inter-eye distance, nose shape, lips (length and height), and skin clarity/texture/color. The facial shape, eyebrow shape, volume and lip contour, and nasal contour and angles are passive of correction only with injectable treatments such as botulinum toxin and fill (Swift and Remington 2011).

Although symmetry is considered a sign of beauty and attractiveness, it is important to consider other principles such as balance and harmony. Beauty is not always symmetrical.

The right and left sides of the face never have perfect symmetry, and yet if in harmony they make the face attractive (Swaddle and Cuthill 1995).

The pattern of Greco-Roman beauty prevailed until the Renaissance, when Leonardo da Vinci determined important measures of body and facial proportion. In frontal view, the face was divided into four segments, in which the nose was equal to

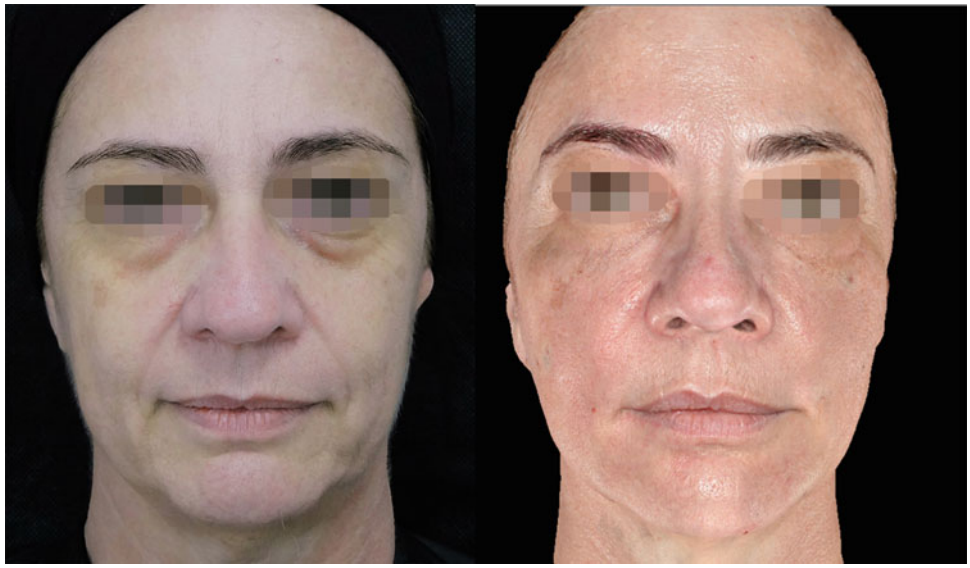

Fig. 6 Pre and post-treatment facial volumization and periosteal support points with hyaluronic acid in the malar, mandibular and zygoma regions. Improvement of nasolabial fold, nasolabial fold and marionett lines

1/4 of the total. In the lateral view, the craniofacial complex was represented by a square, previously delimited by the vertical plane of the face (Fig. 7).

Youth and beauty are exemplified by Dr. Steven Liew, Australian plastic surgeon, as a full and broad medium face, referred as Youth Triangle. Studies reveal that a triangular pattern with the base in the bizygomatic region and angle in the mentum is globally considered attractive to people of different ethnic origins.

This pattern does not correspond to the majority of the population which has its predominant individual characteristics, but it can be achieved by volumizing with fillers in the middle third and or decreasing the masseter with accurate injections of botulinum toxin.

Facial Assessment

Each professional has a personal systematization in the facial evaluation. However, some aspects must always be addressed, mainly because the current facial evaluation applies for both rejuvenation and facial beautification (see chapters ▶ "Hyaluronic Acid Fillers: Codifying the Face for Foundation, Reconstruction, and Refinement" and ▶ "My Personal Experience with Fillers") (Figs. 8 and 9).

- First impression: The first step may seem subjective, but It consists in observing the first impression that the patient transmits: his look, his features, and his countenance. They are perceptions that each face can convey through its appearance. A research project in Germany on facial attractiveness with digitally created faces based on perception of beauty revealed that regardless of ethnicity of the appraiser, there was a similarity between the ideals that make up a compelling face. The processing of attractiveness lasts for milliseconds, where the eyes scan the entire face, while the brain analyzes contours, shapes, characteristics, and quality of the skin and defines whether or not they like it. Facial attractiveness goes far beyond wrinkles and furrows and is a whole set of impression and expression, shapes, symmetries, asymmetries, angles, projections, and proportions.
- Facial shape: The second aspect is the shape of the face and evaluation of the proportions by dividing the face into thirds. The face is divided into horizontal thirds. The upper third

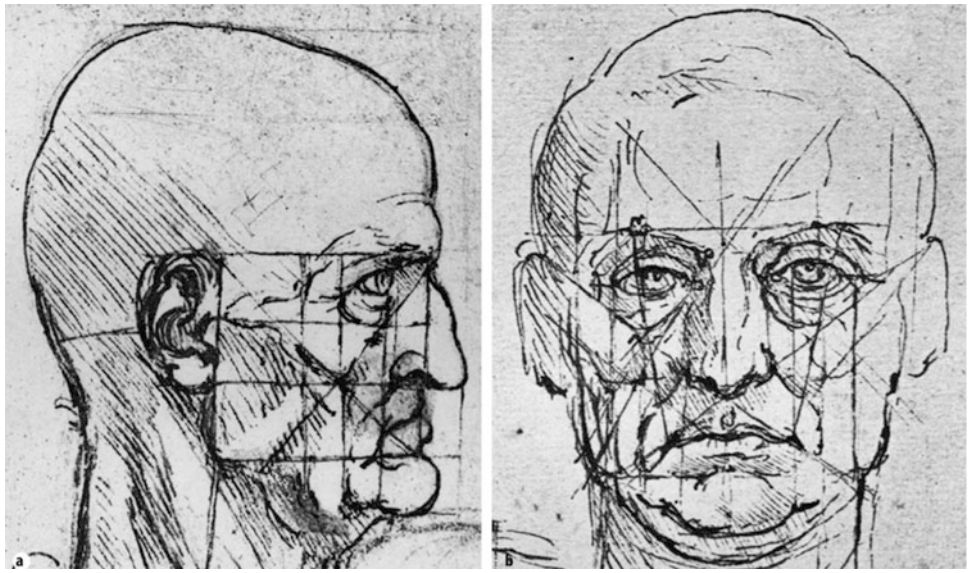

Fig. 7 Facial analysis according to Da Vinci (about 1495). (**a**) The division of the face into thirds; (**b**) the proportions of the face. (Adapted from M. Eisenmann-Klein C. and Neuhann-Lorenz. Innovations in plastic and aesthetic surgery, 2007)

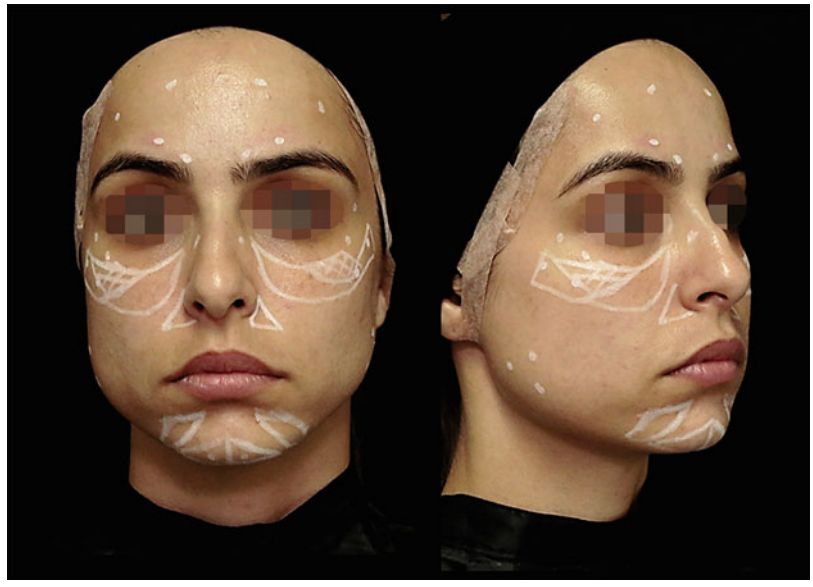

Fig. 8 Frontal and right view of the face before Treatment: Full face beautification with Botulinum toxin and Fillers. Dyposrt ® at the pointed tips

extends from the hairline to the glabella, the middle third from the glabella to the subnasale, and the lower third from the subnasale to the menton.

- We first evaluate the face of all the symmetrization, size, proportionality, and dimensions. Then we evaluated each third of the face, both front and lateral and at 45°. Evaluate the facial contours, nasoglabellar and nasolabial angles, and the convexity of facial projection areas, such as the nose, zygoma, chin, lips, and forehead.
- Dynamic assessment: Then the evaluation of the movements of the mime musculature, presence

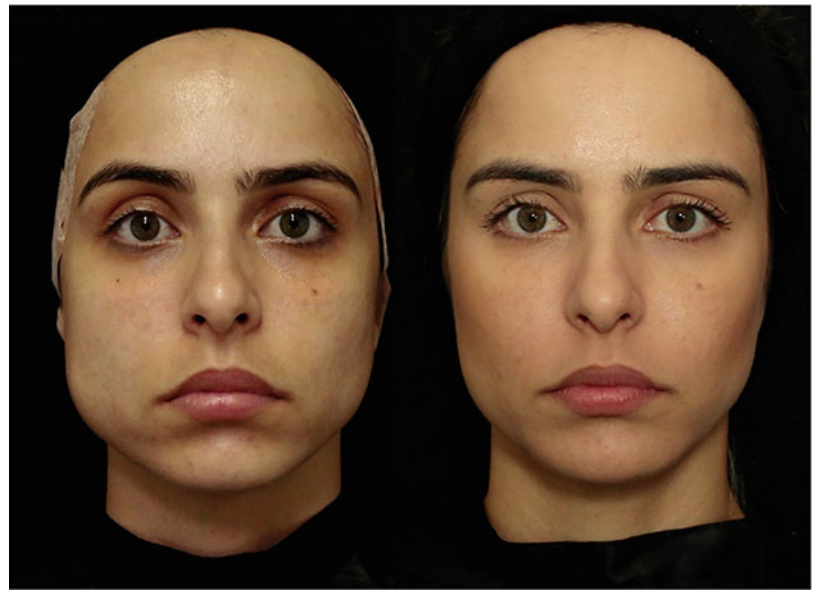

Fig. 9 Full face beautification with Botulinum toxin and Fillers. Frontal view before and two weeks after treatment. The masseter muscle was treated with 15u on each side. Emervel® Touch: 0.2 cc in each tear trough; Emervel® Volume: 1 cc in each mid cheek; Emervel® Classic: 1 cc in the nasolabial folds and mentolabial folds and 1 cc in the mento. Total of 4.4 cc)

of static lines and dynamics, as well as the adipose cushions and their consequent clinical implications in the grooves of the facial projection.

- Skin evaluation: Finally, it is important to observe the general characteristics of the skin, quality, color, texture, tone, hydration, and signs of photoaging that are also fundamental in the set of treatments and in the evaluation of cosmetic patients as well as the early detection of preneoplastic lesions.
- Picture evaluation: The evaluation can be bi- or three-dimensional, with a good clinical evaluation and analysis of anatomical measurements or repairs, photographic analysis, and videos. Currently also made possible by equipment that uses the combination of three-dimensional images, very useful both in the pre- and post-treatment to evaluate immediate results and areas to be complemented (Swift and Remington 2011) (Figs. 10, 11, and 12).

Thirds of the Face

In the upper third we should evaluate:

1. Proportionality between the remaining thirds
2. Dynamic and static wrinkles in the frontal, glabella, and periocular regions
3. Volume and concavity of frontal region
4. Positioning of the eyebrows
5. Volume and concavity of the temporal region. (Figs. 13 and 14)

The frontal region tends to become flat with aging and loss of volume, both the subcutaneous fat and the bone. This aspect of flattening of the curvature of the forehead may be visible also in young patients, as in the case of Asians or in people with great loss of body fat. The frontal-occipital muscle responsible for the elevation of the eyebrows and the creation of transversal wrinkles in some individuals may be very active in young and middle-aged patients, constituting a good indication of the use of botulinum toxin both preventive and therapeutic. The same occurs with the corrugator supercilii muscles. When hyperactive, they accentuate the wrinkles of the glabellar region that can be treated with Botulinum toxin. Techniques of volume replacement in the frontal and temporal region have gained prominence and are very well indicated for the replacement of volumes and contours. A special attention must be given to the glabellar region due to the increased risk of arterial occlusion at this location (see chapter ▶ "Hyaluronic Acid Filler for Forehead, Temporal, and Periorbicular Regions").

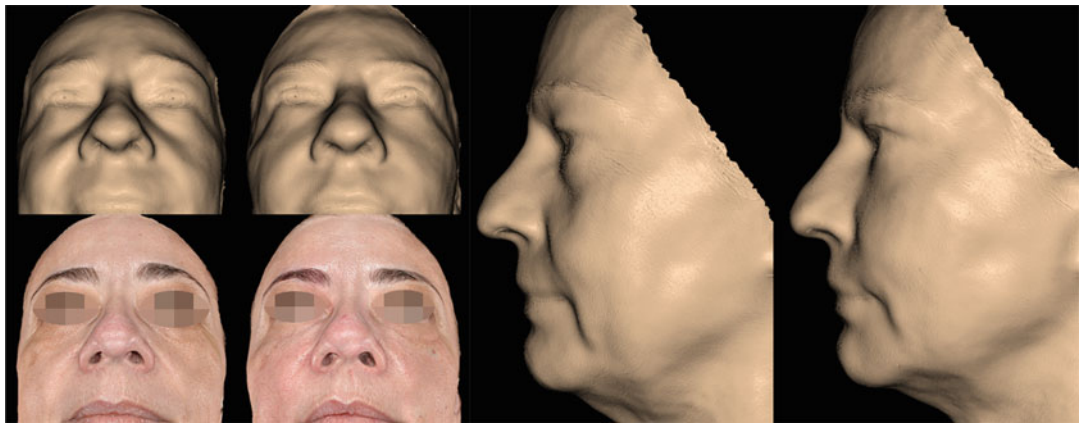

Fig. 10 Image pre and post treatment of facial volumization with hyaluronic acid performed by three-dimensional photography equipment. The method assists in the overall evaluation and 3D visualization of grooves, irregularities of relief and facial contour

In the middle third we should evaluate:

1. Proportionality between the remaining thirds
2. Presence or absence of a negative vector or hypoplastic malar eminence
3. Loss of volume in the orbital region, zygomatic, or infraorbital malar
4. Soft tissue ptosis
5. Accentuation of the nasolabial and palpebromalar groove and nasojugal folds and labiomandibular fold (marionette line)
6. Proportions of the nose and nasolabial and nasofrontal angles

The aging bone and soft tissue in the middle third is accentuated, and the structural deficiency contributes significantly to the aged appearance, even in young patients who present some degree of malar hypoplasia. Loss of projection deepens the nasojugal and nasolabial grooves and accentuates the medial slippage of the deep malar cushions. The piriform fossa widens, and just like the nasal bone, there is loss of support of the alar base and the upper lip. The nasolabial and nasofrontal angles delimit the position and relation of the nose. The upper lip area undergoes lengthening of the cutaneous portion and shortening of the vermilion.

The nasojugal and palpebromalar grooves correspond to the zygomatic ligament and the orbicularis retention ligament, respectively, and mark the location of the junction of the malar region with the eyelid and may be accentuated early in some patients. As the orbital septum attenuates with age, the periorbital fat protrudes, and as the orbicular retention ligament is fixed in the lower palpebral region, the groove accentuates below the bags. It is important to evaluate in these patients the volumetric deficiency in the malar, both bone and soft tissues, because they influence the inferior orbital region.

The application techniques of filling in this region initially aim at the restructuring of the supraperiosteal regions, recovering part of the volume lost in the middle face and its sustentation. The malar mound (SOOF) can then be approached, always supporting the deep malar cushions, before approaching the inferior orbital region and the nasojugal sulcus. The nose can be reshaped with fillers. Biostimulation techniques are increasingly indicated and are prominent throughout the middle region of the face, with care only in the region of the lips and lower eyelid.

The application of botulinum toxin in the middle third is focused on the periorbital, perioral, and nasal region and lift of the upper lip and ala of the nose and in some cases to modulate the smile, mainly in asymmetries (see chapter ▶ "Hyaluronic Acid Filler for the Malar Area") (Fig. 15).

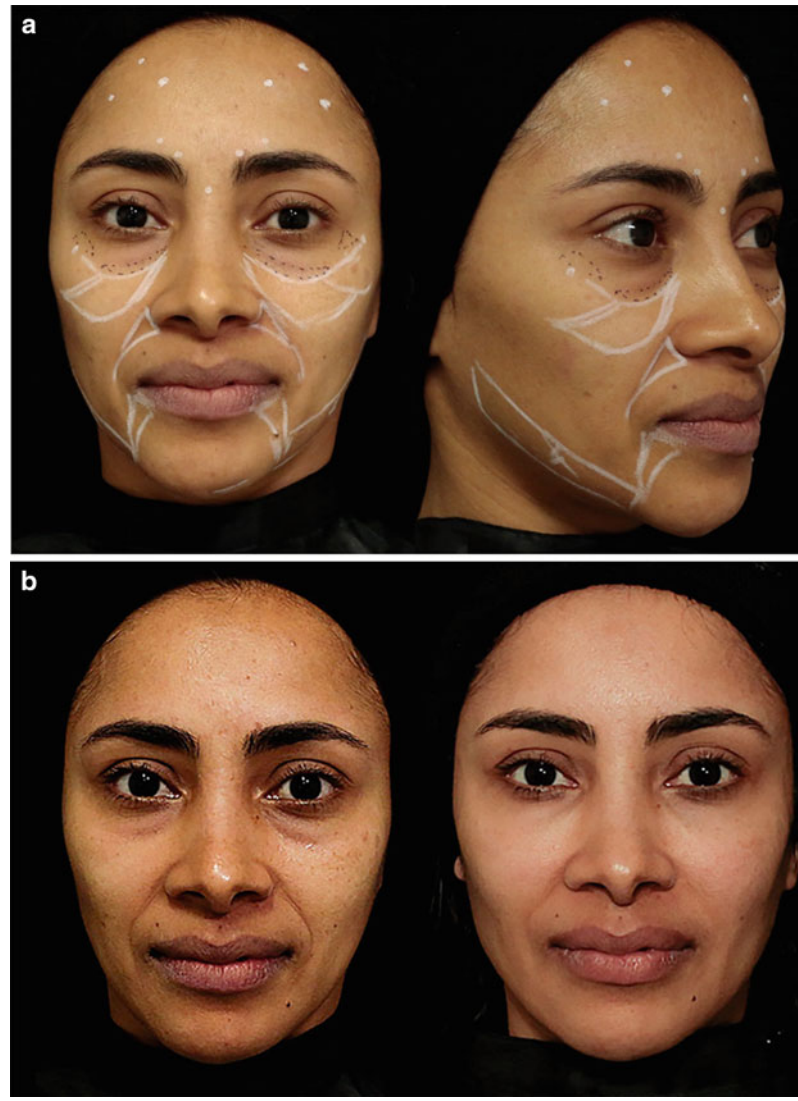

Fig. 11 Beautification and rejuvenation treatment with botulinum toxin and fillers. (**a**) Botulinum toxin treatment was indicated according to the marking only in the upper third with Dysport®. Emervel® Touch: 0.3 cc in each tear trough; Emervel® Volume:5 cc distributed in mid cheek, zigomátic arch and mandibular contour; Emervel® Classic: 2 cc distributed in the nasolabial and labiomandibular folds; and Restylane® Perlane: 1 cc used at the points of bone support. Total of 8.6 c (**b**) Before and 2 weeks after treatment

In the lower third we must evaluate:

1. Perioral region: rhytides, loss of elasticity and volume
2. Lips with proportion, projection, and contour
3. Mental region: volume, mentolabial groove, marionette lines, and mental hypercontraction
4. Submalar region, positioning, and volume
5. Contour loss in the mandibular line
6. Volume and lip contour

In the lower face, treatment strategies are traditionally focused on volume restoration; however, controlling hypermobility is also essential. Botulinum toxin is used as monotherapy or as an adjunct to other procedures in lower face rejuvenation.

Frequently patients only complain of the accentuation of the marionette lines and nasojugal groove. But similar to the middle third of the face, whenever possible the entire perioral area should be treated: lips, commissures, submalar region, chin, and jaw. Treating the chin can soften the face and also stretch the loose skin along the jaw line. The application of volumizers in the mental region may even promote relaxation of the

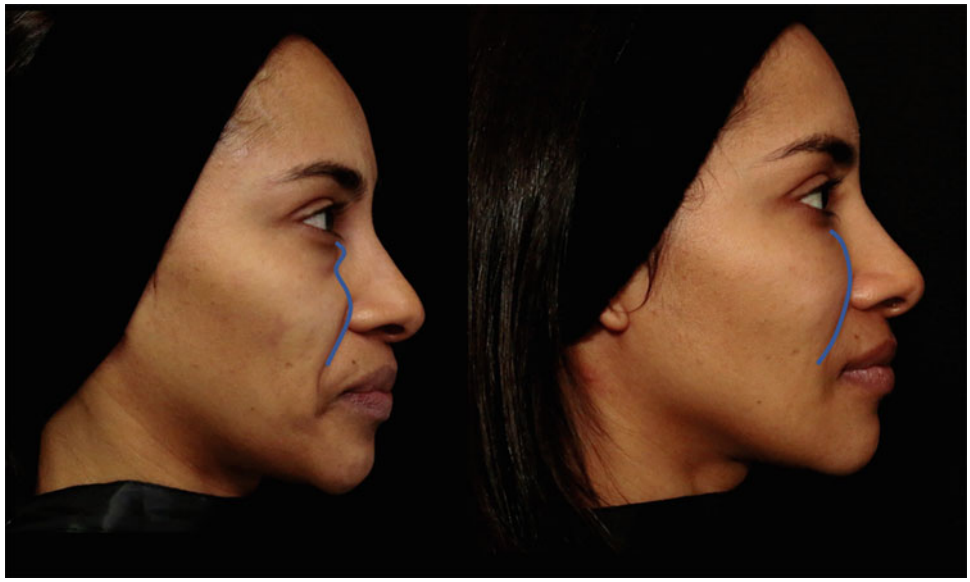

Fig. 12 Profile image showing significant change in the angle of projection of the anterior malar region and correction of depression in the tear trough after treatment of the support and volumization of the malar and zygomatic region. Observe improvement in the definition of the mandibular contour and the lateral region of the cheek

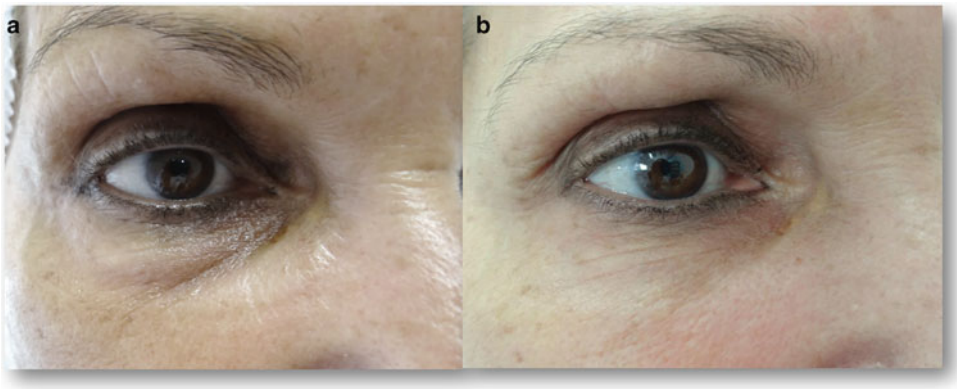

Fig. 13 Orbital region treatment in a 60-year-old patient with palpebromalar sulcus and tear trough: (**a**) before treatment with Emervel® Classic 0.3 cc on each side; (**b**) after treatment the result was sustained for 12 months

musculature acting as biomodulator, even without the association of botulinum toxin (see chapter ▶ "Hyaluronic Acid for Mental and Mandibular Contour"). It is important to evaluate the structure of the lips of each individual: depending on ethnicity, the ratio of the lower lip to the upper lip should be 1.5: 1, except in patients of African or Asian ethnicity, where this ratio can be 1: 1 (Jacono and Rousso 2015) (Fig. 16).

The jaw line defines the lower border of the face laterally. By descent of the overlying fat pads and loosening of the mandibular septum, "jowling" develops as an aging sign. Jowl ptosis and loss of submalar hollow are important features. Volume replacement of the malar area induces a lifting effect that affects not only frontal but lateral components as well. The correction of the esthetic jaw line often needs additional attempts. To reduce caudal-oriented platysmal

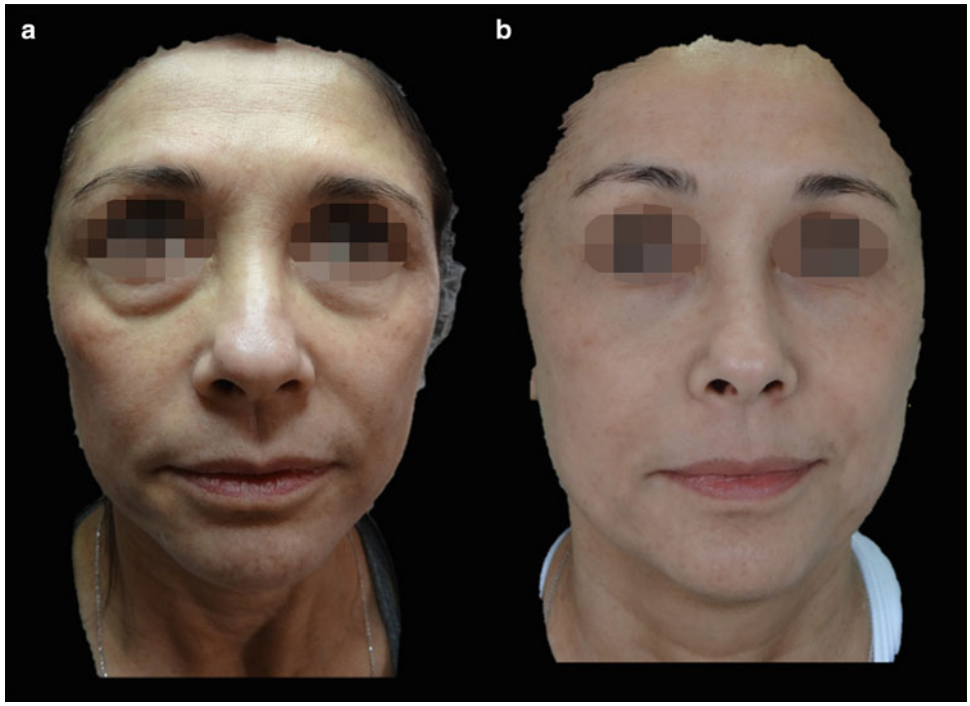

Fig. 14 (**a**) Before treatment: Patient with aging of the middle third of the face and periorbital region, loss of the medial malar fat pad, with protrusion of the palpebral fat pockets and accentuation of the nasolabial and nasolabial sulcus. (**b**) After treatment of the middle third with hyaluronic acid in the nasolabial and nasolabial folds, besides correction of the malar volume and anchorage points in the zygomatic arch. Treatment of pre-jowl marionette lines and grooves with calcium hydroxylapatite

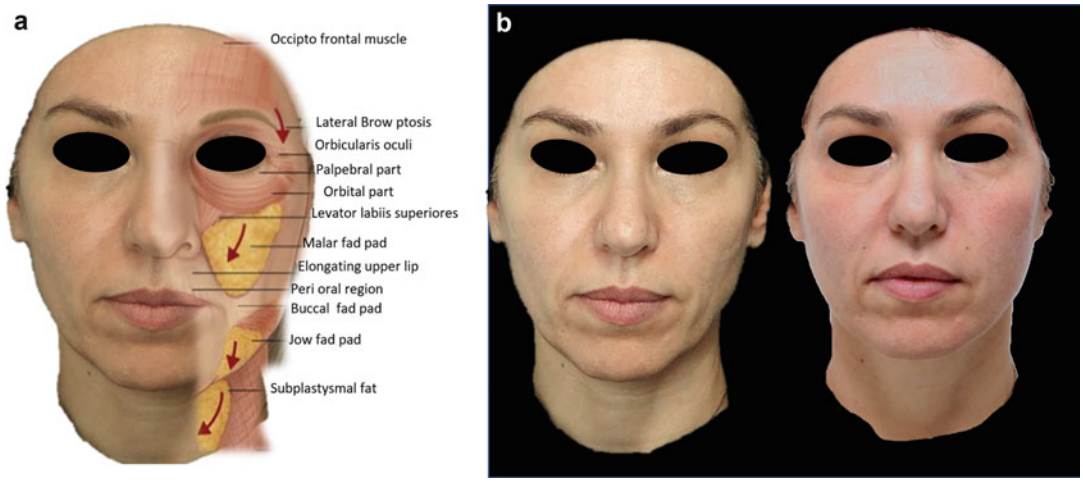

Fig. 15 (**a**) This image represents the early signs of aging of the orbital and malar region. In the transition from the retention ligament to the malar region, there is a decrease in the fad pad malar and consequently the support in the malar region. Beginning of the labiomandibular groove and discrete puppet lines, by dropping the jow fad pad. (**b**) Before and after treatment with "Sculptra" for projection and support of the middle/lower third; correction of the nasolabial fold and puppet lines

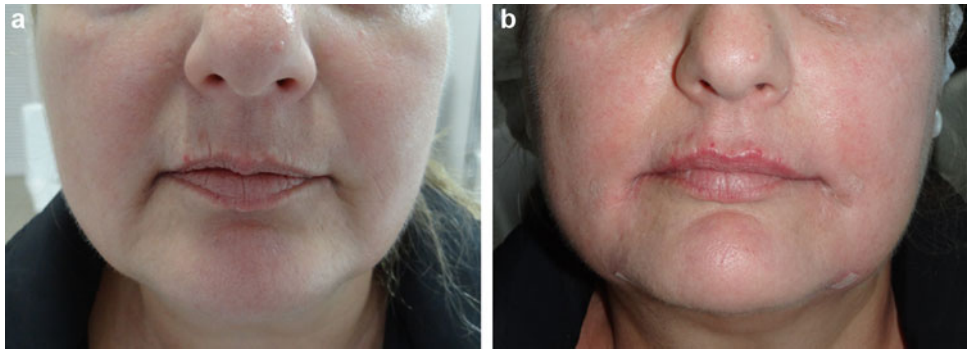

Fig. 16 (**a**) Before treatment. Fifty two-year-old female with aging of the perioral and chin regions, perioral rhytides, decrease in vermilion fullness, downward turn of the oral commissures, lengthened and assimetry appearance of the cutaneous portion of the upper lip and pre-jowl sulcus. (**b**) After treatment of nasolabial fold, marionette line and pre-jowl sulcus with calcium hydroxylapatite filler. Labial augmentation with hyaluronic acid fille

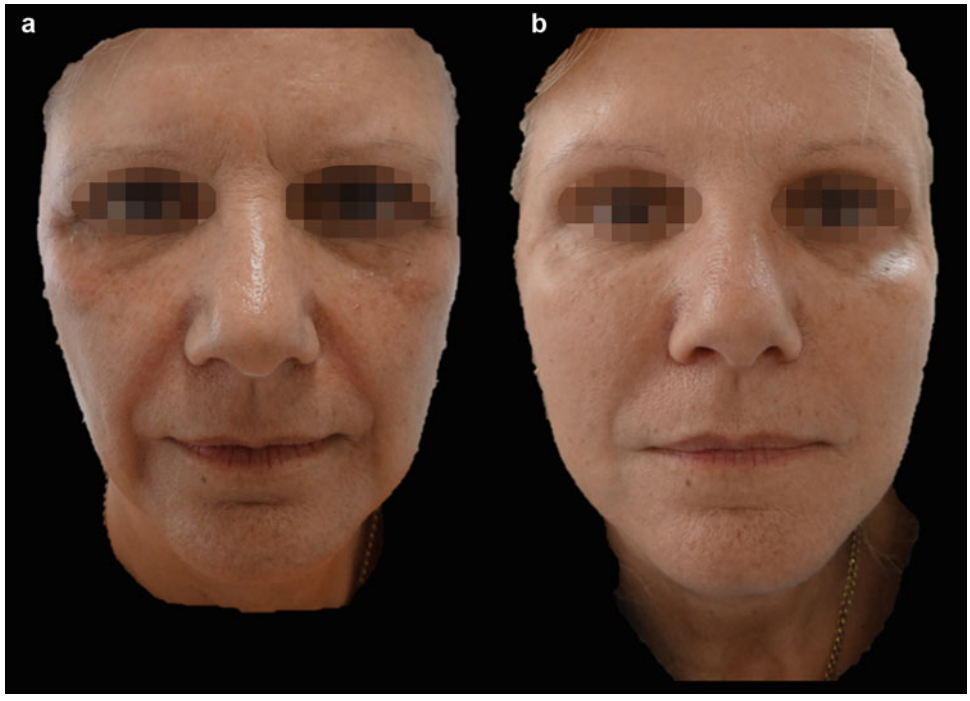

Fig. 17 Patient with intense aging of the middle third of the face, displacement of subcutaneous fat compartments and orbital retention ligaments, with nasolabial groove fat hypertrophy and labiomandibular groove. Before (**a**) and after treatment (**b**) with hyaluronic acid for projection and advancement of the middle third, correction of the nasolabial sulcus, nasolabial sulcus and marionette lines

forces, botulinum toxin is effective (Wollina 2016) (Figs. 17 and 18).

Beauty standards have to take into account that there are considerable differences in anatomy and in what is aesthetically attractive among different cultures, populations, ethnicities, and genders. A female or male face is governed by different principles of therapeutic approach.

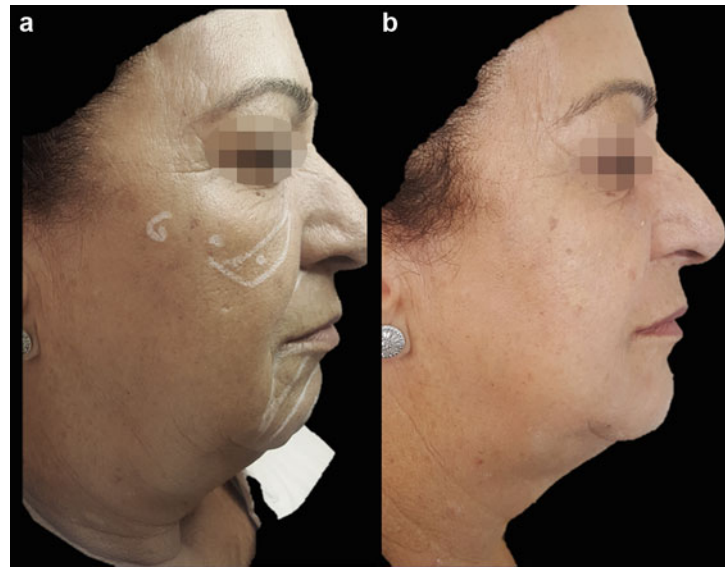

Fig. 18 Patient with intense aging of the mandibular contour, displacement of subcutaneous fat compartments and dehiscence of the mandibular ligament with submandibular fat hypertrophy associated with a defective chin projection. Before (**a**) and (**b**) immediately after treatment with hyaluronic acid for chin projection and advancement

Asian Patient Approach

Patients of different ethnicities do not have uniform characteristics; however the loss of volume during the aging is omnipresent for all of them. The restoration of the volume and the correction of individual or related disharmonies are fundamental strategies both in the prevention and in the individualized treatment of these patients. Compared with Caucasian patients, however, embellishment is a more common focus in Asian patients. The "ideal" oval facial shape can be created using different interventions depending on the characteristics of the patient's baseline (Chao et al. 2017).

Asian patients tend to seek treatments related to beautification interventions prematurely. Asians generally present a shorter face with smoother wider front, wider intercantal distance, flattening of the anteromedial face, lower structural projection of the central third of the face, broader nose, smaller lower third than the upper third, and in some cases retrognatia and microgenia (Liew 2015).

These characteristics induce a demand for fillings in the central region of the face such as the forehead, nose, and chin, especially in younger Asian patients interested in changing the face shape and to a look closer to the feminine ideal of beauty already mentioned "triangle of beauty." Lip augmentation is not usually indicated in Asians. In the cases of older patients, the volumization of these regions continues to be important, but in conjunction with the correction of age-related disharmony.

Male Patient Approach

Although both sexes undergo changes in adipose tissues during aging, as men have less adipose tissue they develop deep wrinkles more prominent than the fine lines observed in women (Sadick 2018).

The male skull is significantly larger than the female skull. The harmonious masculine face has a good proportion between the thirds of the face, a slightly longer face, and a well-defined mandibular line with a well-marked zygomatic prominence. The supraorbital border is more prominent, and the frontal, maxillary, zygomatic, and mandibular bone tend to be wider and more square-shaped (Sundaram et al. 2016).

Slightly visible wrinkles on the front and glabella give the masculine appearance an impression of proficiency and are perceived as signs of concentration. The key to treatment success is to soften the expression. Raising the eyebrows must

be avoided, especially in the lateral portion. A rounded shape tends to look feminine, as well as an increase in anterior malar convexity. The volume replacement in the masculine face should remain in the zygomatic, mandibular, temporal, and mental region. Small corrections in the palpebral or malar region smooth the nasojugal and palpebromalar groove. It is also important to note that temporal hollowing is aesthetically appealing in many men, and therefore lead corrections can be used only to better contour and elevate the lateral orbital region. Injection of fillers in the lips for some men may be indicated, but attention must be paid to avoid a bulky shape. The masculine lips are more straight and thin (Sundaram et al. 2016).

Take Home Messages

- Knowing anatomy related to aging is fundamental to ensure a good planning of treatment in an individualized and safe way for patients
- There is a complex and individual interaction between facial bones, facial retention ligaments, soft tissue lining, facial fat compartments, and underlying skin during the aging process, but in general the restructuring of the central region of the face is the key to success in rejuvenation treatments with fillers.
- It is important during treatment planning to discuss with the patient the possible goals to be achieved and to ensure that he understands the need for maintenance treatment given the progressive nature of the aging process.
- Beauty standards have to take into account that there are considerable differences in facial anatomy and in what is aesthetically attractive among different cultures, populations, ethnicities, and genres.
- Good face assessment and overall planning, including replacement of lost volumes, hyperkinetic area biomodulation, skin biostimulation, and complementary skin treatments, promote effective and longer-lasting results.
- Formulate an individualized treatment plan and always take into account the costs; in the impossibility of the patient to perform several procedures together, focus on the areas of greatest impact initially, and indicate a sequential planning of the other necessary treatments.

Cross-References

- ▶ Facial Anatomy View for Aesthetic Botulinum Toxin Injection
- ▶ Facial Anatomy View for Aesthetic Fillers Injections
- ▶ Hyaluronic Acid Filler for Forehead, Temporal, and Periorbicular Regions
- ▶ Hyaluronic Acid Filler for the Malar Area
- ▶ Hyaluronic Acid Fillers: Codifying the Face for Foundation, Reconstruction, and Refinement
- ▶ Hyaluronic Acid for Mental and Mandibular Contour
- ▶ My Personal Experience with Fillers

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Hyaluronic Acid Fillers: Codifying the Face for Foundation, Reconstruction, and Refinement

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Contents

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_43

Abstract

Techniques for facial aesthetic rejuvenation and enhancement are continuously evolving. The use of hyaluronic acid injectable fillers for rejuvenation is the second leading facial aesthetic procedure, after the use of injectable neuromodulator. The first step to achieve an optimal outcome in facial aesthetics is to understand the whole process of aging, such as bone reabsorption, atrophy of the fat compartments, muscle contraction, dental loss, and thinning of the skin. Hyaluronic acid filler is an important tool to achieve a global treatment of the face, since it is capable to restructure, to contour smoothly and to treat delicate areas as well. In this chapter we are going to describe facial assessment, indications, treatment planning, and procedures according to the anatomic area. Authors will explain the best technique and preferable hyaluronic acid to treat the forehead, temples, eyebrows, zygomatic and malar area, periocular region, chin, mandible, and perioral region.

Keywords

Face aging · Volume loss · Fat compartments · Hyaluronic acid · Fillers · Rejuvenation

Introduction

To effectively rejuvenate the aging face, it is necessary to understand the dynamic aging process. Epidermal thinning and the decrease in collagen cause skin to lose its elasticity. There is also the volume loss caused by fat atrophy in addition to a loss of bony support and projection. These factors lead to soft tissue descent and wrinkling, and contribute to the formation of nasolabial folds, jowls, crow's feet, and the sagging appearance of aged facial skin (Bosset et al. 2002; Fenske and Lober 1986; El-Doyati et al. 2002; Pessa et al. 1998; Shaw and Kahn 2007; Pessa 2000; Shaw et al. 2011).

Soft-tissue fillers can be successfully used to restore volume loss caused by facial aging in several anatomical regions: temporal region, nasojugal groove, malar region, nasolabial fold, mandibular region, chin, and lips. For all these indications, hyaluronic acid fillers may provide excellent results (Andre 2004; Borrell et al. 2011; Bertucci and Lynde 2015; Price et al. 2007).

The Importance of Facial Assessment

The precise assessment of the facial aging is crucial for the treatment planning with hyaluronic acid fillers. The correct assessment is an important step to achieve a good final result.

A convenient method for assessing the morphological effects of aging is to divide the face into thirds (Fig. 1), and it is important to remember that different sides of the face can age differently, what happens frequently.

Upper Third (Forehead and Brows)

Progressive aging brings a loss of subcutaneous fullness to the forehead, brow, temple, and upper eyelid areas, which accentuate the underlying anatomic structures. The bony outline of the skull and supraorbital rims become more evident as do the muscles of the brow (notably corrugator and procerus muscles), and the temporal blood vessels assume an increasingly tortuous appearance (Coleman 2004). Loss of temporal support to the lateral brow, coupled with loss of fullness in the upper eyelid, create the impression of brow ptosis,

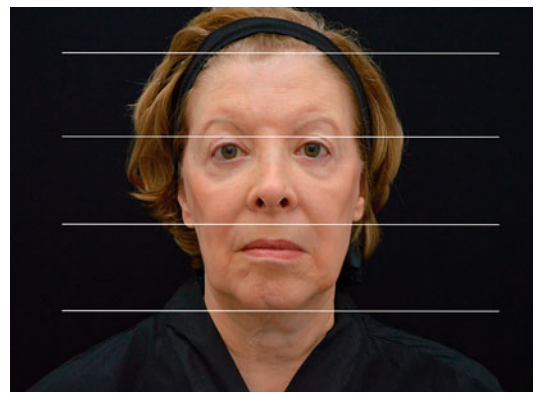

Fig. 1 Horizontal thirds of the face

with the eyebrow seemingly descending to a position at or below the superior orbital rim (Sherris and Larrabee 1996). Weakening of the orbital septum may allow protrusion of infraorbital fat, thereby creating a more bony orbital anatomy (see chapter ▶ "Facial Anatomy View for Aesthetic Fillers Injections" in this volume).

In youth, the subcutaneous fullness of the forehead conceals the muscles of facial expression in this region. As this fullness between the muscles and the skin disappears with age, the intrinsic tone of the glabellar, procerus, and frontalis muscles gives rise to fixed glabellar frown lines, fixed transverse forehead furrows, temporal hollowing, a skeletonized supraorbital rim, and a relative excess of upper eyelid skin are responsible for creating the impression of upper facial aging (Coleman and Grover 2006).

In the female patient, the ideal forehead should have a gentle convex curve 12–14 degrees off of vertical, and the glabellar region should exhibit a smooth contour. The temple should be flat or slightly convex, without any concavity, depression, or hollowing (Swift and Remington 2011; Raspaldo 2012). The aesthetically desirable female eyebrow should be over the supraorbital margin, and the middle aspect should be slightly lower than the lateral aspect. In central aspect, the brow must peak in a vertical line along the lateral limbus of the iris.

The male eyebrow lies at the supraorbital margin and is lower and flatter than in female patient. The lateral end of the eyebrow should be equal to or slightly higher than the medial end, with an even volume distribution along the entire length of the eyebrow obscuring sharp bony edges. The upper eyelid should have fullness that follows the natural arc of the upper eyelid margin, and there should be no hooding (see chapter ▶ "Hyaluronic Acid Filler for Forehead, Temporal, and Periorbicular Regions" in this volume) (Ellebogen et al. 2004).

Middle Third (Midface)

The midface is an important factor in facial aesthetics because perceptions of facial attractiveness are largely founded on the synergy of the eyes, nose, lips, and cheek bones (central facial triangle).

In the midface, age-related loss of subcutaneous fullness in the malar prominence and progressive buccal hollowing result in a less healthy facial proportion. Depletion of the infraorbital subcutaneous tissue accentuates the effect of intrinsic tone in the orbicularis oculi muscles on the overlying skin, giving rise to "crow's feet" rhytides. As the overlying fullness dissipates with age, the inferior border of the orbicularis oculi muscle also become more evident and contributes to the development of the malar crescent over the zygomatic eminence (laterally) and the nasojugal fold (medially). Volume loss in the infraorbital area also leads to the emergence of formerly concealed infraorbital fat pads (palpebral bags) and accentuation of the tear-trough depression, running obliquely from the lateral nose at the level of the medial canthus down to the anterior malar cheek below the middle of the eyelid. Additionally, the minimal transverse depression that runs immediately below the eyelashes deepens with age and extends downwards toward the infraorbital rim.

Secondary to the loss of subcutaneous fullness, downward displacement of infraorbital fat over a weakened orbital septum creates a deeper and wider orbit and double convex deformity of the lower eyelid (Ellebogen et al. 2004). Loss of fullness between the orbicularis oculi muscle and the overlying skin of the lower eyelid brings these tissues into closer proximity and confers a darker coloration to the thin infraorbital skin, resulting in a tired eye appearance. This dark coloration may also be a result of dermal melanin deposition. Fat cheek descends to create the nasolabial fold, leaving behind a cheek concavity that is accentuated by depletion of malar fullness (see chapter ▶ "Hyaluronic Acid Filler for the Malar Area" in this volume).

Aging also alters the cartilaginous nasal skeleton and soft tissue covering (Guyuron 1997). Most of the loss of fullness occurs in the glabella, nasion, and upper dorsum. Flattening of the medial forehead results in blunting of the nasofrontal angle, giving the illusion of increased

nasal length. The attachments between the upper and lower lateral nasal cartilages weaken, causing progressive ptosis of the nasal tip. Pyriform remodeling affects the alar base and, in combination with upper maxillary reabsorption, results in a narrowing of the nasolabial angle and further accentuation of nasal tip ptosis. Chin pad ptosis, which occurs secondary to mandibular bone resorption, further contributes to the appearance of increased nasal projection and length.

Lower Third (Chin, Jawline, and Neck)

With progressively increasing skin laxity, depletion of malar and perioral fat deposits, and reabsorption of alveolar bone, a relative excess of skin occurs in the aging lower face, leading to loss of definition of the jawline. Loss of masseteric ligament support allows descent of the facial fat to the mandibular border, leading to the formation of facial jowls (Ozdemir et al. 2002). Upward retreat of the mandibular border results in exposure of the submental contents, including the submaxillary gland. As the lateral projection of mandibular fullness dissipates, the angle of the mandible appears to merge from the buccal region into the neck. In the chin, loss of lateral and inferior volume results in relative protrusion of the central chin, whereas lateral mental atrophy results in ptosis of the lateral chin, which can create the impression of chin widening when viewed from the front (Coleman 2004).

As the subcutaneous fullness of the mandible recedes, the fat of the jowl, which was previously concealed by the surrounding soft tissues, is revealed. Ptosis of the unsupported skin, chin pad, and facial portion of the platysma muscle, coupled with the downward pull of the platysma muscle, leads to the development of the characteristic jowled "turkey neck" deformity. Protrusion of the large submental fat pad either between the two free borders of the platysma muscle or from behind the submental platysma cover adds to this effect. In addition, contraction of the platysma muscle, caused in part by the need to support the deeper neck and mouth floor structures, gives rise to vertical fibrous band on the neck, whereas laxity in the overlying skin can create horizontal rhythides. As aging progresses, the hyoid bone and larynx gradually descend, resulting in loss or blunting of the cervicomental angle (Coleman and Grover 2006). All these modifications lead to the inversion of the called "youth triangle" (see chapter ▶ "Hyaluronic Acid for Mental and Mandibular Contour" in this volume).

The Treatment with Hyaluronic Acid Fillers

The primary goal in any rejuvenation procedure should be to restore the ample, balanced distribution of facial fullness that exemplifies the youthful face. The fat compartmentalization of the aging face must be smoothed over, and the former primary arcs and convexities of youth, rebuilt (Donofrio 2000).

The deep structural filling for foundation and reconstruction of the face must be done with volumizer hyaluronic fillers that are dense, with high G′ and high cohesiveness. Therefore these products are able to promote projection, volume restoration, and the "lifting effect" (Pierre et al. 2015). These products are deposited on supraperiostal or subcutaneous layers.

The refinement is done with hyaluronic fillers that are softer and with a lower G′. These products are more delicate and used to fill the wrinkles, lips, nasojugal, and palpebromalar groove (see chapter ▶ "Hyaluronic Acid Dermal Filler: Physical Properties and Its Indications" in this volume).

There are also hyaluronic acid products with the function of improving skin quality.

Hyaluronic Acid Filler Injection Technique for Contour Restoration in the Middle Face

The treatment with hyaluronic acid should start with the restoration of the middle third of the face (Callan et al. 2013; Jones and Murphy 2013). This is considered the most important region to be treated because its treatment impacts on the other

two thirds, in both men and women. Besides that, the aspect of tiredness can be improved with the proper treatment of this region.

The maxillary bone forms the skeleton of the middle and medial portion of the face, and by zigoma (body and arc) in the lateral third. Although, the bony remodeling in the middle third of the face is not uniform at the aging process, the maxilla is more susceptible to bony loss than the zigoma during the aging process.

The bony remodeling is associated to atrophy and inferior displacement of the fat compartments, resulting in volume loss of the malar area, which may become concave. This depletion may also be caused by weight loss and genetic predisposition (Braz and Sakuma 2012).

Zygomatic Arc

The filler injection over the zygomatic arc has the goal of treating the bony loss at this region, which can be more discrete than the medial malar loss. It must be done very carefully, because the hypercorrection of the zygomatic region may widen the horizontal diameter of the face, causing a male appearance on women.

The treatment of zygomatic arc should be done at the supraperiosteal and submuscular layer, through needle or cannula.

The application with needle is made with small bolus divided into 2 or 3 spots, with 0.1–0.2 ml of hyaluronic acid each, paying attention to the most desirable projection spots.

Regarding cannula technique, from 21 to 25 gauges, the injection is made through retroinjection. The cannula enters posteriorly to the most projected spot towards the nasal alar base, inferiorly to the inferolateral portion of orbital rim and the total volume of hyaluronic acid injected normally range from 0.2 to 0.3 ml.

Malar Region

The main goal of treating the malar area is to restore the medial projection of the region (Rohrich et al. 2008).

The first step must be the demarcation of the area to be treated, which should be performed in a totally individualized way. With the patient in seated position and superior light, the injector should observe the illuminated and shadow areas.

The "V deformity" is commonly observed in patients with bony reabsorption and atrophy of the fat compartment of the facial middle third. The superior limit is the inferior orbital rim; anteriorly, the nasolabial fat compartment; inferiorly, the jowl fat; and posteriorly, the masseteric cutaneous ligament.

The recommended technique to treat the malar area is the use of cannula, on the subcutaneous layer, by retro injection or fanning technique. Needles should be avoided at this region because of the proximity of infraorbital foramen.

A safer point for cannula entry is lateral to hemi-pupillary line, around 2 cm below the zygomatic prominence. The total volume injected is variable, ranging from 0.3 to 3 ml on each side, depending on the volume loss of the region.

Nasojugal and Palpebromalar Grooves

Perhaps one of the most notable signs of aging is the nasojugal groove and its lateral extension, the palpebromalar groove. These grooves correspond to the location of the tear trough ligament and orbicularis retaining ligament, respectively, and mark the location of the lid-cheek junction (Medelson et al. 2002; Moss et al. 2000; Hwang et al. 2008; Ghavami et al. 2008).

The nasojugal groove, or tear through deformity, extends inferolaterally from medial canthus to mediopupilar line. Laterally to this point, it is possible to observe in several patients, another groove, the palpebromalar groove. In many cases, with the aging process, both grooves merge in only one continuous groove, which delimitates clearly the protrusion of orbital fat, cranially, and the malar region, distally.

According to Hirmand classification, the nasojugal groove can be divided in three degrees: degree I, patient has only volume loss on nasojugal groove; degree II, there is volume loss at lateral and medial orbital area and flattening of the medial

malar region; degree III, there is total depression of medial and lateral grooves, with severe volume loss at anterior malar and zygomatic region (Hirmand 2010; Braz and Aquino 2012).

These grooves bring a sad, tired, or aging aspect to the face. They are considered a very challenging area to treat, because hypercorrection, superficial injection, or inappropriate material can bring unacceptable results.

The treatment of nasojugal groove aims to smooth the junction between the inferior eyelid and the nasolabial region. Small quantities of hyaluronic acid are injected (0.1–0.5 ml) on each side, supraperiosteal or intramuscular. The entrance point can be the same one for the malar injection. Superficial injections should be avoided to prevent the Tyndall effect and noticeable nodules. Because of the hydrophilic properties of the hyaluronic acid, the groove should be corrected around 80% initially and then evaluated after 2 weeks.

The proper selection of the patient to be injected is very important to achieve a satisfactory result and must be performed with caution in patients with moderate to severe laxity of the eyelid and fat protrusion, in which it should be considered surgical correction.

This region should be always evaluated together with the malar region, and, if necessary, revolumizing the malar area should be performed first.

Nasolabial Folds

The aspect of the nasolabial fold in the aging face may vary according to race, gender, and ethnicity.

The goal of the treatment of the nasolabial fold by injecting hyaluronic acid is to soften the depth of the sulcus. It is important to remember that the treatments of the malar loss result in the improvement of nasolabial fold. Therefore, the initial approach of the malar region leads to a lesser volume requirement in the nasolabial. The superior region of the nasolabial fold (perinasal triangle) is the deepest because of the bony remodelation of the pyriform aperture and maxilla (Shaw et al. 2011).

The filling of the nasolabial fold should not be performed with large volumes of hyaluronic acid to avoid complications, such as edema and vascular compression.

It is important to remember that the nasolabial fold is right over the angular artery in more than 90% of the patients (Yang et al. 2014), so the injection with needles should be performed in the intradermal plan or deeply supraperiosteal. A 21–25 G cannula can be used on the subcutaneous layer (Figs. 2, 3, and 4).

Hyaluronic Acid Filler Injection Technique for Contour Restoration in the Upper Face

Improvement of the upper third of the face involves the treatment of the temples and the forehead.

The goals of the volumization treatment of the temporal region is to reestablish the convexity of the temples, sustain the lateral portion of the superior eyelid, raise the lateral portion of the eyebrow, and decrease the periorbital rhytides.

The volume replacement of the frontal region aims to reestablish the anterior convexity of the upper third, raise the eyebrows and decrease the skin excesses of the upper eyelids.

The eyebrows are the frame for the eyes and the face, and can also be improved by hyaluronic acid injection.

Temple Volumization

For temple volumization, the first step is to identify the superficial temporal artery and vein. Look for the junction of the temporal crest or fusion line with the orbital rim, and identify the area of greatest volume loss. Position the needle 1 cm superior to the lateral orbital rim and 1 cm lateral to the temporal crest. Insert the needle perpendicular down to bone, aspirate for nearly 7 s, and then inject very slowly using a supraperiosteal bolus injection. Moderate pressure with the index finger of the free hand placed superior to the needle along the hairline will

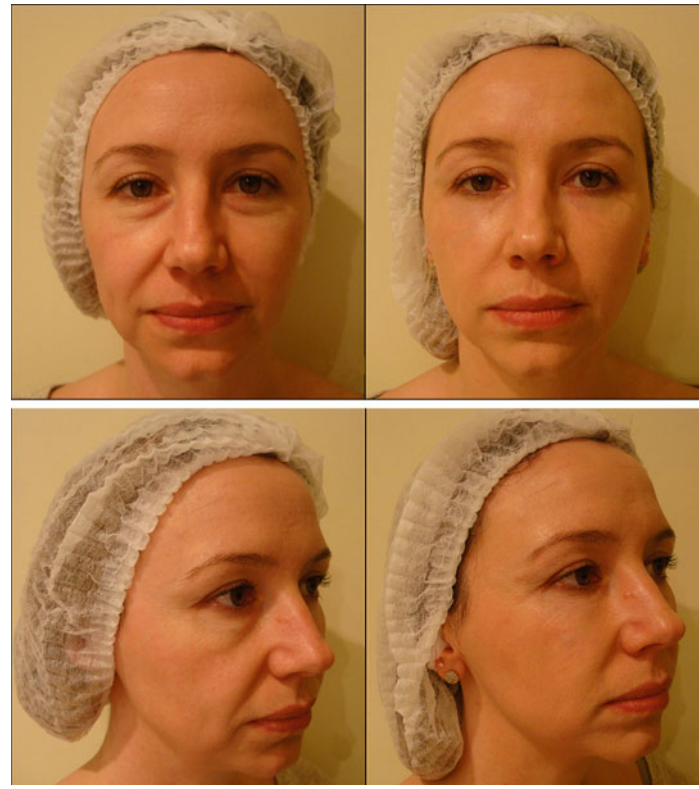

Fig. 2 Thirty-six-year-old female patient. (**a**) Frontal view. Before: significant malar loss, with marked nasojugal groove and nasolabial fold. After: result with injection of (each side): 0.5 ml over zygomatic arc (high G′ HA); 0.5 ml on medial malar region (high G′ HA); 0.3 ml on nasojugal groove (low G′ HA); 0.5 ml on nasolabial fold (intermediate G′ HA). (**b**) Oblique view. Before and after injection with significant improvement of the midface

Fig. 3 Forty-two-year-old female patient. (**a**) Frontal view. Before: moderate malar fat loss, with visible palpebromalar and nasojugal groove. After: result with injection of (each side): 0.3 ml on zygomatic arc (high G′ HA); 0.2 ml on medial malar region (high G′ HA); 0.5 ml on palpebromalar and nasojugal groove (low G′ HA). (**b**) Oblique view. Before and after injection with significant improvement of the midface

prevent economic loss by spread of product under the hair. Injection speed is slow, maintaining the needle on bone throughout the injection. Once the needle is removed, pressure on the injection site for several minutes is warranted in the event that a deeper vein is pierced, to avoid late-occuring bruise. Gentle molding of the temple region may be required after injection of typical volumes in the 0.5–1 ml range for most temporal hollows. Severe volume loss may require up to 2 ml per

Fig. 4 Thirty-nine-year-old female patient. (**a**) Frontal view. Before: moderate malar loss, with marked nasojugal groove and nasolabial fold. After: result with the injection (each side): 0.3 ml on zygomatic arc (high G′ HA); 0.4 ml on nasojugal and palpebromalar groove (low G′ HA); 0.5 ml on nasolabial fold. (**b**) Right oblique view. (**c**) Left oblique view. Before and after injection with significant improvement of the midface. (**d**) Lateral view: noticeable improvement of the anterior malar projection

side and multiple treatment sessions may be needed.

Selecting a supraperiosteal location high in temporal fossa (as previously described) minimizes the risk of intravascular events because of the relative avascularity of this region and the thin fibers of the temporalis muscle of the upper region. The deep temporal arteries and the middle temporal artery are located more posteriorly to this point, and their calibers are small, as they diminish in size from their origin at the second portion of the internal maxillary artery.

Finally, avoid deep needle injection into the lower or posterior fossa above the zygomatic arch, as internal maxillary branches are present, with a risk of palate necrosis.

It should be noted that the deep periosteal injection high in the fossa may lead to temporary (24–48 h) visible congestion of the temporal venous plexus lying in the subcutaneous tissue.

Superficial cannula injection may be attempted with careful observation of cannula position, because superficial treatment of the temporal region may lead to superficial irregularities that require massage over the ensuing days (de Maio et al. 2017).

Forehead Contouring

Dynamic forehead lines are usually treated with a neuromodulator, but hyaluronic acid fillers are used to treat deep horizontal wrinkles and create a smooth contour across the forehead (Raspaldo et al. 2012).

The product is injected at six sites along the forehead wrinkle. For first injection, position the needle near the lateral end of the wrinkle and at least 2 cm above the eyebrow and aspirate before injection. Insert the needle fully, inject very slowly using a supraperiosteal bolus injection, and inject deeply to avoid the forehead and temporal vessels and nerves. The needle tip must be on bone beneath the galea to access this avascular plane. Moving medially along the forehead, the second and the third injections are given on the same facial side at least 2 cm above the eyebrow, with aspiration before each injection. Again, inject very slowly using a supraperiosteal bolus injection, and inject deeply to avoid the supraorbital and suprathroclear vessel bundles, and also the superficial temporal vessels of the transverse frontal branch. Continuing to the other side of the face, perform the other three injections in the same manner. Total volume injected normally range from 0.2 ml to 1 ml, depending on the concavity found in the region. Avoid scratching the periosteum to reduce pain and swelling. Remember that massage is mandatory for delivering a uniform and smooth forehead contour (de Maio et al. 2017).

Eyebrow Shaping

The position and/or shape of the eyebrow may change with aging. Fillers can enhance eyebrow contour and volume and may be used for improving the elevation of the eyebrow tail in cases where botulinum toxin provides insufficient eyebrow lifting (Raspaldo et al. 2012).

When using needles, injections are made at two sites. Identify the orbital rim to avoid inadvertent injection into the orbital cavity. For the first injection, position the needle and aspirate before injection. Insert the needle at the lateral end of the eyebrow, inject very slowly using a supraperiosteal bolus injection, and then massage upward to shape. Injections in the lateral aspect of eyebrows are intended to promote support of the roof. Avoid overcorrection of the eyebrow with filler, because it can result in an unduly prominent eyebrow appearance or cause eyelid edema. The second injection should be made in the same manner medial to first injection along the eyebrow. Be careful to avoid the supraorbital foramen when injecting lateral to it.

The eyebrow shaping can also be performed by retro injection with cannula, on the submuscular (orbital portion of orbicularis oculi muscle) plan. Even with the cannula, it is important to avoid the supraorbital and suprathroclear foramen (de Maio et al. 2017) (Fig. 5).

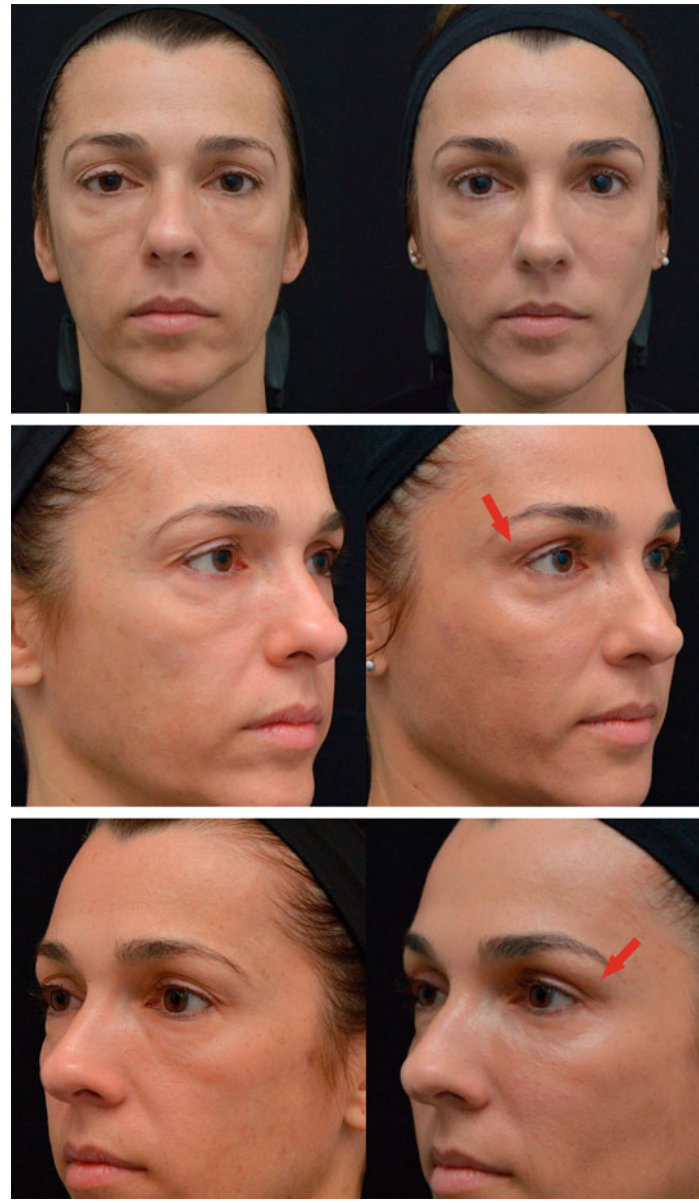

Fig. 5 Forty-three-year-old patient. (**a**) Frontal view. Before: patient with tired appearance. Severe malar loss and moderate temple loss. After: result with the injection (each side): 0.5 ml on zygomatic arc (high G′ HA); 0.5 ml on medial malar region (high G′ HA); 0.5 ml on temporal fossa. (**b**) Right oblique view. Significant improvement of malar projection and noticeable improvement of eyebrow positioning and hooding of the superior eyelid (arrow). (**c**) Left oblique view

Hyaluronic Acid Filler Injection Technique for Contour Restoration in the Lower Face

The contouring of the inferior third of the face is given by the inferior mandibular margin. A sharp mandibular line, a mentual region with proper proportions, and a marked mandibular angle bring a youthful and attractive appearance to the face.

The restoration of the angle and mandibular line is indicated to restore the facial contouring that is lost during the aging process. The ideal selection of patients includes that ones with laxity and mild to moderate loss of facial contour. It can be also used in male patients to improve the virility aspect of the face, since the masculine face has a sharper definition regarding the line and mandibular angle.

The mandibular contouring can also be performed in women with "heart shape" face, to enhance the inferior limit of the face.

The mentual filling complement the contouring of the inferior third of the face, cooperating with facial triangulation and facial rejuvenation, as well as in the treatment of hypomentalism. Mild to moderate hypomentalism can be solved with hyaluronic acid fillers, with no need of orthognathic surgeries or silicone implant.

After the recontouring of the lower third with the treatment of mandible and the chin, treatment of the perioral area is crucial to achieve a proper rejuvenation of the lower face.

Mandible Contouring

The treatment of mandible contouring is usually performed with cannula, from 21 to 25 gauges and 38 to 50 mm of length. The cannula allows the treatment of a larger area with fewer punctures. By retro injections and bolus, the hyaluronic acid is injected on subcutaneous layer or on the supraperiosteal plan.

To redefine the mandibular angle and the mandibular line, it is important to demarcate the region with the most prominent ptosis, which normally correspond to jowl fat, which should not be filled. Normally, the entry of the cannula is immediate after the jowl fat. The cannula is then inserted on the supraperiosteal or subcutaneous plan towards the mandibular angle, injecting 0.3–0.5 ml of hyaluronic acid by retroinjection. Immediate molding must be performed with moderate pressure for the proper accommodation of the product. At this region, it is important to be careful with the mandibular branch of the facial artery. After the treatment of the mandible body length, the cannula should be repositioned for the treatment of the mandibular ramus. This is performed by entering the cannula right below the mandibular angle. In the subcutaneous plan, 0.1–0.2 ml of hyaluronic acid is injected by retroinjection.

For better correction of the mandible, it is also necessary to treat the lateromentual region, which is located between the mandibular ptosis (jowl fat) and the lateral margin of the mentual muscle (Reece et al. 2008). This region must be also filled with cannula, which enters immediately anterior to jowl fat. The cannula must be inserted towards the chin, injecting 0.1–0.2 ml of hyaluronic acid by retroinjection, supraperiosteal, or on subcutaneous plan.

Relaxing of the platysma muscle is also important for mandibular definition, since its fibers merge with the masseter, depressor angular oris, mentual, risorius, and oral orbicularis fibers.

Chin Treatment

The treatment of the mentual region can be performed with needles and/or cannula. The needle technique is performed in the supraperiosteal plan, splitting the hyaluronic acid in two spots that correspond to the two portions of the mentual muscle, injecting around 0.2–0.5 per side, or even more, for more severe cases.

Regarding the cannula technique, the delimitation should be the following: draw a semicircle around the chin to the mandibular bone, a vertical line between the two portions of mentual muscle and a horizontal line at the basis of the semicircle. After that, draw a parallel line 1.5 cm above the described line. The formed rectangle corresponds to the area that should be treated with hyaluronic acid. The cannula is inserted 1 cm laterally to the rectangular area, in the supraperiosteal plan, up to the center of the treated rectangle of the same side. It is injected with 0.2–0.5 ml of hyaluronic acid on each side (Braz et al. 2011).

The submentalis fat probably influences the depth of the lip-chin crease. Adding volume to this compartment decreases the depth of the lip-chin crease noted with age.

Application of botulinum toxin in the mentual muscle for its relaxation contributes to an even better result of chin remodeling.

Perioral Region

The perioral region can be defined as the lower one third of the face. It is bounded by the

subnasale and cheek-lip groves superiorly and the mentum inferiorly.

The lower one third of the face can be further divided into thirds with the upper one third, including the upper lip, and the lower two thirds, including the lower lip and chin.

The oral commissure should lie within a vertical plane drawn from the medial limbus of the iris.

Lips

Volume and defined contour are characteristics of young lips. An esthetically pleasing upper lip will possess a soft M arch known as Cupid's bow. Its apical portions meet the inferior aspect of the philtral ridges. The "ideal" proportion of superior lip with the inferior is 1:1.6, namely, the lower lip generally has more vermillion show and fullness than the upper lip. However, on profile the lips shape must be convex and the superior lip projects 2 mm anteriorly to inferior lip (see chapter ▶ "Hyaluronic Acid Filler for the Lips and Perioral Area" in this volume).

With the aging process, lips lose definition and the lips tend to become flatter. Their ratios change as the upper lips elongates. Cupid's bow is lost and the oral commissures descend.

Many factors can predispose a person to premature aging, such as heredity and the size and fullness of the lips in youth. Other factors, such as sun exposure and cigarette smoking can advance this process. As the skin thins and the supporting orbicularis muscle atrophies, vertical rhytids develop at or above the vermillion border. Fullness, prominence, and definition are lost. Laterally, as the oral commissure descends and the cheek soft tissue loses support, marionette lines become prominent.

The final goal of lips filling is to improve its tridimensional relation to the rest of the face, accordingly to ethnicity, cultural factors, age, and gender (Klein 2005; Carruthers et al. 2008; Sarnoff et al. 2008; Fulton et al. 2000).

Lips are formed by an internal portion, *labial mucosa or wet lips*, by a transition zone, *lip vermilion or semi mucosa*, and an external portion represented by the skin and annexes. At the limit between the internal portion, labial *mucosa*, and the transition zone, *labial vermilion*, it is where the fibers of orbicularis oris muscle fibers are found.

The fibers of the orbicularis muscle delimit two fat compartments:

- A superficial compartment, below the vermillion and above the orbicularis muscle
- A deep compartment, below the orbicularis muscle and above the labial mucosa. This is an important anatomic landmark because the superior and inferior labial arteries are found at this compartment.

According to that, lips are divided in three anatomic areas. The filling technique considers this division, as the treatment of each one promotes a different result.

- Lip contour: The filling of this area brings definition to the lips. The product is retro injected linearly on the dermis of the vermilion border.
- Lip vermilion or dry lip: Filling of this area promotes anterior projection of the lips, recreating the convex shape. The filler is injected on the superficial fat compartment, above the orbicularis oris muscle. Retro injection or bolus can be performed.
- Labial mucosa: Filling of this area promotes volume augmentation of the lips, since the dental arch projects this area anteriorly. The filler is injected by bolus on the deep fat compartment, below the orbicularis oris muscle. Whereas the labial arteries are located on this compartment, it is recommended to aspirate before injection to reduce the risk of intravascular, to inject slowly and to interrupt the injection in case of sudden pain or whitening. For safety reasons, it is highly recommended the use of microcannula at this region (Braz and Mukamal 2011).

The hyaluronic acid fillers used for lips treatment are that for superficial and intermediate dermis, preferably with lidocaine.

Labial Commissure and Labiomentual Fold

The signs of aging of perioral region result from a combination of factors that include fat loss, thinning of the dermis and bone remodeling. Repetitive contraction of the depressor angular oris and platysma also contribute. Clinically, it is noticeable the labial commissure ptosis and deepening of the labiomentual fold, also called the marionette lines (Braz et al. 2013; Weinkle 2010).

Fig. 6 Thirty-nine-year-old patient. (**a**) Frontal view. Before: patient with moderate to severe medial malar loss, with marked nasojugal groove. After: result with the injection of (each side): 0.3 ml on zygomatic arc (high G′ HA); 0.5 ml on medial malar region (high G′ HA); 0.4 ml on tear through (low G′ HA); 1 ml on mentual region. (**b**) Left oblique view. Noticeable improvement of malar projection and nasojugal groove. (**c**) Lateral view showing better malar and chin projection in addition to a sharper cervicomentual angle (demarcation line)

If the main goal is to elevate the labial commissure and/or treat the labiomentual fold, the hyaluronic acid is retroinjected on the lateral part of the inferior lip and on the adjacent skin, building a horizontal pillar that support the commissures, followed by three vertical supporting pillars made by retroinjection that form an inverted triangle. A small bolus in the modiolus can also help raising the oral commissure. Injection of botulinum toxin on the depressor anguli oris and platysma also helps to improve this region.

The vertical rhytides can be filled by linear retroinjection. Better results are obtained with injection of botulinum toxin to relax the orbicularis oris muscle.

To enhance the columns of the filter, it is important to remember that they are not parallel and look like an inverted V that narrows towards the columella (Figs. 6, 7, 8, 9, and 10).

Hyaluronic Acid Filler for Refinement and Skin Quality

Since the improvement of mechanical properties of skin exceeds the time of permanence of hyaluronic acid in the skin, studies show that the hyaluronic acid is able to promote the extracellular matrix restoration, stimulating the collagen synthesis and elastic fibers, by mechanical elongation of the fibroblasts. Therefore, this process raises the possibility of rejuvenation by hyaluronic acid injection (Landau and Fagien 2015; Wang et al. 2007).

For injectable hydration, hyaluronic acid with or without cross-link can be used. The hyaluronic acid without cross-link, used in mesotherapy, shows controversial results.

The injection must be performed by micropunctures, distant 0.5–1 cm on superficial dermis, over the rhytides or all over the wrinkled skin. When the product is non-cross-linked, the injection should be very superficial, with papule formation that will disappear in a few days. Regarding cross-linked products, the papule formation should be avoided and immediate massage after the procedure is recommended. The pain during the injection is bearable under topical anesthesia. For a better stimulation, treatment series are recommended, with 2 or 3 session every 2 weeks (non-cross-linked hyaluronic acid) or monthly (cross-linked hyaluronic acid) (see chapter ▶ "Hyaluronic Acid for Skin Booster on the Face" in this volume).

This procedure can be performed in the face, neck, décolletage, and hands and may be associated with other procedures like lasers, peelings, and other fillers for better results (see chapter ▶ "Hyaluronic Acid for Skinbooster® on the

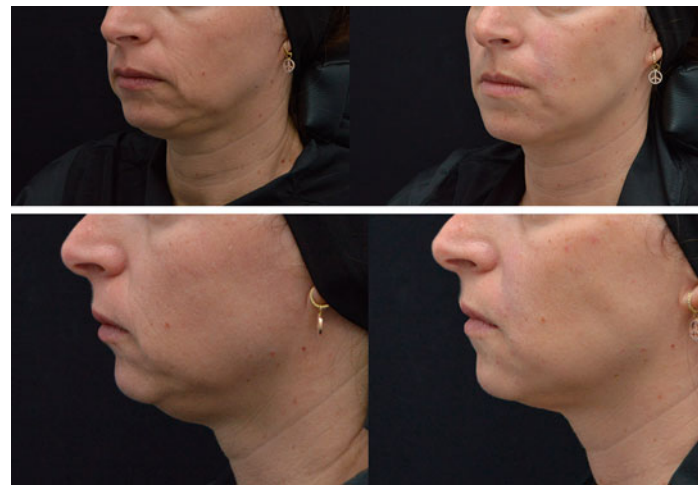

Fig. 7 Forty-seven-year-old female patient. (**a**) Oblique view. Before: patient with hipomentalism and inferior third laxity. After: result with the injection of: 1 ml on mentual region; 0.5 ml on pre-jowl region (each side). (**b**) Lateral view. Significant improvement of chin projection and mandible contouring

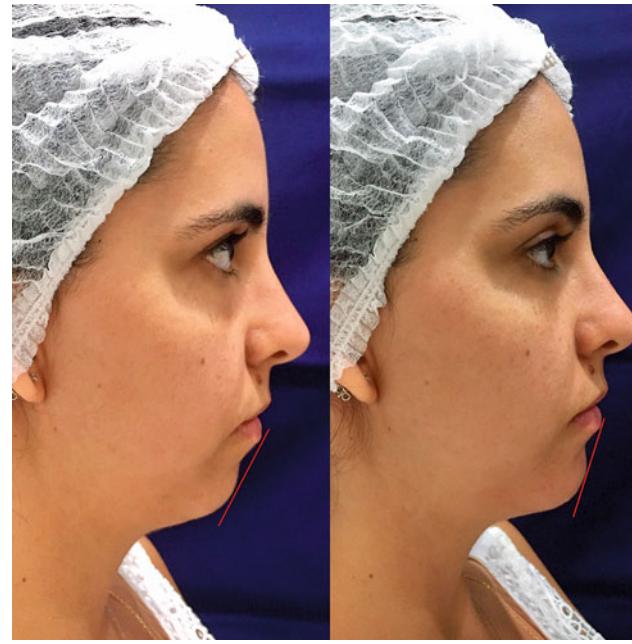

Fig. 8 Twenty-seven-year-old patient with severe retrognathism. Before and after injection of 4 ml of high G′ HA on mentual region. Great improvement of chin projection

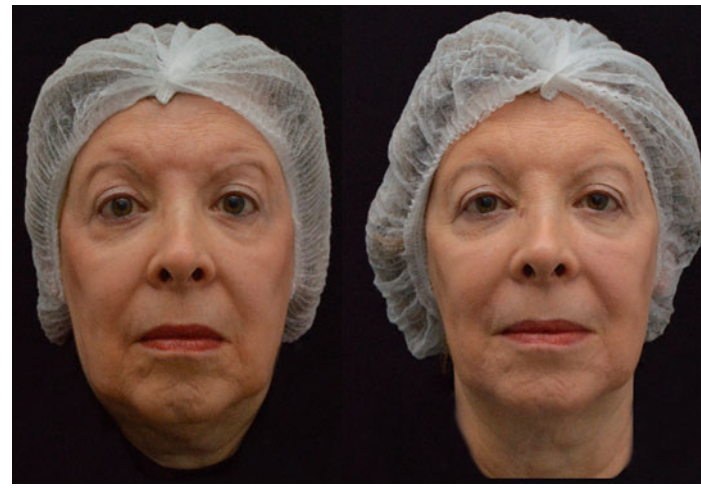

Fig. 9 Seventy-three-year-old female patient. Before: Patient with evident orbital rims and jowls. After: Results after the injection of (each side): 0.5 ml on zygomatic arc (high G′ HA); 0.3 ml on medial malar region (high G′ HA); 0.5 ml on pre-jowl region (high G′ HA); 1.4 ml on mentual region (high G′ HA). Marked improvement at the orbital area, chin, jowling, and even anterior cervical area

Neck and V Shape Neckline Area" in this volume) (Fig. 11).

Conclusion

The aging is a complex process and involves dramatic modifications in the skin, fat, muscular, and bone tissues. For this reason, all the structures should be treated to achieve a satisfactory result in rejuvenation.

Hyaluronic acid fillers can restore the volume loss caused by facial aging, by promoting reconstruction and recontouring of the face. They can also be useful to treat more delicate areas, like periocular and perioral regions, just as to improve skin quality.

Fig. 10 (continued)

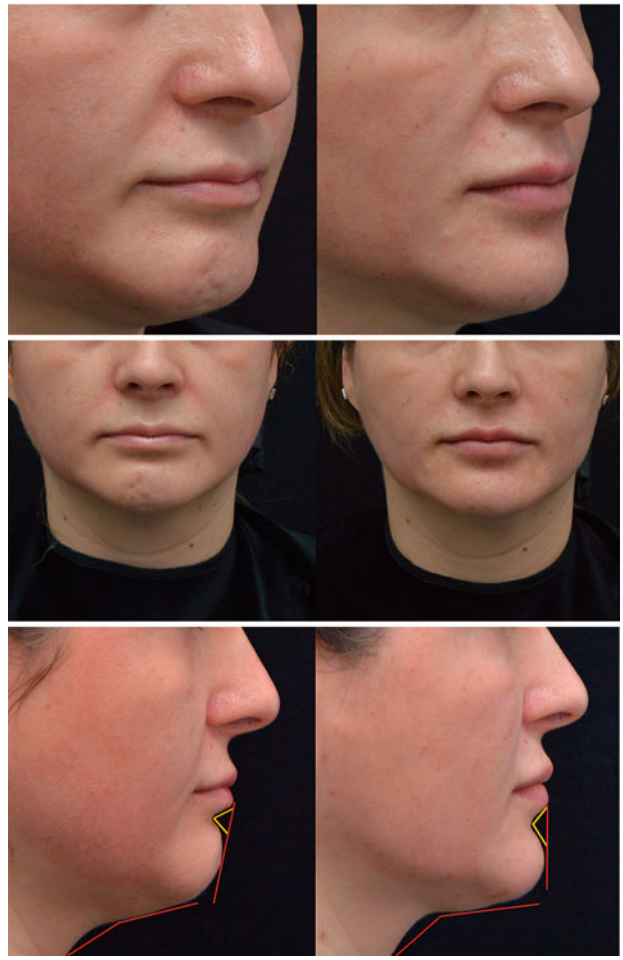

Fig. 10 Forty-two-year-old patient. (**a**) Before and after global facial treatment. The injections were made: 0.5 ml on zygomatic arc, each side (high G′ HA); 0.2 ml on medial malar region, each side (high G′ HA); 0.7 ml on temporal region, each side (high G′ HA); 1 ml on the chin (high G′ HA); 0.3 ml on the pre-jowl, each side (high G′ HA); 0.7 ml on mandibular contour, each side (high G′ HA); 1 ml on lips (intermediate G′ HA). (**b**) Left oblique view. (**c**) Right oblique view. (**d**) Left lateral view. (**e**) Right lateral view. (**f**) Close to the right oblique view, showing lips eversion and projection and mentual improvement. (**g**) Close to the frontal view, showing lips eversion and projection and mentual improvement. (**h**) Close to right lateral view, showing lips eversion and projection, chin elongation and projection, and improvement of the cervicomentual angle (demarcation)

Take Home Messages

- To effectively rejuvenate the aging face, it is necessary to understand the dynamic aging process.
- Epidermal thinning, fat atrophy, loss of bony support lead to soft tissue descent and wrinkling.
- The precise assessment of the facial aging is crucial for the treatment planning with hyaluronic acid fillers.
- The primary goal is to restore the ample, balanced distribution of facial fullness, which exemplifies the youthful face.
- The fat compartmentalization of the aging face must be smoothed over, and the former primary arcs and convexities of youth, rebuilt.

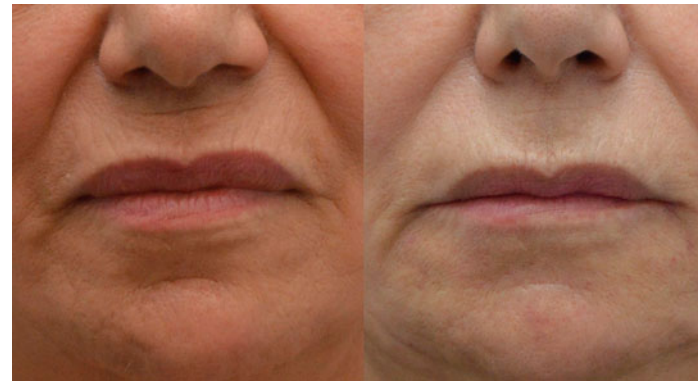

Fig. 11 Seventy-five-year-old patient. Before and after injection of 1 ml of cross-linked HA for skin quality improvement at perioral region. Results after 2 months

- The deep structural filling for foundation and reconstruction of the face must be done with volumizer hyaluronic fillers that are dense, with high G′ and high cohesiveness. Therefore these products are able to promote projection, volume restoration, and the "lifting effect."
- Volumizer HA filler should be deposited on supraperiostal or subcutaneous layers.
- The refinement is done with hyaluronic fillers that are softer and with a lower G′. These products are used to fill the wrinkles, lips, nasojugal, and palpebromalar groove.
- The treatment with hyaluronic acid should start with the restoration of the middle third of the face. This is considered the most important region to be treated because its treatment impacts on the other two thirds, in both men and women.

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Hyaluronic Acid Filler for Forehead, Temporal, and Periorbicular Regions

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_18

Abstract

Hyaluronic and injectable filler has been used for soft tissue augmentation and tissue support to correct deformities caused by aging. It is a safe procedure with minimal patient downtime. A thorough knowledge of anatomy and boundaries of each region, as well as the evaluation of the correct indications for each technique, is fundamental to obtain success, avoiding complications, mainly for temporal, orbicular, and frontal regions. The vascular system of these regions needs special attention as it can cause the most severe filler's procedure complications such as arterial occlusion, ischemia, and embolism. In this chapter, the anatomy of these regions and the best techniques were explored.

Keywords

Temporal · Forehead · Periorbicular · Injection · Hyaluronic acid filler · Facial anatomy

Introduction

Hyaluronic acid (HA) filler injections have been used for soft tissues volume augmentation and tissue support to correct deformities caused by aging. It is a safe procedure with minimal patient downtime. Some relevant issues must be known to acquire a good result with filler procedures and avoid complications, for instance: the knowledge of anatomy and boundaries of each region and the correct indications for each technique and product (Tamura 2013).

The detailed understanding of anatomical areas, affected by bone and fat pad absorptions, and gravity changes must be known by dermatologists in order to treat the main facial areas damaged by aging process. In addition, the dynamic of the mimic muscles must be analyzed to avoid unnatural facial expressions. Ischemia is the most severe complication of this procedure, that's why the vascular system, mainly of the glabella, ocular, nasal, and frontal regions, needs a special attention. It can be caused by arterial occlusion associated with filler injection or embolism (DeLorenzi 2014).

Anatomy for Fillers

The discussion of facial anatomy in this chapter is an introduction to the filler injection techniques in the forehead, temporal, and periorbital areas. An assessment of the influence of aging process on the facial structures requires a strong domain of the skin structure, such as facial segments, bones, musculature, vascularization, sensory and motor innervation, and lymphatic drainage.

The epidermis is composed of four distinct layers: the stratum corneum, granulosum, spinosum, and basale. The dermis is made of extracellular matrix with collagen and elastic fibers, glycoproteins, glycosaminoglycans, and proteoglycans. It is well vascularized and contains nerve endings, which make intradermal injections more painful than those applied in the subcutaneous tissue. Located immediately beneath the dermis, the subcutaneous layer is comprised of fatty tissue, which is divided into the areolar (with vessels and nerves) and lamellar layers. Subcutaneous layer thickness, arrangement, and the presence of fasciae or cavities are extremely important in the facial aging analyzing from a volumetric perspective (Tamura 2010a). Recent studies revealed that the facial fat is organized in many dynamic

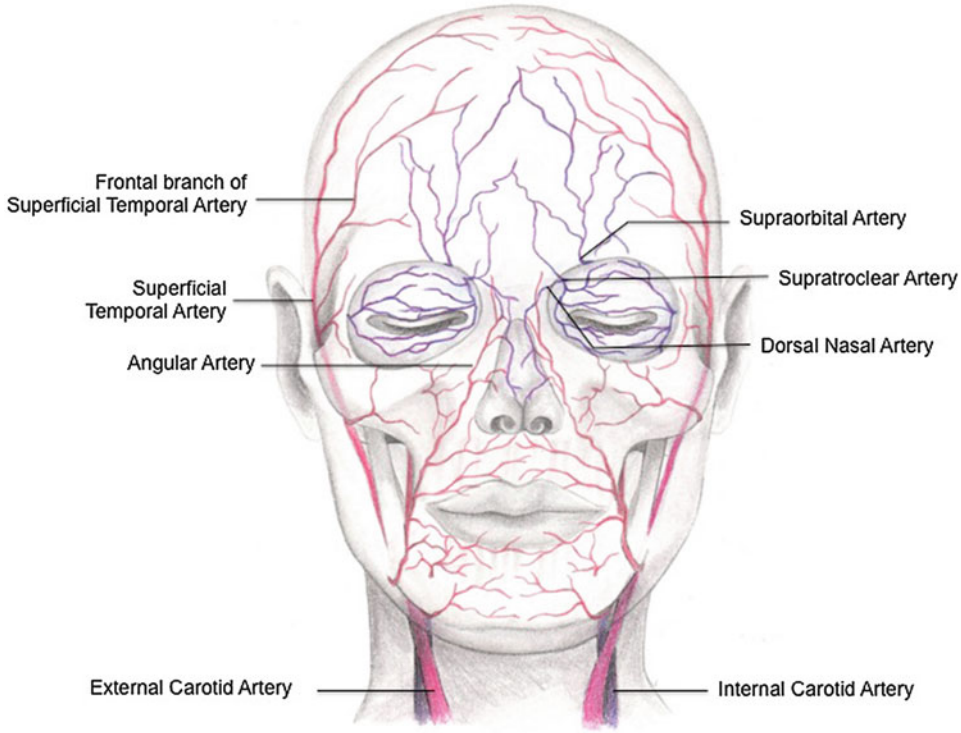

Fig. 1 Facial vascular system and the anastomosis between terminal branches of external and internal carotids. The anastomosis regions should be avoided because of the risk of arterial occlusion related to the injection of fillers

compartments that can be evaluated, augmented, and modified depending on the evolution of the facial aging (Fitzgerald and Rubin 2014).

During the study of facial vascular system, attention must be primarily focused on reports of arterial occlusion related to the injection of fillers (Fig. 1). Some anatomical particularities of each regions discussed in this chapter will be described below.

Forehead

The anatomic boundaries of the forehead are the eyebrows and nasal root (inferiorly), the zygomatic arch (inferolaterally), and the hairline (superiorly). In patients with a receding hairline, or alopecia, the superior border of the forehead is determined by the superior extend of the frontalis muscles. The forehead may be subdivided into a single central and two lateral or temple regions, and the transition between them is the superior temporal line (Sykes 2009).

The skin of the forehead is thick, well vascularized, and densely adherent to the underlying subcutaneous tissue, forming a soft tissue layer that is relatively inelastic. The epidermis and dermis are thicker in the forehead than in the inferior third of the face, and the subcutaneous fat attaches to the underlying galea aponeurosis by a fibrous septa, which contains vessels, nerves, and lymphatics (Sykes 2009). The galea aponeurosis is a thin tendinous sheet of connective tissue that is the fibromuscular extension of the superficial musculoaponeurotic system (SMAS) of the temple and lower face. The loose areolar tissue, located below the galea aponeurosis (subaponeurotic areolar layer), is a well vascularized, firmly layer connecting the

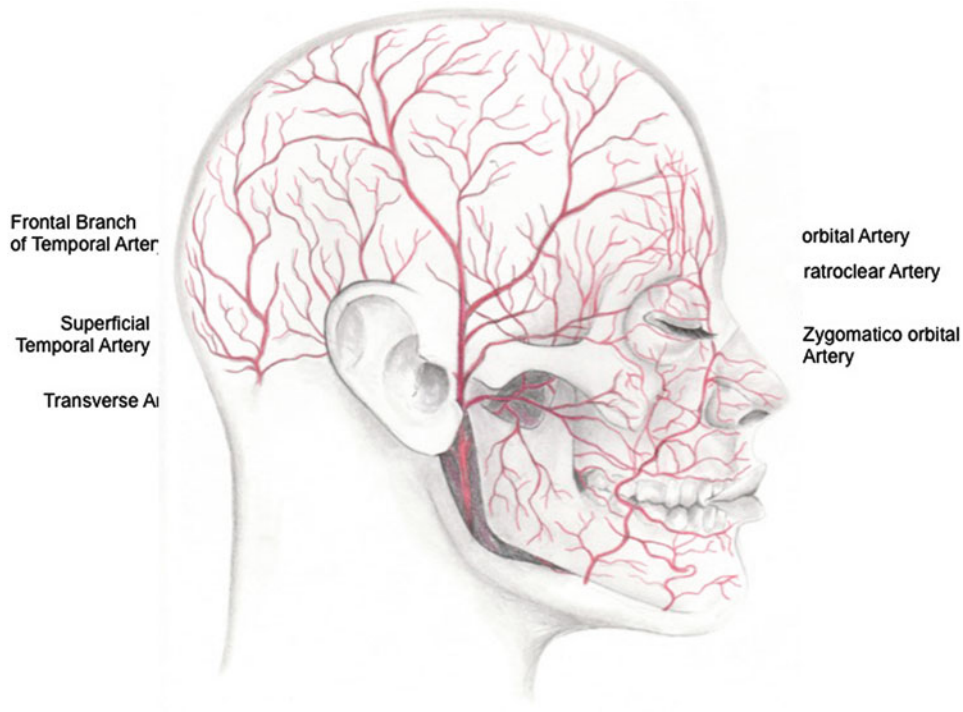

Fig. 2 Arterial systems of the temporal and frontal regions

galea aponeurosis with the periosteum (pericranium) (Tamura 2010b). The periosteum is a thickened layer of connective tissue, which is densely adherent to the outer surface of the skull and cover the frontal, zygomatic, and maxillary bones continuously with the periorbital at the orbital rims.

The temporal branch of the facial nerve leaves the temporal fossa and travels on the deep surface of the frontalis muscle, supplying the frontalis, corrugator supercilii, procerus, and orbicularis oculi muscles (Fig. 2).

The sensory innervation of central forehead is supplied by the supratrochlear and supraorbital nerves. The latter is responsible for the anterolateral region of forehead sensitivity and emerges from the area between the medial and central thirds of the superior orbital margin, extending superiorly and laterally on the internal surface of the frontalis muscle and galea. The frontal branches of temporal nerve are located inside the temporoparietal fascia and are responsible for the motor innervation of the frontalis muscle.

The temporal, frontal, and parietal regions are irrigated by the superficial temporal artery, a terminal branch of the external carotid artery, and drained by the superficial temporal vein, the main vein of the temporal region.

Temporal Region

The temporal region is bounded by the superior temporal line (superiorly), the zygomatic arch (inferiorly), and the frontal process of the zygomatic bone (anteriorly). The temporal hairline courses variably and obliquely through the temporal region. The skin of this region covers the frontal, sphenoid, parietal, and temporal bones. This area has important transition zones with the forehead and the lower face.

The skin in the temporal region is thinner than the forehead region, and it has a great amount of dense connective tissue. The deep fat layer is dense in this area, and the temporal extension of the Bichat's deep fat pad can be found. The hair-

bearing region is vascular with thick skin. The superior and inferior temporal septa represent the superior and inferior boundaries of the temporal fat compartment, respectively. This compartment spans the forehead to the cervical region. It is the most lateral cheek fat compartment and has an identifiable septal boundary medially called the lateral cheek septum.

The temporoparietal fascia (also known as superficial temporal fascia) is a thin, flexible, and vascular layer that lies just beneath the subcutaneous fat and is tightly connected to the overlying skin. The temporoparietal fascia forms the analogue of the superficial musculoaponeurotic system (SMAS layer above the arch in the temporal fossa). At the superior temporal line, the temporoparietal fascia becomes continuous with the epicranial aponeurosis of the forehead and scalp. The deep temporal fascia (also termed the temporalis muscle fascia) is a thickened layer of connective tissue which surrounds the underlying temporalis muscle. The deep temporal fascia divides into a superficial (also called the intermediate fascia) and deep layer, approximately 2–3 cm above the zygomatic arch, which ensheathe the deep temporal fat pad and split again to envelop the zygomatic arch.

The temporoparietal fascia also contains the temporal branch of the facial nerve. The deep temporal fascia contains the middle temporal vessels which along with the deep temporal vessels supply the temporalis muscle. The middle temporal artery is a branch of the superficial temporal artery, which is a terminal branch of the external carotid artery (Fig. 2). It irrigates the temporal, frontal, and parietal regions, through branches with similar names. Superficial temporal artery and vein are visible as a linear projection on this area. Due to these factors, vascular structures should be taken into account during the injection of fillers in the temporal area. The main vein in the temporal region is the superficial temporal vein, which drains the temporal, frontal, and parietal regions.

Periorbicular Region

The eyes are located in the orbital bone cavities that are subdivided into superior, lateral, inferior, and medial borders. The frontal bone forms the superior or supraorbital margin that ends laterally in the zygomatic process of the frontal bone. The zygomatic and frontal bones form the lateral margin, while the inferior margin is constituted by the maxilla and the zygomatic. The transition between the outer periosteum and the inner periorbital (the inner lining of the orbital bones) of the orbit is called the arcus marginalis, a thickened connective tissue layer. The arcus marginalis is densely adherent to the entire orbital rim except at the inferolateral region of the orbital rim where a small recess (the recess of Eisler) is found (Sykes 2009). The orbicular region can be divided into lateral and medium canthal, superior and inferior lacrimal, and superior and inferior eyelid portions. The bony orbital rim is free of significant vascular structures from the base of the anterior lacrimal crest to the lateral canthal tendon. The maxillary, lacrimal, and frontal bones constitute the medial margin of the orbit. Below the inferior margin of the orbit, in the mid-pupillary line, the maxilla presents the infraorbital foramen for the passage of the infraorbital nerve and vessels. The supraorbital foramen, which houses the supraorbital nerve and vessels, is located in the medial portion of the orbit. Those structures are located just lateral to supratrochlear nerve and vessels.

The orbicularis muscle of the eye is a circle muscle that originates from the palpebral and orbital ligaments and acts as a sphincter (Tamura 2010c). The orbicularis muscle can be divided in three portions: tarsal, palpebral, and orbicular. The palpebral portion of the orbicularis muscle is strictly attached to the maxilla, where it stems without a dissectible anatomical plane deep to the muscle. Laterally, however, along the lid/cheek junction, the attachment between the orbicularis muscle and the underlying bone is ligamentous (the orbicularis retaining ligament), which creates a dissectible plane deep to orbicularis muscle in this area.

The skin overlying the palpebral orbicularis muscle (eyelid skin) is thin, with no subcutaneous fat. The skin over the orbital orbicularis muscle (cheek skin), in contrast, was thicker and was detached from the underlying orbicularis muscle by the malar fat pad. The suborbicularis oculi fat

(SOOF) is located on top of the lowest portion of the zygomatic bone and under the orbicularis muscle. It is separated from the periorbital fat by the thin orbital and malar septum. Malar fat pads, located below the orbital margin level, can result from the ptosis of the SOOF. Ptosis and pseudo herniation of the SOOF and orbital fat occur as part of the aging process.

In 1993, Flowers coined the term "tear trough deformity" in order to designate a natural depression extending inferolaterally from the medial canthus to the mid-pupillary line. This depression is a consequence of the anatomic attachments of the periorbital tissues caused by the following: (a) fixation of the orbital septum at the level of the inferomedial portion of the arcus marginalis; (b) existence of a triangular gap limited by the lateral portion of the angular muscle on one side and the medial portion of the orbicularis oculi muscle on the other; and (c) the absence of fat tissue from the central and medial fat pads subjacent to the orbicularis oculi muscle in the area below the groove (Flowers 1993).

The lid/cheek junction, or palpebromalar groove or nasojugal groove, extends around the lateral half of the inferior orbit (Fig. 3) (Haddock et al. 2009). Haddock et al., in 2009, suggested that the anatomical features that explain these external landmarks known as the tear trough and lid/cheek junction exist in three different planes: at the skin level, at the subcutaneous plane, and at the suborbicularis plane (Haddock et al. 2009). The eyelid skin above the landmark and the cheek skin below the landmark have different textures and thicknesses, and, virtually, there is no fat between the skin and the muscular junction, contributing for its visibility as a cutaneous landmark. In the subcutaneous plane, the tear trough and lid/cheek junction are correlated with the junction of the palpebral and orbital portions of the orbicularis muscle. The cephalic border of the malar fat pad corresponds precisely with the tear trough medially and the lid/cheek groove laterally and is located strictly at the junction of the palpebral and orbital portions of the orbicularis oculi muscle. In the suborbicularis plane, the tear trough and the lid/cheek junction differ. Along the tear trough, the palpebral portion of the orbicularis oculi muscle is rigidly attached to the bone, with no dissectible anatomical plane deep to the muscle. However, along the lid/cheek junction, the orbicularis muscle has a ligamentous attachment to the bone by means of the orbicularis retaining ligament. Unlike the tear trough region, there is a plane deep to the muscle into which material can be injected or surgical dissection performed (Haddock et al. 2009).

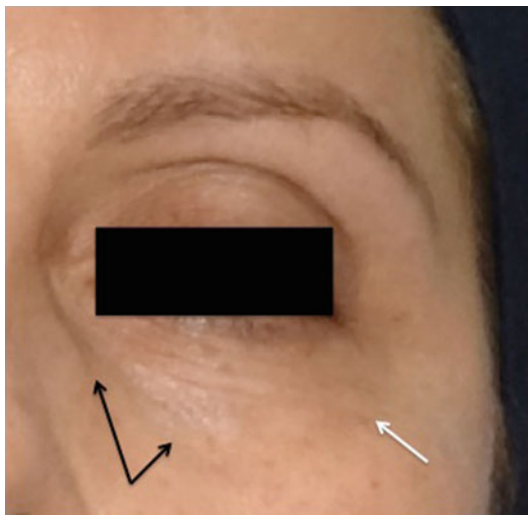

Fig. 3 The tear trough deformity is the natural depression extending inferolaterally from the medial canthus (*black arrows*). The lid/cheek junction extends around the lateral half of the inferior orbit (*white arrow*)

Kane described the tear trough as a depression centered over the medial inferior orbital rim, bounded superiorly by the infraorbital fat protuberance and inferiorly by the thick skin of the upper cheek with its abundant subcutaneous fat, suborbicularis oculi fat, and portions of the malar fat pad. This author suggested that the tear trough is deeper medially because of the very little fat beneath the skin of this region and becoming more shallow laterally (Kane 2005).

Some branches of the trigeminal nerve are responsible by the sensory innervation of the periorbicular region. Palpebral branches of the ophthalmic nerve innervate the upper eyelid and terminal branches of infraorbital nerve are responsible for innervation of the lower eyelid

and the skin. Branches of the facial nerve make the motor innervation. Frontal branches of the facial nerve are located inside the temporoparietal fascia and are responsible for the motor innervation of the cephalic portion of the orbicularis oculi muscle. The zygomatic nerve innervates the orbicularis oculi muscle's inferior bundle (Tamura 2010c).

The central artery of the retina is a branch of the ophthalmic artery, arising from the internal carotid artery. The occlusion of the central artery of the retina results in blindness. The retina's veins follow the arteries, ending in the cavernous sinuses. The palpebral veins have connections with the angular, ophthalmic, and superficial temporal veins. The angular and ophthalmic veins' anastomosis allows communication between the palpebral medial and lateral nasal regions and the cavernous sinuses, where there is a possibility of intracranial infection. The infraorbital artery originates in the pterygomaxillary fissure (close to the maxillary tuberosity) and penetrates the orbit and leaves the face through the infraorbital foramen. Its terminal branches irrigate the soft tissues in the middle third of the face (lower eyelid), external nose, and upper lip (Fig. 4).

Chronologic Aging of the Temporal Region, Forehead, and Periorbicular Area

Facial changes related to chronologic aging occur as a consequence of thinning of the epidermis and dermis, atrophy of subcutaneous fat layers, structural changes of the bones, and weakening of underlying muscles. These anatomical alterations are observed in the regions of the temporal, frontal, and periorbicular with some typical characteristics of each area, which will be described below.

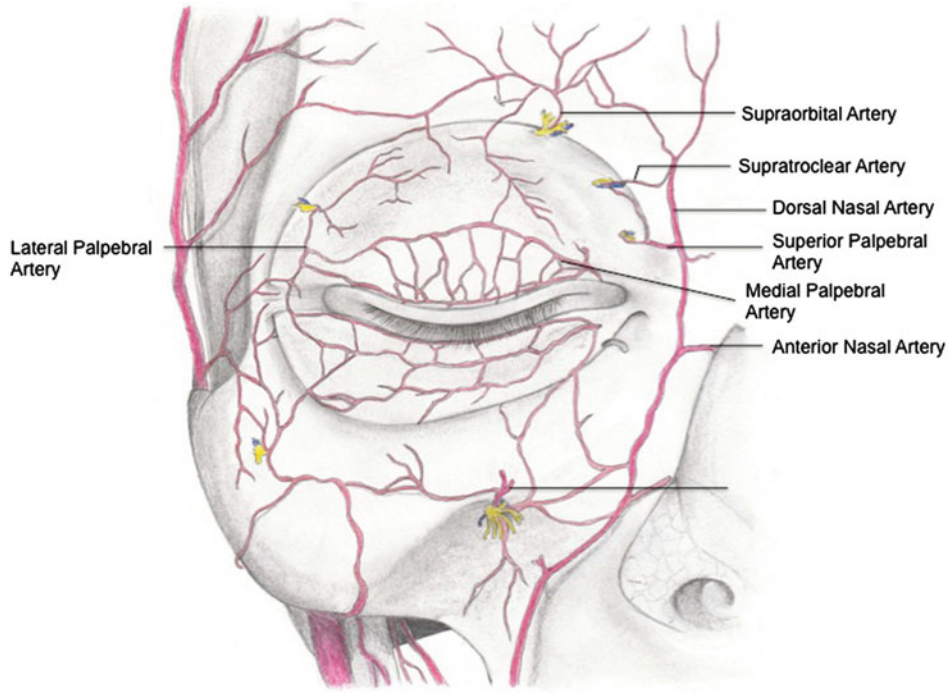

Fig. 4 The infraorbital artery leaves the face through the infraorbital foramen, and its terminal branches irrigate the soft tissues in the middle third of the face (lower eyelid), external nose, and upper lip

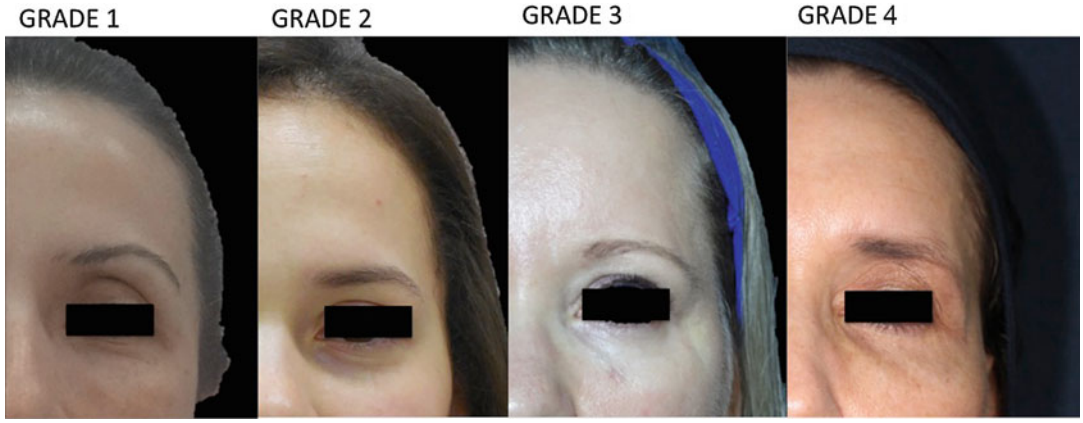

Fig. 5 Four-point temporal aging scale

Forehead

Age-related changes in the frontal region are the loss of elastic fibers, the loss of volume of soft tissue, and the wrinkles caused by the repetitive contractions of forehead elevator muscles. Volume loss and volume descent of the soft tissue below the frontal eminence results in suprabrow concavity which contributes to the brow descent, also caused by gravity (Busso and Howell 2010). Therefore, one of the hallmarks of facial rejuvenation is the reposition of the eyebrow and the replenishment of the concavities of the frontal region.

Temporal Region

The more the years pass, the more concave the temple becomes, and the bony margins of the region appear more prominent, mainly the zygomatic arch and the temporal line (Sykes 2009). Different layers of the temple are affected by chronologic aging as 1) the temporal fat pad diminishes in size, 2) the temporalis muscle loses volume, and 3) the temporal bone becomes more concave. The brow loses soft tissue support with aging and turned to down position or less projection of the region.

Raspaldo created a four-point temporal aging scale to assess this region (Fig. 5) (Raspaldo 2012):

- Grade 1: Normal, convex, or straight temporal fossa.
- Grade 2: Early signs of a slight depression (hollow).
- Grade 3: Concavity of temporal fossa, with some visible temporal vessels; the eyebrow tails also droop.
- Grade 4: Skeletonization of the temporal fossa, bones being visible; severely visible veins and artery; severe concavity of the temporal fossa.

Periorbicular Region

Aging of the periorbital region is a physiologic process caused by several factors, including bone absorption, loss of volume, thinning of the epidermis, and changes in collagen and elastic fibers, leading to the appearance of pigmentation and static and dynamic wrinkles. A decrease in hyaluronic acid concentration and skin hydration results in increased skin wrinkling, especially in the region around the eyes, where the skin is very thin.

Greater skin laxity of the lid/cheek junction and the midface ptosis of aging contribute to the tear trough deformity by accentuating the herniation of orbital fat. Also, as the patient ages, the globe descends within the orbit, the infraorbital fat is displaced anteriorly, and this anterior bulge deepens the tear trough. With age, further loss of soft tissue and, importantly, a loss of osseous support induce the tear trough to deepen further (Kane 2005).

Table 1 Classification system of the tear trough deformity based on clinical evaluation by Hirmand

Class	Clinical description
I	Patients have loss of volume, limited medially to the tear trough. These patients can also have mild flattening extending to the central cheek
II	Patients exhibit loss of volume in the lateral orbital area in addition to the medial orbit, and they may have moderate deficiency of volume in the medial cheek and flattening of the central upper cheek
III	Patients present with a full depression circumferentially along the orbital rim, medial to lateral

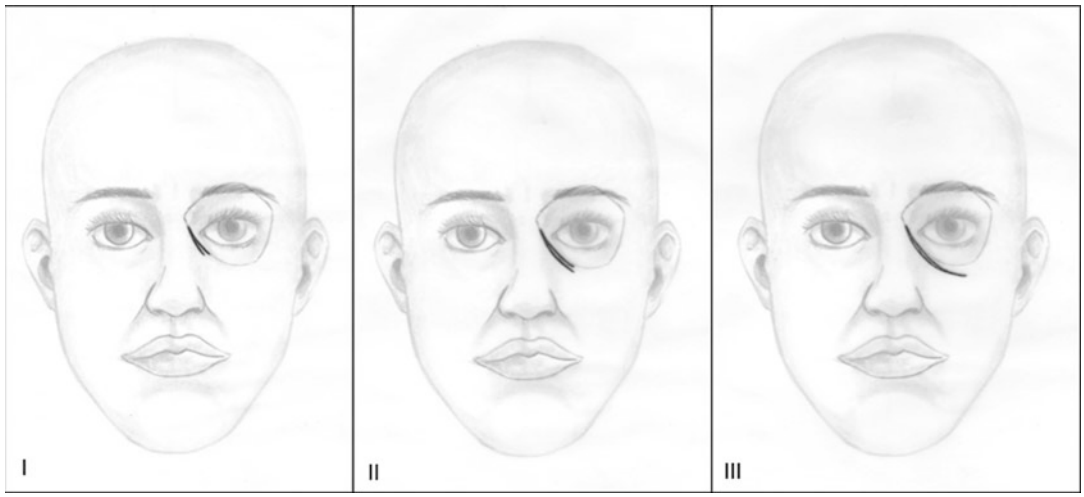

Fig. 6 Classification system of the tear trough based in Hirmand

In 2010, Hirmand proposed a classification system of the tear trough deformity based on clinical evaluation (Hirmand 2010), which can correlates with the aging changes of the periorbicular region (Table 1) (Fig. 6).

Fillers According to the Region

The characteristics of the filling agent, such as molecular weight, particle size, viscosity, and recommended level of implantation, influence the depth, volume, and distribution of the chosen filler. In most areas of the face, the dermis has less than 1 mm of thickness, but it has variations according to the different facial regions. The choice of the type of filler and injection depth is affected by this dermal thickness variation. The dermis, for example, is extremely thin in the periorbital, eyelid, nasal dorsum, and cutaneous lip regions. Successful treatment of such areas depends on selection of the appropriate superficial dermal filler. A lighter product of smaller particle size and lower viscosity is the best choice, with adjustments made in depth, volume, and distribution of the filler according to the anatomic variation in dermal thickness (Sherman 2009). For deeper rhytides associated with underlying volume loss, correction may be best achieved with implantation at or below the level of the dermal subcutaneous junction with hyaluronic acid filler with high elastic and viscosity characteristics.

Knowledge of filler characteristics, anatomy, and wrinkle/volume assessment allows the professional to choose the best fillers for optimal results. The superficial injection of a heavy product of larger particle size or highly viscous filler, for instance, may result in nodule formation or contour irregularities. Injection of a

Fig. 7 Before and after treatment of the forehead with hyaluronic acid filler, in a frontal view

Fig. 8 Before and after treatment of the forehead with hyaluronic acid filler, in a lateral view

lighter product of smaller particle size or less viscous filler for correction of volume loss will lead to undercorrection. Fine lines are best treated with superficial injection of lighter products of smaller particle size or fillers with lower viscosity, whereas moderate to deep wrinkles may be managed with a middle to deep dermal injection of heavier products of larger particle size or fillers with higher viscosity. Volume restoration for dermal atrophy, fat loss, and deeper structural changes related to aging is best handled with deeper implantation at or below the level of the dermal subcutaneous junction (Sherman 2009).

Hyaluronic Acid Fillers for Temporal, Frontal, and Periocular Regions

The patient must be prepared with hair cap or band to fend off the hair of the area to be assessed and treated. Aqueous chlorhexidine 0.5% is the preferred substance to do asepsis of the whole face before and after drawing the points that will be treated and also before each puncture of the skin. Anesthetic ointment containing lidocaine can be used to make the procedure more comfortable for the patient and must be removed completely with chlorhexidine soap or alcohol 70% before the treatment. After the patient seats, the areas to be treated should be marked with easily removable white eyeliner, because the laying down position can change the areas of loss of volume, shadows, and sulcus.

Forehead

Patient must be examined carefully to find exactly the best area to treat, because this is not a common area to be approached in rejuvenation treatments. The beautiful forehead has a gentle vertical convex ogee curve from trichion to supraorbital ridge. Also, flattened or sloping brow greater than 15 degrees from vertical is often undesirable for the female forehead. So, the anatomical target for filler injection in the forehead depends on the bone curvature, the thickness of the skin and the frontalis muscle, and the position of the brow, characteristics that can change with the aging.

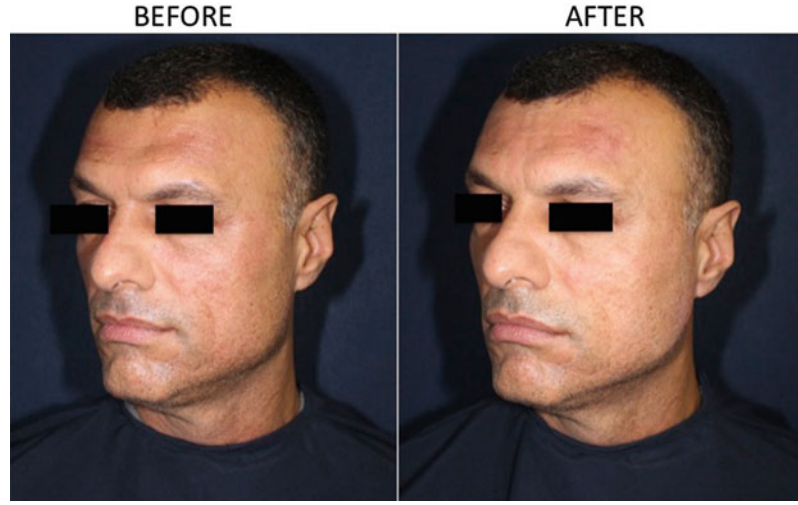

Fig. 9 Before and after treatment of the forehead with hyaluronic acid filler, in an oblique view

Laterally, the target space extends into the temporal compartment below the temporal-cheek fat. Medially, supraperiosteal injections remained lateral to the projected location of the supraorbital nerve, slightly more than 1 cm from the supraorbital notch or foramen. Injections medial to the projected location of the supraorbital nerve should be performed at the subcutaneous level. The filler should be placed at the supraperiosteal level behind the galeal fat pad using retrograde injection with cannula or vertical periosteal depots with needles. The amount of filler deposited was determined according to a visual end point (reconstitution of the suprabrow arch or desired brow lift) with a total volume ranging from 1.5 to 3.0 ml. Finally, the area must be massaged to ensure even distribution of the product throughout the deficit area (Busso and Howell 2010).

Replacing concavity by convexity improves surface anatomy and can correlate with brow lift in patients with brow descent from tissue loss (Figs. 7, 8 and 9). Different brow shapes can be generated to accommodate patient preferences (Busso and Howell 2010). The potential planes for injection of fillers in the peribrow region are the immediate subcutaneous plane (with cannula) or the plane between the galea aponeurosis and the periosteum (with cannula or needle). The injections should be placed lateral to the supraorbital neurovascular bundles to avoid an intravascular injection or damage to the nerves (Sykes 2009).

Temporal Region

Augmentation of the temple can be done with a variety of filling agents, but hyaluronic acid fillers has been the most used in last years because of its advantages, which have already been explained in previous chapters of this book. Depending upon the stage of temporal aging at baseline, the dermatologist can establish the optimum hyaluronic acid product and volume required to do the treatment (Moradi et al. 2011).

The preferable plane to treat depends on the patient examination and physician technique, which can be anterograde, retrograde, and depot injection, to achieve expansion of the tissue. In the treatment of the temporal fossa, injections must be made as deep as possible and positioned under the deep temporalis fascia to give more volume projection and to avoid the facial nerve. In this region, subcutaneous injection is less effective because the subcutaneous soft tissue is strongly adhered to the skin and is more dangerous because of the vessels. In addition, it is not recommended to inject into the sliding space (the Merkel space), because the product will move and disappear quickly (Raspaldo 2012).

Thus, the potential planes for augmentation of the temporal region are (1) superficial to the temporoparietal fascia (immediate subcutaneous plane), (2) just deep to the temporoparietal fascia

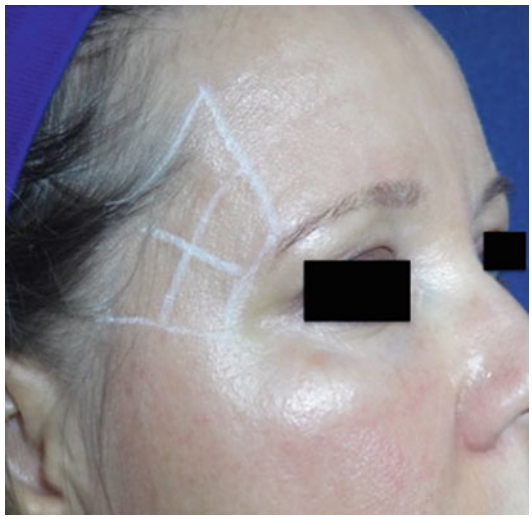

Fig. 10 Temporal borderlines and drawing of the four sections to improve the safety of the procedure

(between the superficial and deep fascia), and (3) deep to the temporal muscle (Sykes 2009).

Raspaldo et al. developed a pattern of four sections physically drawn onto the patient to improve the safety of the procedure (Raspaldo 2012), as follows (Fig. 10):

- The inferior horizontal limit: the zygomatic arch.
- The curved anterior limit: lateral part of the orbit (orbitomalar apophysis).
- The curved superior limit: the linea temporalis (temporal crest) fusion zone between the frontal, parietal, and temporal bones, where the periosteum, the deep temporal fascia, and the periorbital retaining ligaments are attached.
- The posterior limit: the posterior limit of the visible temporal fossa. For a bald patient, the posterior landmark is the end of the linea temporalis, at the junction of the parietal temporal and occipital bones. It roughly follows the curve of the ear.

With these four sections determined, a vertical line at the halfway point of the zygomatic arch and a horizontal line from the lateral canthus are drawn to separate the temporal region in four quadrants (Fig. 10). The safest and most effective point to refill is the anterior-inferior quadrant, so this area should be treated first (first refill zone). The temporal fossa quadrant is the deepest area, because the needle must penetrate to a depth of 1–1.5 cm. If it shows an insufficient result, a second injection should be performed at the junction of the linea temporalis and the superior orbital rim (second refill zone). After the treatment of these two zones, an injection can then be performed into the posterior-inferior quadrant, which is situated at the most lateral section of the zygomatic arch (third refill zone). And if the depression is severe, injection of the last quadrant, the posterosuperior area, can be made (fourth refill zone) (Raspaldo 2012).

The temporal aging scale created by Hervé Raspaldo in 2012 can be used as a guideline to the injection of fillers in this area, demonstrated in the Table 2 (Raspaldo 2012).

Generally, patients show a persistency of the results of at least 6 months (Figs. 11 and 12), and if they return to touch-up injections, this effect can last for a longer time (Moradi et al. 2011).

Periorbicular Region

After the patient seats, the tear trough deformity and lid/cheek junction are marked with easily removable white eyeliner. Some important factors that must be evaluated to repair this region are:

- Skin quality, as patients with thick, smooth skin will have better results than those with thin and extremely wrinkled skin
- Definition of the hollow, as a more defined hollow is more tractable to fillers
- The orbital fat pad, as larger fat pads are more difficult to correct due to "puffiness" caused by the injection
- The color of the overlying skin, as the filler may improve shadowing but will not improve dark pigmentation

The skin is inspected carefully for visible vessels before each needle stick. The skin of the lower lid is spread and held at some tension with the

Table 2 Raspaldo temporal aging scale of the temporal region and guideline to treat this area (Raspaldo 2012)

Four-point temporal aging scale	Guideline to the treatment with hyaluronic acid filler
Grade 1: Normal, convex, or straight temporal fossa	No treatment
Grade 2: Early signs of a slight depression (hollow)	0.4–0.8 ml of HA filler per side or 0.5–1 ml per side of a volume-restoring product
Grade 3: Concavity of temporal fossa, with some visible temporal vessels; the eyebrow tails also droop	1–2 ml of a volume-restoring product per side
Grade 4: Skeletonization of the temporal fossa, bones being visible; severely visible veins and artery; severe concavity of the temporal fossa	2–4 ml of a volume-restoring product per side

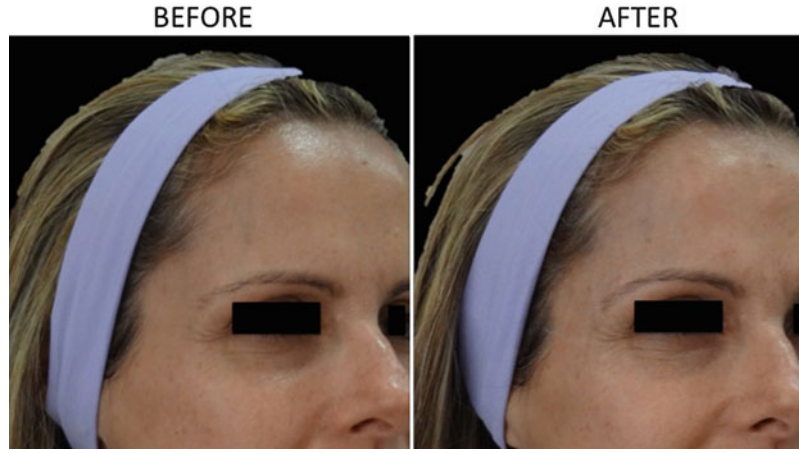

Fig. 11 Before and after treatment of the temporal region, with hyaluronic acid filler, in an oblique view

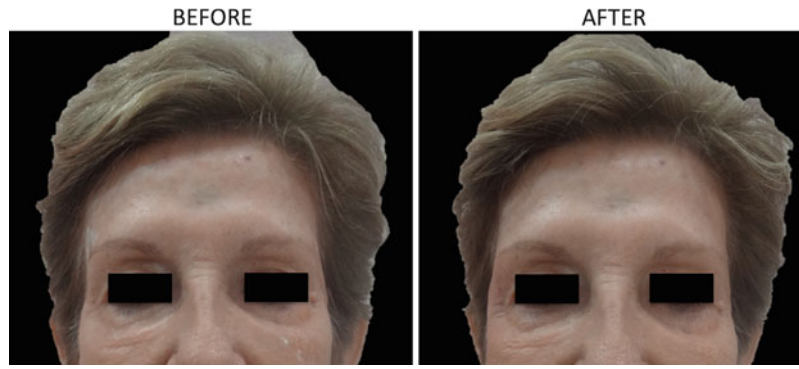

Fig. 12 Before and after treatment of the temporal region, with hyaluronic acid filler, in an oblique view

noninjecting hand. The use of cannulas is less painful, produces less edema, and is safer because the chance of injuring vessels and nerves is smaller than with needles. Different techniques can be used to inject hyaluronic acid in the periorbital region, and each dermatologist may have your favorite one based on personal experience and patient security. When fillers are injected in the nasojugal fold or laterally, it is important to be careful with the medial and lateral palpebral ligaments, which acts as a barrier preventing the dispersion of the product beyond it. Hence, fillers should be administered in the submuscular plane and in small amounts in the inferolateral orbital fold, followed by massage to assist dispersion (Figs. 13, 14, and 15) (Tamura 2010a). When large volumes of fillers are injected in the tear trough during a periocular sculpture, the appearance of edemas is common because the

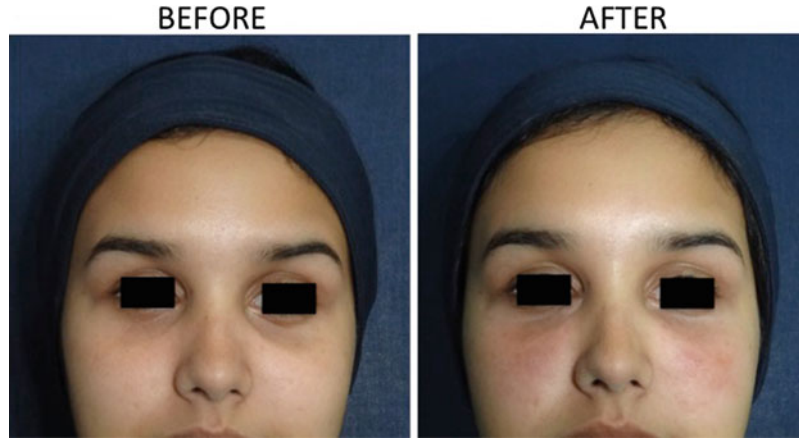

Fig. 13 Before and after treatment of the tear trough deformity and lid/cheek junction region with hyaluronic acid filler, in a frontal view

Fig. 14 Before and after treatment of the tear trough deformity and lid/cheek junction region with hyaluronic acid filler, in an oblique view

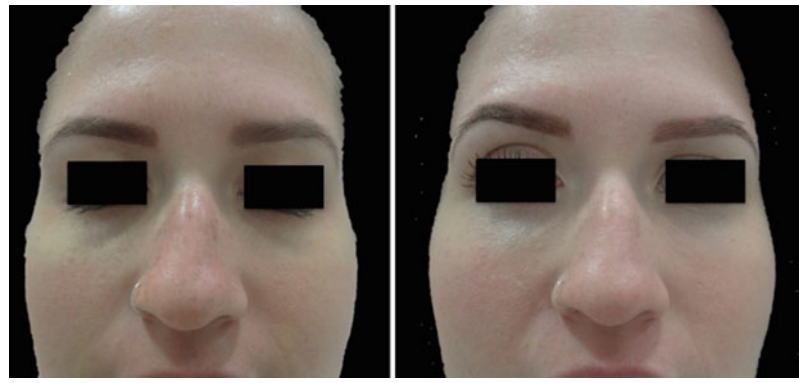

Fig. 15 Before and after treatment of the tear trough deformity and lid/cheek junction region with hyaluronic acid filler, in a frontal view

palpebral lymphatic system is very delicate and not prepared for traumas or procedures.

A consensus group of European and North and South American aesthetic experts assembled at an academic workshop to develop keys to optimal outcomes for augmentation of the cheek and infraorbital hollow. This consensus group recommended vertical supraperiosteal depot technique (VSDT) or linear threading for infraorbital hollow augmentation.

Vertical Supraperiosteal Depot Technique (VSDT)

VSDT uses only single, small depots of soft tissue filler materials that are placed via a vertical injection in a location directly on the periosteum. Due to the bony support, only very little material is needed to produce a pronounced correction at the surface of the skin. The intention in using this technique is to avoid overcorrection. The filler should be injected at the supraperiosteal level along or below the orbital rim under the defect or both, protecting the edge of the rim to prevent deposition of filler above that structure. Most of the filler should be injected underneath the orbicularis oculi muscle whenever possible. Serial injections using VSDT, implanting 0.02–0.05 ml per perpendicular injection point just above the bone 2–3 mm apart, are recommended (Sattler 2012).

Linear Technique

The linear technique is preferred if the cheek has been augmented, using an entry point beneath the lateral and, in some cases, also the medial canthus. The cannula (or needle) should be placed perpendicular to the skin, advanced to the periosteum, and moved forward until it reaches the top of the nasojugal fold. This technique allows for deep injection using retrograde linear threading along the orbital rim. The injected volume depends on the severity of hollowing, and repeated treatments may be required for optimal augmentation.

Other Techniques

A half-inch 30 or 32 gauge needle is inserted for injection through the skin at the most lateral extent of the tear trough advancing fully and the hyaluronic acid gel is injected deep in the supraperiosteal plane calmly. The hyaluronic acid gel is placed beneath the insertion of the medial orbicularis muscle at the maxilla and continues laterally inferior to the orbicularis retaining ligament. The injection is repeated above and below the original site of the injection to yield a smooth contour. The volume range is 0.1–0.3 ml per eyelid, with most patients requiring 0.2 ml. The area is then inspected, and additional passes are made as needed to yield a smooth contour. Lastly, the area is massaged lightly and compressed with finger pressure only (Lambros 2007).

Another possible technique could be done. The dermatologist must direct the needle diagonally up toward the medial canthus and plunge deep into the skin through the muscle right up to the periosteum where about 0.2 ml of HA is deposited supraperiosteally to a visual end point of optimal correction. Then the needle is slowly withdrawn, and the material is not injected while the needle is moving back; superficial injections are intended to give a Tyndall effect in this area. The direction of the needle is then changed vertically up toward the mid-pupillary line and plunged again into the periosteum where another 0.2 ml depot injection is given. A third injection is given only if there is loss of tissue below the lateral orbital rim. The direction of the needle is changed diagonally up toward the lateral canthus to give another depot supraperiosteally. Palpating the infraorbital rim with the noninjecting hand ensures protection of the globe during the movements of the needle. Instead of needles, cannulas of 25 or 27 gauge can be used with the same technique to reduce the risk of intravascular injection.

The area is gently massaged for a distribution of the product. However, vigorous massage should not be done in this area, in order to avoid pushing the substance toward the globe (Sharad 2012).

Post Injection Care

- The patients should apply ice on the region at the night of the procedure.
- The patients should avoid strong or extended pressure over the treated area.
- The patients should be informed about aftercare such as avoiding massage, strenuous physical activity, and exposure to extreme cold or heat for up to 6 h after treatment.
- It is important to schedule follow-up sessions to assess the clinical result. Touch-ups may be performed in the follow-up sessions if required.

Complications

The injection of almost any dermal filler might be associated with some adverse effects (Sherman 2009). The most common ones are described below.

Immediate Complications

- Pain: HA fillers with lidocaine are more comfortable for patients as the pain is alleviated. Some patients experience mild pain for 1 or 2 days in the areas of the injections. When the temporal region is treated, they may complain about pain when chewing or biting for 3–5 days after treatment.
- Erythema.
- Swelling and bruising: This can be minimized by applying firm pressure and ice packs before and after the treatment session.
- Asymmetry.
- Migraine.
- Ischemia and necrosis of the skin.
- Nerve lesions.

Delayed Complications

- Orange-brown staining: Injection in the dermis or supraperiosteum with any kind of filler may also be associated with bruising and subsequent deposition of hemosiderin, giving an orange-brown or rusty, stained appearance to the skin that may take months to resolve on its own. Preinjection ice application, proper depth of injection, discontinuation of anticoagulants at least 7 days before injection, and a smooth, gentle technique may help avoid this complication.
- Postinflammatory hyperpigmentation: It is often seen in darker skin types due to bruising and hematoma and might last for a very long period being difficult to treat.
- Puffiness: Overcorrection with HA products in the temporal, frontal, and periorbital area also may cause a puffy, edematous appearance of the region because of the hydrophilic nature of the filler. The edema might seem to wax and wane, fluctuating in patients with allergic predispositions or in response to dietary intake of salt.
- Nodules.
- Infections: Although they are extremely rare, they can present as single or multiple erythematous and fluctuant nodules that are best treated with antibiotics against frequent skin bacteria including *Staphylococcus epidermidis* or *Propionibacterium acnes*. Filler injections should not be performed if there is an infection in the adjacent site.

Take Home Messages

- Hyaluronic acid injectable fillers for frontal, temporal, and periocular regions have been reported for aging treatment with good results.
- The vascular system of these regions needs special attention as it can cause the most severe filler's procedure complications such as arterial occlusion, ischemia, and embolism.
- A thorough knowledge of anatomy and boundaries of each region and the evaluation of the correct indications for each technique are fundamental to obtain success, avoiding complications, mainly for temporal, orbicular, and frontal regions.
- Different layers of tissue (skin to bone) can be filled with HA, according to the region and to the aim that the dermatologist wants to reach.
- Different techniques can be used in the same area.
- It is fundamental that dermatologists have a very detailed knowledge of anatomy and good experience with fillers before starting to do procedures in forehead, temporal, and periocular areas.

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Hyaluronic Filler for Nose

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Contents

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_19

Abstract

One of the revolutionary treatments with fillers is the correction or the beautification of the nose, which can play an important role in facial rejuvenation. In order to achieve good results, we should individualize the treatment according to the patient, considering the proportion between the face and the nose, the angles between nasal structures, ethnic characteristics, and the concept of beauty. A perfect knowledge of the local anatomy and vast experience in the field are crucial to minimize complications when using fillers for nose sculpting.

Keywords

Fillers · Hyaluronic · Nasal · Nose

Introduction

The nose has several distinct meanings in human culture. It might define different human races and ethnicities, such as African, Asian, European, and Arabic. It also represents different social states culturally, like honor, respect, adultery, aristocracy, and diseases, leading to a variety of emotional reactions. Some cultures have made the amputation of the nose mandatory to do justice and to stigmatize due to some kind of dishonorable act, such as adultery, robbery, and others. On the other hand, it not only represents the ethnicity but is also a sign of beauty. Almost all oriental communities aim to change the nose, which is known as *westernization*, attaining beautification and high social status.

The nose represents a visible protruding part of the face. The oval openings at the anterior part are called nostrils. The nasal bones and cartilage (upper and lower lateral cartilages), including the septal cartilage, which separates the nostrils, are responsible for its shape. Generally, the size of the nose is larger in males than in females.

The root forms the top of the nose, and there is an indentation at the point of its conjunction to the frontal bone. The thin projection of the bone at the midline on the lower nasal margin is the anterior nasal margin that holds the cartilaginous center of the nose.

The nose is a part of the respiratory system and responsible for the sense of smell. The hair in the nose clean the air of the particles through the tubercles where it is humidified and warmed on its way to the lungs.

Anatomy of the Nasal Area

Bones and Cartilage

The nasal and maxilla bones form the nasal structure (Fig. 1) that ends anteriorly by a piriform aperture. The soft tissue of the external nose is on a cartilage structure (medial and lateral) that attaches to the piriform aperture through a fibrous tissue. The dome is the junction of the medial and lateral cartilages (Fig. 2); the shape of the tip of the nose depends on these structures, and its support depends on the skin, the ligaments, and the cartilage. The superior limits of the nasal aperture are formed by the nasal bone laterally and inferiorly limited by the maxilla. The nasal cavities are divided by the nasal septum. The anterior portion of the septum is formed by cartilage, and the ethmoidal and vomer bones form the posterior portion (bone portion). At the lateral wall, there are three or four curved plaques of bone called turbinates (Fig. 3), and the space below each one is called nasal meatus. At the medial area is the inferior limit is the piriform aperture, that presents the anterior nasal spine is located (Tamura 2010a). The nasal bones articulates with the frontal bone superiorly, with the frontal process of the maxilla laterally, and with the nasal cartilage inferiorly.

Innervation

The dorsum of the nose is innervated by the infratrochlear, dorsal, supraorbital, and the anterior ethmoidal nerves. The septal mucosa and the superior nasal area are innervated by the anterior ethmoidal nerve.

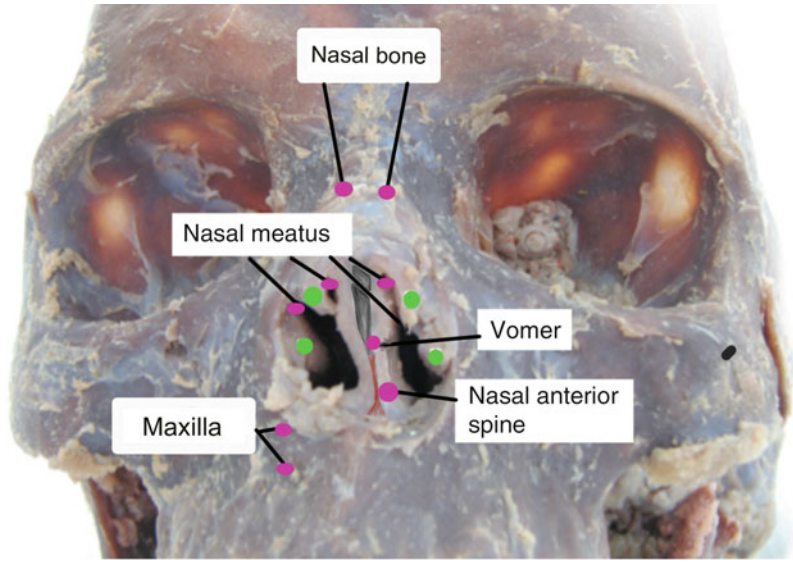

Fig. 1 Bones of the nose: nasal bone, maxilla, the vomer, and the nasal anterior spine. The nasal turbinates are in green

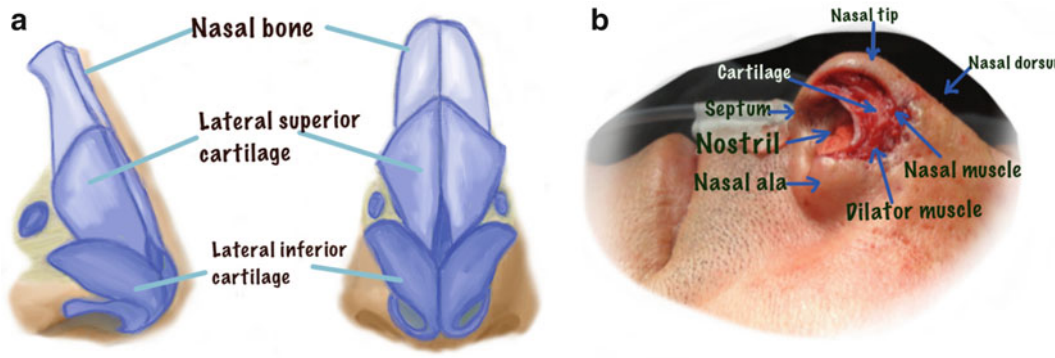

Fig. 2 (**a**) Cartilages of the nose: lateral superior cartilage and lateral inferior cartilage. (**b**) Nasal structures and a better view of the nasal and dilator muscle

The supratrochlear (branch of the trigeminal) emerges from the orbit between the periosteum and the orbital septum, at the medial supraorbital margin, and innervates the medial and central frontal area such as the nasal radix. The infratrochlear nerve is a branch of the nasociliary (trigeminal n.) and it is responsible for the sensitivity of the nasal radix. The external nasal nerve is a branch of the anterior ethmoidal (trigeminal n.) and innervates the dorsum, apex, and the ala of the nose. The external nose is innervated by the infraorbital and also has a sensitive function at the maxilla area.

Musculature

The nasal muscle inserts at the nostril, where it is called "dilator of the nostrils" as it opens the nostrils. The transversal part of the nasal muscle with the collaboration of some surrounding muscles (zygomaticus and labial levator pars nasalis) elevates the tip of the nose. The depressor of the nasal septum muscle acts at the nasal tip and at the superior lip; it shortens the superior lip and pulls the tip of the nose downward during the smile mimic (Tamura 2010a).

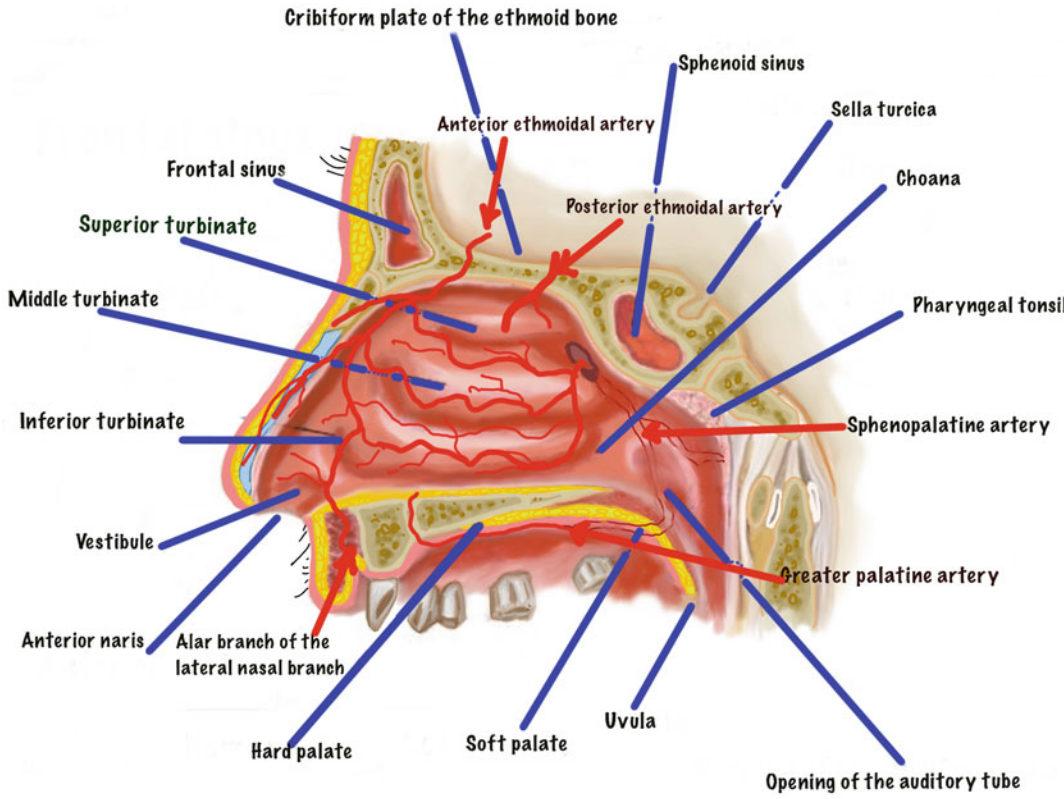

Fig. 3 At the lateral wall, there are three or four curved plaques of bone called conchae (turbinate), and the space below each one is called nasal opening. The anterior nasal spine is located medially at the inferior limit of the piriform aperture presents the anterior nasal spine. In this picture, we can also see the arterial supply of the inner nose

Vascular System

The main artery that irrigates the lips and the nose is the facial artery and its branches. The angular artery (Fig. 4) is a terminal branch of the facial artery that irrigates the lateral area of the dorsum of the nose, near the radix. The facial artery also provides branches to the lips, superior and inferior labial arteries, and to the nasal ala. Because of its characteristics and extension, if the filler is injected inside the artery, the arterial blood flux is interrupted, causing ischemia, necrosis, and subsequent scars in the area involved. The columella and lateral nasal, the most common branches of the superior labial artery, irrigate the nostril, the dorsum, and the apex (tip) of the nose. The nasal dorsum artery, which is a branch of the infraorbital artery, irrigates the radix and the nasal dorsum. One of its branches joins the angular artery at the radix of the nose, and the other branch anastomoses with the external nasal artery. The lateral veins are about 2–3 mm on the alar sulcus, and at the columella level they run deeply at the nasal base and end at the tip at the subdermic plexus. They are tributaries of the angular vein that drains the entire external nose.

The inner part of the nose has a rich vascular supply to change the humidity and temperature of inspired air. Both internal and external carotid arteries irrigate this area. The ophthalmic artery is a branch of the internal carotid artery; from this originate the anterior and posterior ethmoidal arteries that descend into the nasal cavity through the cribriform plate.

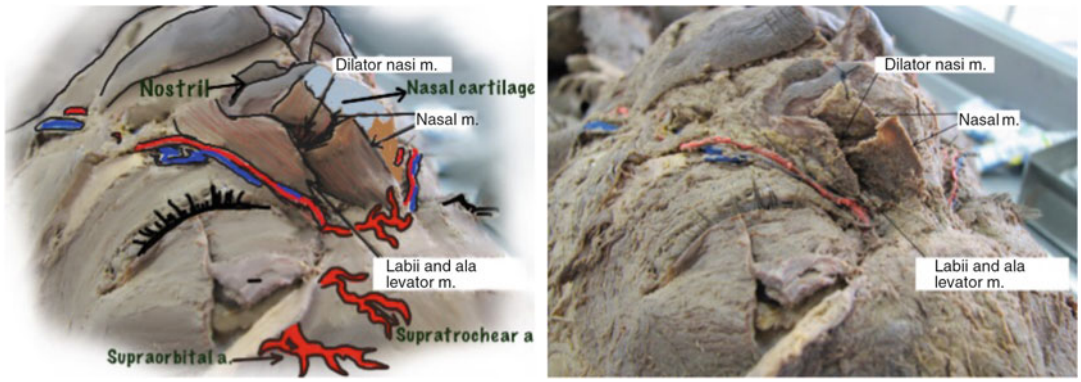

Fig. 4 Arterial supply and musculature of the nose

The sphenopalatine, greater palatine, superior labial, and lateral nasal arteries originate from the external carotid artery. For a rich blood supply, these arteries form anastomoses with each other, especially at the anterior portion of the nose. The veins frequently follow the arteries and drain into the pterygoid plexus, the facial vein, or into the cavernous sinus. A few nasal veins may sometimes join the sagittal sinus, that is, a dural venous sinus, turning this route into a potential pathway for the spread of infection from the nose into the cranial cavity (Tamura 2010b).

Types of Nose

There are different views about the classification of the nose according to different authors. One of the basic differences is the ethnic individual characteristic that might classify it into a dozen types. But in a simplified way, there are basically three kinds that we should know: the Caucasian, the Asian, and the African nose.

Caucasian

It is high and narrow, with thin skin and strong cartilage. As the skin is not thick, the tip of the nose can be very well defined in a plastic surgery or with a filler injection. There is a subtype, the crooked nose or pinched nose that has a greater curved projection of the nose and sometimes leads to a fallen tip, accentuated when the patient smiles. When the bone and cartilage protuberance is over-projected, it might lead to a nonaesthetic nose.

Asian

The nose is short, without projection of the dorsum, and the nasal bridge is large and low. It is referred to as a flat nose due to larger nostrils and the round shape of the tip (Byun and Kim 2013).

African

The nasal basis is larger, the nostrils are also enlarged, the dorsum is shorter, and the tip is round.

In this case, the ethnic differences need to be respected, as in different countries the concept of beauty changes. One important issue is the hyper-valorization of occidental beauty, which some oriental natives aim to achieve.

Although at least 14 different nasal types have been described in the literature, we propose the following classification to exemplify the diversity of nasal characteristics: the Roman, the flat, the celestial, the Greek, the hawk, the fleshy, the prominent, the plane, the hook, the narrow, the short, and the high (Fig. 5).

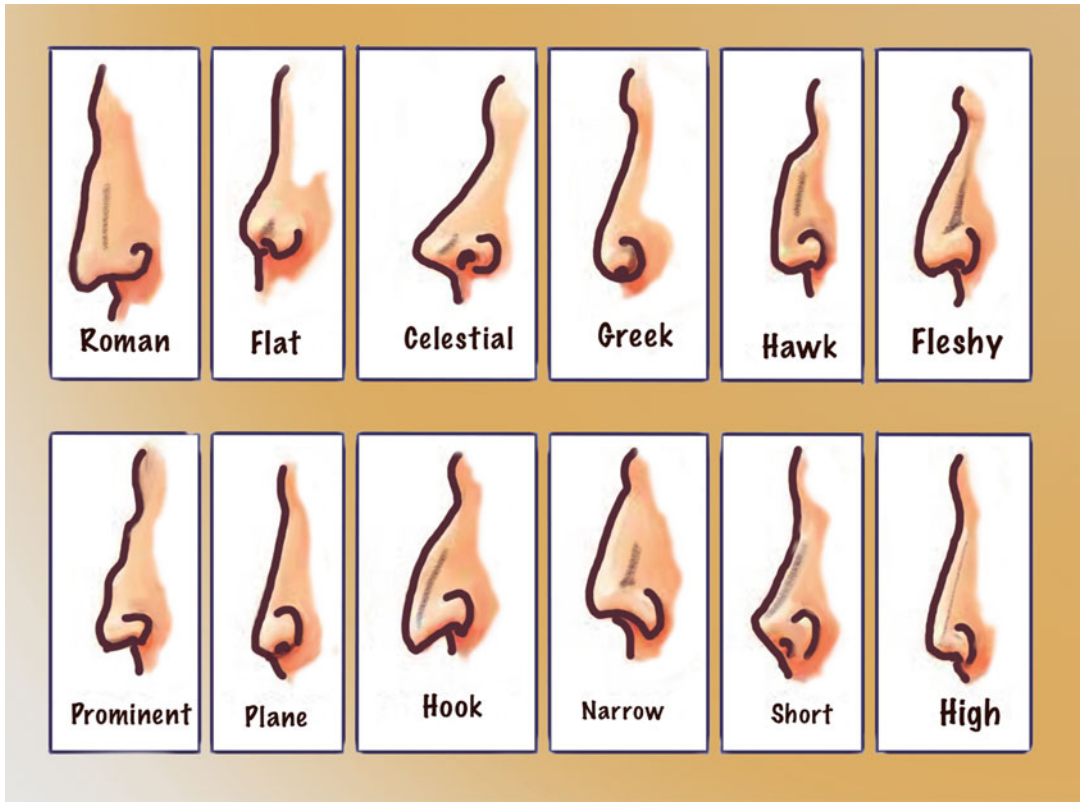

Fig. 5 Nasal types: the Roman, the flat, the celestial, the Greek, the hawk, the fleshy, the prominent, the plane, the hook, the narrow, the short, and the high

Basic Concepts of a Beautiful and Proportional Nose

Facial Measurement

The ideal proportion of the length of the nose is one-third of the facial length, located at the middle third. Longitudinally, the ideal nose width is one-fifth of the face width and is located at the medial line of the face (Fig. 6).

Bottom View

Considering the below view, the nose is divided into two parts. The anterior half composes the tip, the infratip and part of the anterior nostrils openings. The posterior half is divided by the columella, composing the majority of the nasal opening right on top of the nasal base. The ideal angles from the face to the nose, the base of the nose, the tip, and the relationship of the chin with the nose are illustrated in Fig. 7.

There are also differences based on gender, as shown in Fig. 8. For males, the angle from the nose to the chin is around 90° , and for females, the angle is wider, around 105°. From the nasal root to the frontal area, in males, the angle is about 115° and in females, 120°. The nasal dorsum projection is about 2 mm higher in males than in females.

Fillers

Today, hyaluronic acid fillers are by far the best choice to reshape the nose. Some studies also recommend hydroxyapatite calcium as

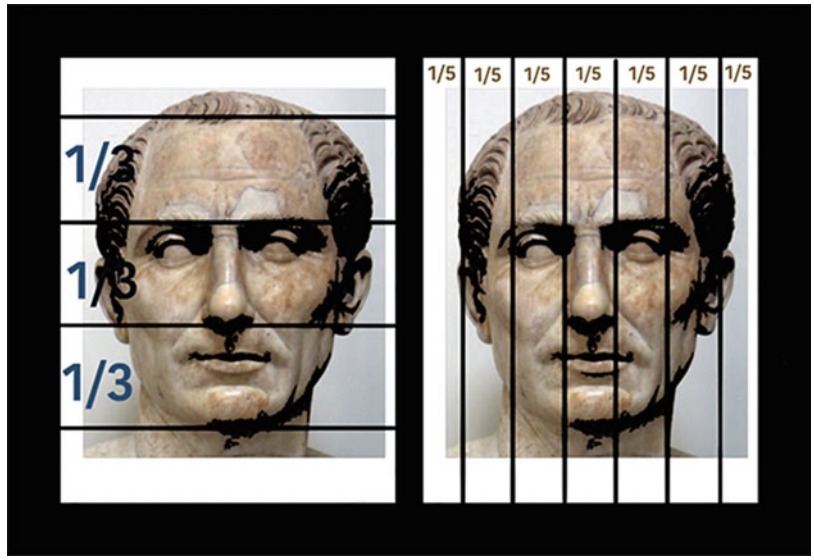

Fig. 6 Nose and facial proportion

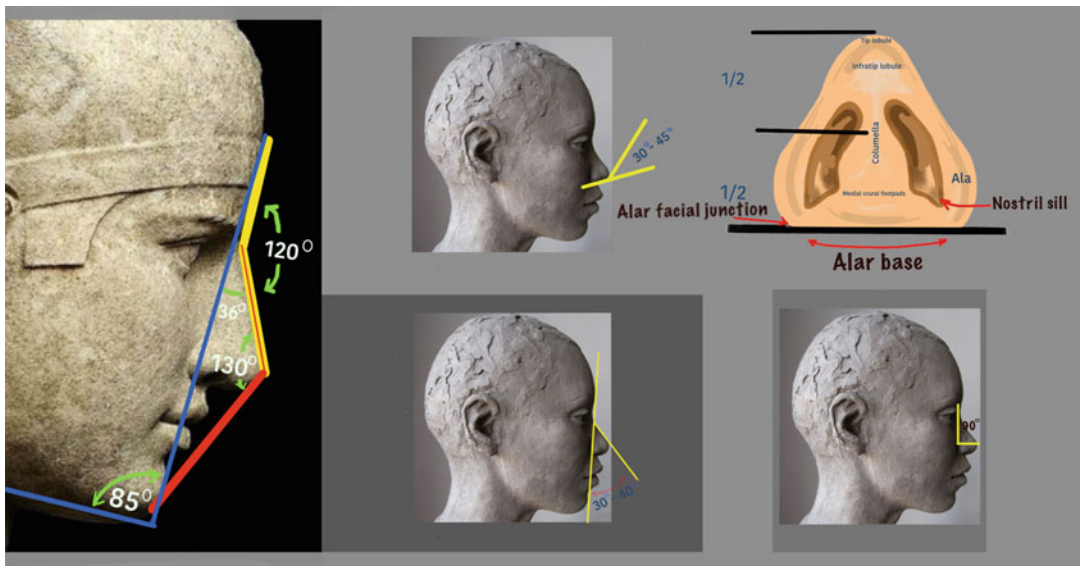

Fig. 7 Facial-nose angle proportions

another option. Depending on the indication, the technique and the product choice vary from author to author. But their expertise and knowledge of anatomy are clearly the most important points. Also these fillers are not permanent and are better suited to a series of indications. We will discuss our experience for each site, and later as a complex reconstruction not related to a specific defect.

Anesthetic Techniques

In the market, there are numerous fillers with lidocaine in their composition, leading to a less painful injection. The use of fillers is a good option to promote the correction and beautification of the nose. It should be injected according to the topographic anatomy. Depending on the

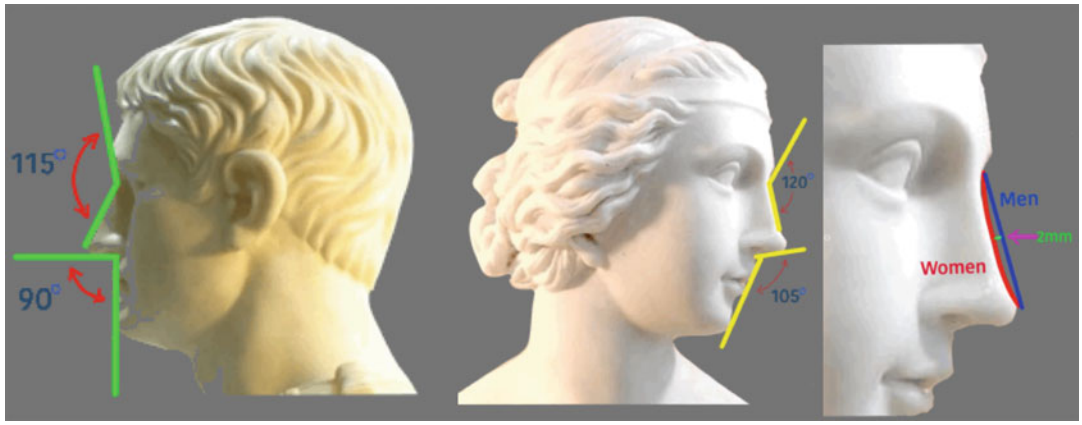

Fig. 8 Differences between males and females in the facial-nose angle proportions

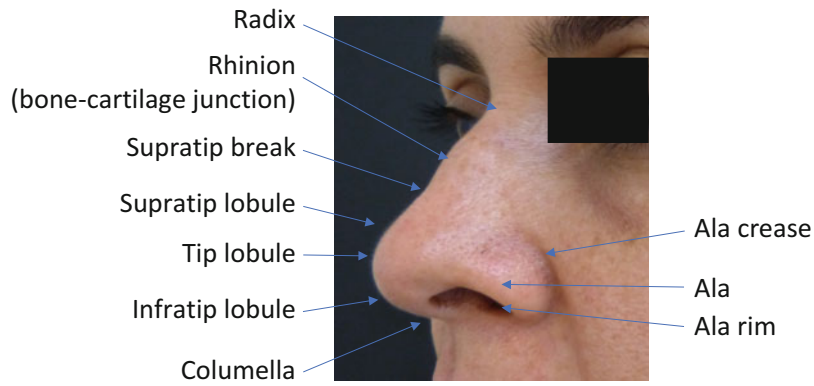

Fig. 9 Topographic anatomy of the nose

volume, location, and technique, a simple topical anesthetic, vibro-anesthesia, cold packs, or cold air devices can be enough (Fig. 9). When a complex reconstruction is planned, or the patient is too sensitive, anesthetic at the cannula insertion point or a neural blockade can be used. We can block the supraorbital and infraorbital nerves to minimize the pain. On the other hand, the patient will not be able to alert us if something is not going well, as vascular occlusion is normally painful. We can block the supraorbital and infraorbital nerves to minimize the pain.

Tiny simple corrections may be performed by injecting the fillers with a needle, but cannula is the best option for complex corrections to avoid intravascular injections. The arteries and veins are located at the subcutaneous layer, just below the skin, and the skin of the nose changes its thickness abruptly when comparing the skin of the tip against the radix. When we inject the filler with a needle, it is better to insert it just above the cartilage and the bone. When using a cannula, the filler is usually placed at the subcutaneous layer, and although a cannula should be safer, thinner cannulas might also lead to artery canalization. We should be extremely careful whichever technique is chosen. Still, even with a cannula, the best layer would be just above the cartilage and bone, and this leads to a painful procedure that will need a better neural blockade. Although many do not believe in aspiration before the injection of fillers with a needle and even less with cannulas, we would always try to do so when treating dangerous zones.

Radix

Radix is the trickiest area to be managed because of the complexity of arteries that are present in this area. There might be a transversal artery and local anastomosis with part of the angular, the infraorbital, and the trochlear. This region is better filled with a cannula, especially if we are reshaping a new radix for Asians (correction of epicanthus) or correcting it for other purposes (rectifying or reshaping the dorsum). Due to the orbital curve, it is easier to insert the cannula from the bottom to the top (Coimbra et al. 2015).

Dorsum

In general, fillers are used to correct a deviation or depressions above the tip, but it is also possible to reconstruct a small nose or define its line and width. At this place, a needle can be justified if it is to be inserted down to the cartilage and the bone, but if other areas need to be corrected, a cannula would be advisable (Coimbra et al. 2015).

Tip of the Nose

To fill the tip, smaller volumes are injected. For this reason, the easiest technique is to insert the needle from the tip to the dorsum, injecting filler just above the cartilage. The correction might be indicated for a depression or a defect or to hide the fold between the cartilage.

Septum and Columella

Although vessels might be found at the septum, it is one of the safest areas at the nose to be filled. Most of the times, the artery is tiny and the ethmoidal arteries and collaterals from the upper lip also irrigate this area. Injecting the filler deeply, inserting the needle to the bone, touching it if possible, we effectively arise the septum and the tip of the nose. Complementary to this injection, we angle the needle and direct it to the tip through the columella and fill it in a retrograde line to reshape it to straighten up. When the patient needs only a straight columella, the insertion of the needle could be in the direction from the tip toward the septum (Fig. 10).

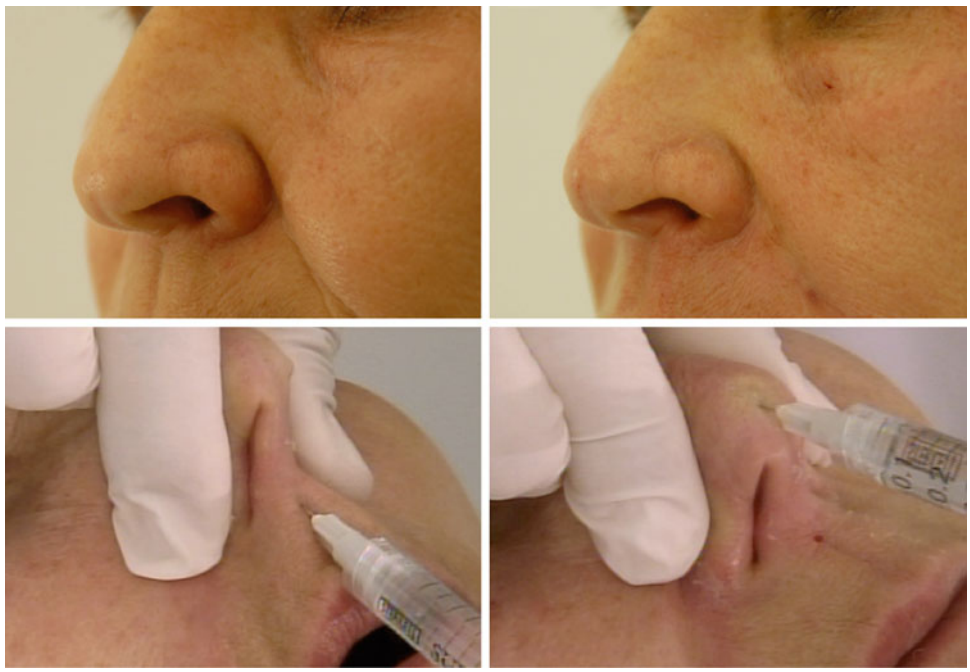

Fig. 10 Technique to fill up the columella and the tip of the nose

Nostrils

If the aim is to correct little defects with tiny amounts of fillers, the injection might be performed with a needle with caution from the middle of the nostril to the tip. When the correction is lateral, attention must be doubled. Injection might be just above the cartilage and with small amounts to avoid ischemia. Even more care should be taken if the aim is to close the nostrils as correction of the African or Asian nostrils. The technique is to inject the filler lateral to the nostrils, exactly parallel to them. This is where the worst complication can occur: occlusion or ischemia of the angular artery leading to nostril, tip, and lateral nasal dorsum necrosis. It can occur either as a direct injection inside the artery or as a local outside compression.

One possible technique is to fill a tiny amount at the nasolabial fold (dermis/subcutaneous), lateral to the nostril, and then direct the needle to the bone. That is the region where we inject a bigger amount, but always slowly, checking the skin color or any complaint of pain, checking that the needle stays down to the bone. We should always aspirate carefully and slowly before injecting the filler.

Defects of Other Etiologies and Complex Reconstruction of the Nose

Plastic surgeons might use fillers as an alternative for unexpected undesirable outcomes from a surgical reconstruction. But fillers cannot substitute surgery in all cases. Remember that it is not a straight nose, full of fillers, and out of proportion that leads to beauty. The African or Asian nostrils are inherent to the racial differences, and they should only be corrected if the patient feels like it, not generalizing one unique concept of nasal beauty for everybody.

Complications

The worst of the complications is arterial embolization, leading to tissue necrosis (small or larger areas) or amaurosis. As discussed above about the vascular complexity, any intra-arterial injection might lead to a tragic outcome. The radix is the most dangerous area due to various possibilities of internal and external carotid arteries (Carruthers et al. 2014).

Ischemia and necrosis begin in general with the complaint of pain right on the top of the injection. The tissue becomes pale, and when we test the blood supply, there is no response (Park et al. 2014).

The treatment of these complications is described in other chapters, but tips like avoiding large needles or thinner cannulas, using smaller syringes, injecting slowly with tiny amounts, avoiding treating patients with previous nasal surgeries, and being aware of the regional anatomy are given here (Casabona 2015).

If there are signs of amaurosis, retrobulbar injection of hyaluronidase (2–4 ml) is recommended immediately. Some authors suggest using intravenous hyaluronidase as we do in ischemic cardiac patients. The benefit of ocular massage and intravenous mannitol to reduce intraocular pressure is also described.

Filler complications such as allergic reactions, overcorrection, and asymmetries should be treated properly.

Take Home Messages

- The facial artery is the main artery that irrigates the lips and the nose. When filling the nose, doctors should be more careful owing to the vascular complexity of this region.
- The angular artery is a terminal branch of the facial artery that irrigates the lateral area of the dorsum of the nose, near the radix. Furthermore, the facial artery provides branches to the lips and to the nasal ala. Due to the characteristics of the facial artery and the extension of tissue that it nourishes, any injury caused by filler injection, such as occlusion, spasm, or compression, may lead to necrosis, ischemia, and subsequent scars over a large facial area.
- The ophthalmic artery is a branch of the internal carotid artery from which originate the anterior and posterior ethmoidal arteries that descend into the nasal cavity through the cribriform plate.
- The worst complication is the arterial embolization, which leads to tissue necrosis and

amaurosis. The radix is the most dangerous area, due to the possibility of injury in the branches of internal and external carotid arteries.

- Some tips for basic precautions during filler procedures are as follows: avoiding large needles or thinner cannulas; using small syringes; injecting slowly and gently, with tiny amounts; avoiding treating patients with previous nasal surgeries; being aware of the regional anatomy; having hyaluronidase in the office; and having the emergency contact number of the vascular surgeon or ophthalmologist.

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Hyaluronic Acid Filler for the Malar Area

Ricardo Limongi Fernandes

Contents

Abstract

Until the 1990s, the concept of rejuvenation was reduced essentially to the absence of lines and folds. During the last decade, there have been significant advances in the technology embedded in hyaluronic acid (HA) products, as well as a refinement of application techniques that, together, also permitted the HA to become a gold standard as a volumizing agent. The main modification in the facial aesthetic treatment has been the exchange of the two-dimensional focus, to the appreciation of the three-dimensional concept, which also recognizes volumetric losses due to bone resorption, gingival retraction, and redistribution of facial fat as signs of aging. The concept is based on balance and facial harmony, respecting patients' gender, ethnicity, and objectives, and allows for more natural results without "frozen" or distorted expressions. The aim of this chapter is to show a practical view of the use of HA for volumizing the malar region (important anatomical concepts, areas of risk, kinds of fillers and rheological concepts, techniques with needle and cannula, adverse events and treatment of complications), with literature-based information and tips from the author. The midfacial area (malar area) is the starting point for the three-dimensional approach in rejuvenation treatment. The use of HA in this area is effective and safe.

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_20

Keywords
Hyaluronic acid · Malar area · Filler · Rejuvenation · Cheek · Injectable · Complication · Zygomatic arch · Fat compartments · Midfacial

Introduction

Until the 1990s, the concept of rejuvenation was reduced essentially to the absence of lines and folds. Patient satisfaction, ease of application, manufacturers support, biocompatibility, non-toxicity, non-oncogenicity, reversibility, duration of effect, and excellent results obtained made hyaluronic acid (HA) the gold standard soft tissue filler. During the last decade, there have been significant advances in the technology embedded in the HA products (Fernandes 2011), as well as a refinement of application techniques that, together, permitted also the HA to become a gold standard as a volumizing agent. Soft-tissue volume loss, particularly in the midfacial area (malar area), is one of the hallmarks of the aging face. Age-related volume loss, increased skin laxity, fat loss/redistribution, and diminished support from underlying muscles and bones result in the observable and sometimes profound changes seen in the aging face (Sherman 2009). The malar area is the starting point of the three-dimensional approach in rejuvenation treatment (Gassia et al. 2013). The aim of this chapter is to show a practical view of the volumizing HA for malar area.

Hyaluronic Acid for Malar Area

Anatomy/Areas of Risk

The most important anatomical concepts about malar volumizing are:

Our treatment area is limited medially by medial portion of the maxilla and laterally by the zygomatic arch, cranially by the ocular orbit. The most important structures of risk emerge from the infraorbital foramen, as follow: (1) Infraorbital nerve: it is a sensitive nerve, branch of the maxillary nerve, and trigeminal branch. (2) Infraorbital artery: it is a branch of the maxillary artery and emits the orbital and alveolar branches. (3) Infraorbital vein: It drains the bottom of the orbit.

Avoiding trauma to these structures is mandatory. We must know their exact location as they are exactly in our path of treatment.

In many patients, infraorbital foramen is palpable. When it is not, we predict it is between the inner corner of the iris and the pupillary line, at the maxilla. The infraorbital nerve can serve as an "alarm," acting as patient's pain response, indicating where not to be injected. For this reason, it is recommendable to avoid nerve block when treating this area. For the same reason, the use of HA with lidocaine is questionable when using needle to inject HA.

We must remember the orientation of infraorbital foramen to avoid injuries. It is not a perpendicular tunnel at the maxilla but has a tangential (craniocaudal) orientation. Even with cannulas (especially if thinner than 25G), it is possible to catheterize the foramen (with nerve/vessels injury risk), so we should not direct our needle/cannula from caudal to cranial way when close to it.

Midfacial soft tissue descent has been observed in response to decreased craniofacial support, which can occur in congenital craniofacial hypoplasia or following trauma. This leads to a hypothesis that the loss of underlying bony support for any reason, including aging, promotes soft tissue descent on the face.

As craniofacial support (the "table") decreases, it leaves less surface area for the outer soft tissue envelope (the "tablecloth") causing it to fold or sag (Vleggaar and Fitzgerald 2008). Young people have the malar region well-projected and well-defined thin mandibular contours. With age, there is a loss of malar fat, bone retraction, and skin flaccidity that leads to a ptosis of the lower third of the face and generating a skeletal appearance of the mid-third of the face. The aim of using the HA in malar area is to restore the volume lost in this area and to reduce proportionally the aspect of jowl, enhancing facial contours.

The subcutaneous (superficial) fat pad of the face is partitioned into multiple, independent compartments, limited by different anatomical units and with a proper vascularization. What has been referred to as malar fat is composed of three anatomical units, including medial (central), middle, and the lateral-temporal cheek fat. Some of the structures referred to as "retaining ligaments" are formed simply by fusion points of abutting septal barriers of these compartments (Rohrich and Pessa 2008).

There are significant differences in the face shape between male and female. A male face is longer, with sharp corners and squarer. The malar area is angular and laterally flat, with almost no forward projection, the mid and lower cheek is flat or concave. Shadows on male face are straight, with sharp and angular edges. These gender differences must be respected to achieve natural results.

Kinds of Fillers

From the beginning of HA era in the 1990s to present, HA fillers have evolved technologically. They have improved durability, versatility (gels with distinct rheological characteristics and tissue expansion capacities), and safety. These changes have allowed the HA to become a good volumizing agent. This has also permitted the use of larger amounts of HA, which is essential when thinking of volumizing.

There are no identical or similar HA fillers among different brands. The rheological characteristics are unique and differ from one to the next, especially depending on whether they are monophasic or biphasic, on the molecular weight of HA, on the technology and degree of crosslinking, and on the concentration of HA.

The main rheological parameters are cohesivity and elasticity. Cohesivity is a measure of resistance to deformation. The more cohesive, the higher tissue projection and the lower propensity to spread itself inside the tissue (generating better-defined contours).

Elasticity is a measure of a structure's ability to resume its original position when stretched, defining its elastic recoil capacity and lifting effect. High cohesive volumizers are more adequate for sharp shapes goals. On the other hand, less cohesive volumizers tend to be the best choice to achieve round shapes with natural results. Sometimes more, sometimes less, volumizer HAs are always high cohesive gels. Low cohesive gels, despite the perfect tissue integration we notice in dermis, are usually not indicated for deep injections due to their lower capacity of tissue projection. Non-crosslinked HAs have no tissue expansion capacity and are definitely not indicated for this purpose. Generally, the very high cohesive gels are used in the deep facial fat, objectivating fixed projection of tissue. The high cohesive (but not very high) and high elastic are the best for the superficial fat, as part of a dynamic structure.

Techniques

The main techniques used for volumizing malar area are *bolus* and retro-injection. Both can be performed either with needles or cannulas. For convenience and safety, respectively, *bolus* technique is preferably performed with needles and retro-injections with cannulas.

The application plain should always be the deepest possible. Supra-periosteal is desirable. This ensures that the volumizer is always covered by fat, muscles, and skin; providing more natural results while avoiding palpable nodules. We should never forget that the periosteum is sensitive; therefore, we must touch it gently (when necessary) with our needles or cannulas.

We should take advantage of the natural projections of the bones and inject the volumizer just above them. This ensures greater capacity of tissue projection. If applied on the valleys of the bones, the projection will be low. Volumizing areas with no bone base of support should be discouraged. With the absence of this "table," the HA injection results on expansion for all directions (360°), and the result on the skin surface (main goal) will be poor.

Deep injections tend to be less painful when compared to intradermic injections. Therefore,

topical anesthesia or anesthetic buttons at the entrance of the cannulas are usually enough to make it comfortable. As mentioned before, for safety reasons, infraorbital nerve block should be discouraged. Additionally, the anesthetics used for the block create an extra temporary volume, which makes difficult the prediction of HA volume to inject in that area. Although being a less painful area (if compared to intradermal injections or lips), we must remember that, as a rule, the volume injected is substantial, so we should inject gently and slowly to avoid quick painful tissue expansion.

When volumizing the malar area, we seek to maintain flat and sharp shapes in men and convex and round in women. To achieve these goals, in men, treatment with needles (in serial bolus or linear retro-injections) should be encouraged; on the other hand, the use of cannulas appear to be more adequate for female malar volumizing. Although not a formal rule, it seems easier to obtain sharp shapes with *bolus* technique and round shapes with the aid of cannulas.

In general, female pattern of filling includes anterior projection, with substantial volume in the medial cheek fat compartment, gently decreasing volume laterally to create smooth and round shape. Higher volumes are sometimes acceptable. The use of cannulas is highly recommendable to this objective. Besides being safe and less painful, it naturally helps to achieve this pattern. On the other hand, in men, anterior projection should be discouraged. The volume injected in each of the three fat compartments of the cheek tends to be similar in men. Treatment with needles with multiple points of application in *bolus* technique at the zygomatic arch may help to create a sharp edge. Sometimes a linear retro-injection like a frame at the base of the zygomatic arch can contribute to the design of the male pattern, by accentuating the malar projection that, associated with a mandibular projection (natural or through application of HA in that area), maintains the concavity of the lower part of the middle third of the face. The use of large amounts of volumizer in men should be strongly contraindicated. HIV-associated facial lipoatrophy is the main exception for this rule (Derek and Jared 2016). The goals in men are traditionally much more definition than volume. Volume and projection are sometimes welcome for women.

The amount of HA injected per patient is variable. On average, amounts between 2 and 3 ml (for both sides) are good cost/performance volumes. Depending on individual factors, higher volumes can be considered.

My Experience

In my experience, the malar area is the first step in restoring facial volume. Defects on lower lids, nasolabial folds, and jowls are attenuated after treating this area.

A good way to identify the candidates for malar volumizing is through observation of lights and shadows. Penumbra areas are the targets of our treatment.

There is no need to massage treated areas when immediate results seem good. The skin will be more projected the less flattened the HA is.

Some argue aspiration reduces the risk of intravascular injection. In my experience, it is not such safe procedure, as aspiration can provide a false sensation of safety. Depending on the viscoelasticity of the gel, on the negative pressure, on the size of the needle, and on the gap time of observation, it may be impossible to notice the retrograde flow of blood into the syringe, even with the needle inside the vessel.

Duration of effects is multifactorial and very difficult to predict. It depends on individual characteristics, quality of skin, kind of filler, amount of filler used, and technique. Effects may vary from a few months to more than 4 years. A good dialogue with the patient is mandatory.

We usually deal with great amounts of HA in the malar area. It behaves, then, like any other implant in contamination risk. An extra care on antisepsis is mandatory to the safety of this procedure.

There is no strong evidence to contraindicate fillers in patients with controlled autoimmune or collagen diseases. In response to alerts that began in the early 1990s, when some physicians and lawyers claimed a correlation between collagen injections and subsequent polymyositis and

dermatomyositis (PM/DM), the US Food and Drug Administration took this possibility very seriously, but after review decided in 1995 that "a causal relationship" between collagen injections and PM/DM or other connective tissue diseases listed has not been established. Furthermore, as wound healing is normal in scleroderma patients, dermal fillers are not a formal contraindication, according to Lemperle et al. (2014).

Results Pre-post

See Figs. 1, 2, 3, and 4.

Adverse Events (EAs)

The malar area is a quite safe area for volumizing. Incidence of severe adverse events in this area is low. However, there is much more information (Andre 2004; Cohen et al. 2013) about EAs when HA is used intradermally, (Duranti et al. 1998; Lupton and Alster 2000; Raulin et al. 2000; Shafir et al. 2000; Micheels 2001; Lowe et al. 2001, 2005; Honig et al. 2003; Fernandez-Acenero et al. 2003; Narins et al. 2003; Bergeret-Galley 2004) comparing to volumizers. As we know, EAs are related to the quality of the material, investigator experience, speed of injection, injection technique, and injection volume. Injection technique and injection volume in volumizing indications are different from intradermal applications. These particularities of volumizers can be related to a different pattern of EAs. In my point of view, we can perhaps face to a higher risk of bacterial infection and hypersensitivity reactions comparing to intradermal HA filling. Mobility of the implant is an adverse event usually related to larger injection volumes (Delorenzi et al. 2006), however, rarely found in intradermal filling. On the other hand, some adverse events regularly seen in superficial injections like bluish to gray discoloration, acneiform eruption, visible papules, bleaching, and traces of needles are not found when volumizing the malar area (Pons-Guirard 2003; Olenius 1998).

Some early EAs are expected in any volumizing. They can be caused either by the injection itself or by the implanted HA. Palpable material, slight asymmetry, slight hyper- or under-correction, swelling, pain, tenderness, erythema, bruising, induration, and itching are the most common related EAs.

Late adverse events may include hypertrophic scars formation and immunologic phenomena such as late-onset hypersensitivity and foreign body granuloma. Hypersensitivity to nonanimal hyaluronic acid gel is most likely secondary to impurities of bacterial fermentation (Friedman et al. 2002). Intermittent swelling followed by the development of palpable and/or painful erythematous nodular papulo-cystic lesions from weeks to months after the injection, may evolve into aseptic abscesses, that sometimes drain through a fistula is the most common evolution (Fig. 5). Other characteristic is recurrence. These reactions often occur after patients have had their second or third injection (US- FDA 2008). Histopathological analysis may show non-granulomatous (chronic suppurative inflammatory process with eosinophilia) or granulomatous reactions.

The mechanisms underlying the activation of the immune system and leading to chronic granuloma formation are not yet clear. Granulomatous reactions may be triggered by various factors, notably biomaterials. These late reactions related to HA fillers are immunogenic in nature, but an infectious origin cannot be discarded. It is important to differentiate two possible sources of bacterial presence: (1) bacteria are directly inoculated into the filler or reach the filler from distant sites, and (2) distant or systemic infection may provoke inflammatory harmful immune-mediated reactions to the fillers in the absence of bacterial colonization of the implant filler (Alijotas-Reig et al. 2010). Clinically, stone consistency nodule and delayed onset may suggest granulomatous reaction. Nevertheless, granuloma is an anatomopathological diagnosis. True granuloma appears late (mostly after 6–24 months) at all injected sites approximately at the same time; they grow rather fast.

Patients should be informed of the possibility of major complications like vascular trauma,

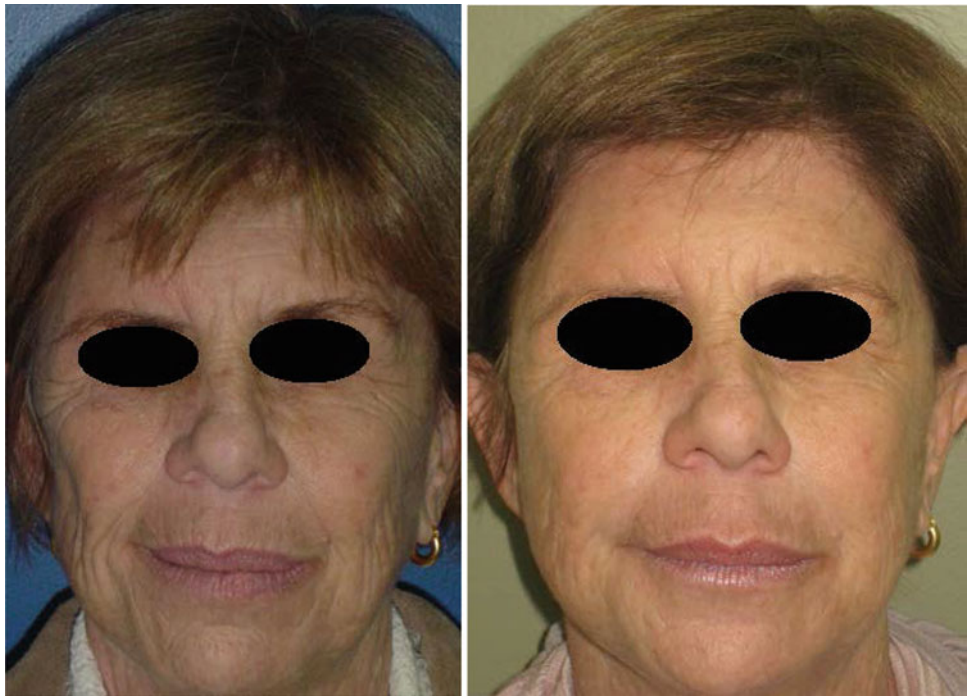

Fig. 1 A 64-year-old female patient before and 4 years after three sessions of HA filler in the malar area (total 6 ml on the *right* and 3 ml on the *left side*). Initial asymmetry was due to oncological brain surgery with metallic bone prosthesis

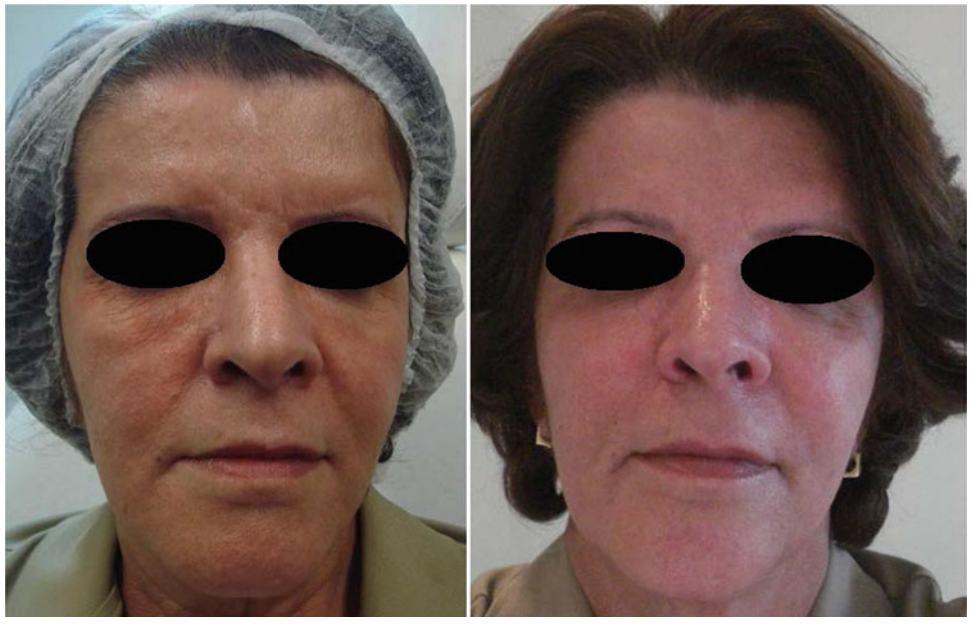

Fig. 2 Female patient with constitutional asymmetry before and immediately after injection of HA in the malar area (2 ml on the *right* and 1 ml on the *left*)

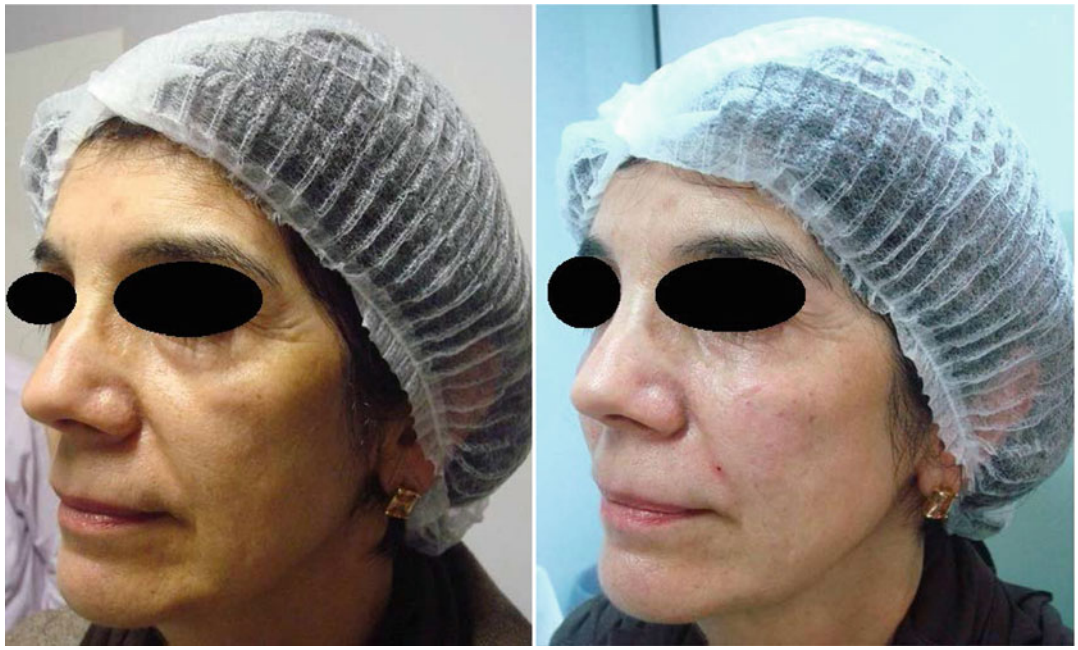

Fig. 3 Before and immediately after volumizing the malar area with HA (1.5 ml each side). Notice the areas of light and shadow on the malar region before treatment and the cannula entrance hole on the *left* nasolabial fold after treatment

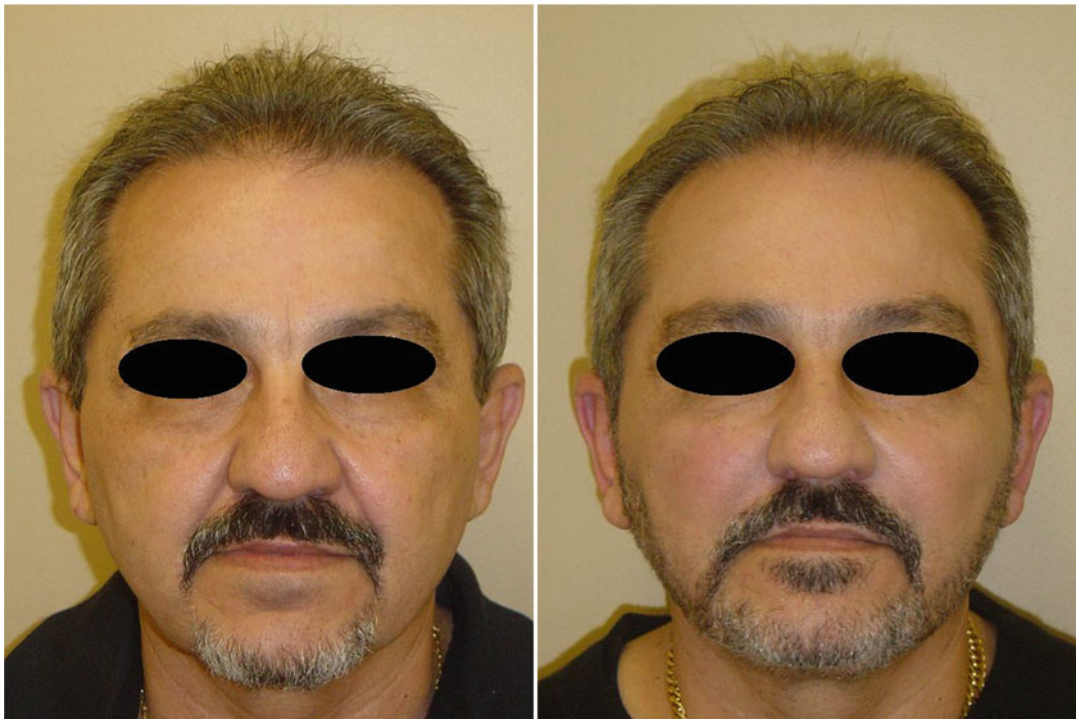

Fig. 4 A 59-year-old male patient before and after volumizing the malar area with 1.5 ml on each side. The nasolabial folds were filled intradermally with a less cohesive HA (1 ml each side)

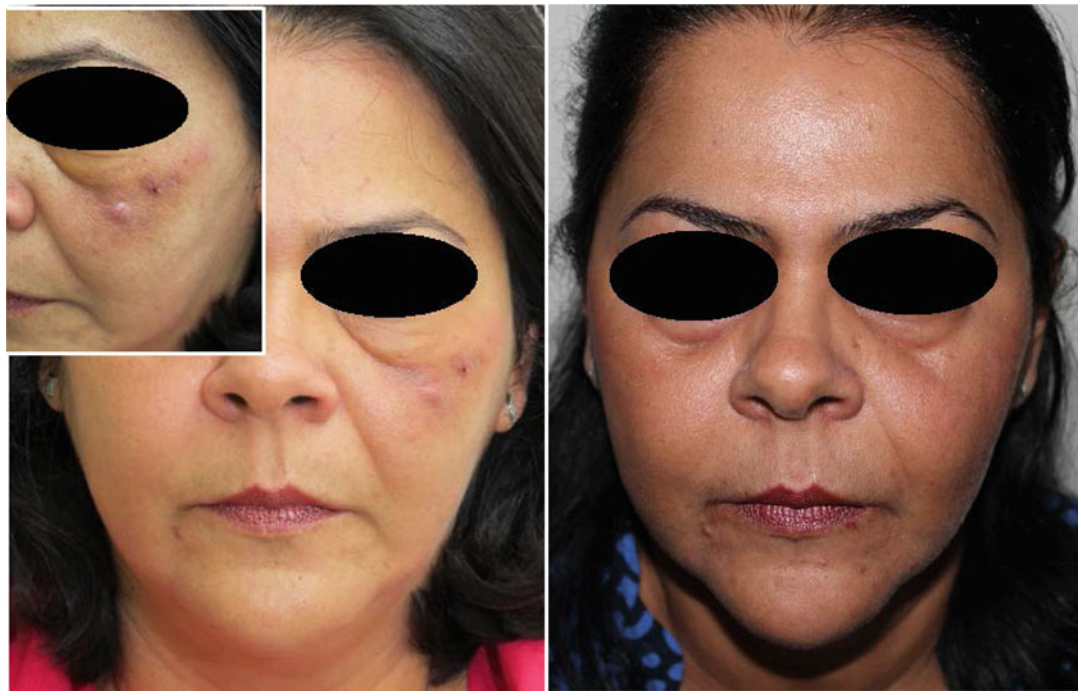

Fig. 5 A 49-year-old female patient with hypersensitivity reaction to HA in malar area. Before and 6 months after treatment. The pretreatment figure shows, in detail, the fistula of aseptic abscess, which was completely solved

compression, and arterial embolization (Schanz et al. 2002). Injection necrosis is a rare but important complication associated with dermal fillers. Necrosis can be attributed to one of two factors: an interruption of vascular supply due to compression or actual obstruction of vessels by direct injection of the material into a vessel itself (Cohen 2008).

Complications and How to Deal with Them

The expected early EAs above described tend to disappear within 1 or 2 weeks spontaneously with symptomatic treatment.

In cases of intense or persistent swelling, corticosteroids is indicated. It is preferable to use betamethasone (0.05 mg per kg per day) due to its great anti-edema property.

Persistent hypercorrection can be precociously treated by incision and drainage. A blade is inserted directed toward the nodule and expressed (Matarasso et al. 2006).

Hypersensitivity reactions usually regress with no sequelae with the triple therapeutic scheme: Hyaluronidase injection (once a week while reaction persists) + antibiotics (macrolides – clarithromycin or lincosamides – Clindamycin) for 14–21 days + oral prednisolone (0.5 mg/kg/day while reaction persists).

Because of the often recurrence, treatment with corticosteroids may last long. All precautions related to corticosteroids side effects must be taken: chest X-ray, bone densitometry, lipid, hypertension, and hyperglycemia monitoring should be considered. For treatment longer than 3 months, ophthalmologic evaluation and supplementation of calcium carbonate (1.5 g per day) and sodium alendronate (70 mg per week) is recommendable.

In my experience, I use the following rules to reduce prednisolone:

- Less than 2 weeks with dose higher than 40 mg per day: decrease one third of the dose each 3 days

- Less than 2 weeks treatments with dose inferior than 40 mg per day: suspend
- Treatments between 2 weeks and 2 months with dose higher than 40 mg per day: decrease one fourth of the dose each week
- Treatments between 2 weeks and 2 months with dose higher than 15 mg but lower than 40 mg per day: decrease one third of the dose each week
- Treatments between 2 weeks and 2 months with dose lower than 15 mg per day: decrease one third of the dose each 3 days
- Treatments longer than 2 months with dose higher than 40 mg per day: decrease one fifth of the dose each 2 weeks
- Treatments longer than 2 months with dose higher than 15 mg but lower than 40 mg per day: decrease one fourth of the dose each 2 weeks
- Treatments longer than 2 months with dose lower than 15 mg per day: decrease one fourth of the dose each week

True granuloma usually regresses after intralesional steroid injections (triamcinolone acetonide). Oral corticosteroids can be associated.

Concomitance of HA reactions and other infectious conditions nearby is quite common. Investigation of periodontal disease and chronic sinusitis should be encouraged, especially when there are suggestive signs and symptoms.

In cases of arterial occlusion and embolization, immediate application of hyaluronidase in the whole treated area (400–1500 U) is necessary. Emergency approach by an angiologist or vascular surgeon and, eventually, by an ophthalmologist is indicated to minimize sequelae. Blanching, sudden orbital pain, visual changes, nausea, vomiting, or sudden headache are the most important signs and symptoms of severe adverse events.

Take Home Messages

- The main modification in the facial aesthetic treatment has been the exchange of the two-dimensional focus, based on the treatment of lines and folds, for the appreciation of the three-dimensional concept, which also recognizes volumetric losses due to bone resorption, gingival retraction, and redistribution of facial fat as signs of aging. The concept is based on balance and facial harmony, respecting patients' gender, ethnicity, and objectives, and allows for more natural results without "frozen" or distorted expressions.
- The midfacial area (malar area) is the starting point for the three-dimensional approach in rejuvenation treatment. The use of HA in this area is effective and safe.
- The perfect diagnose is always mandatory. From the beginning (recognizing aging process and programming the best way to intervene) to the possible late complications, understanding the etiologies of them (and choosing the right way to treat them) is imperative for all physicians dealing with malar area volumizing (Cassuto 2010).
- The treatment of complications should be aggressive and initiated as soon as possible after occurrence (Lemperle et al. 2014).
- If you are not 100% convinced that a serious adverse event has not occurred, keep the patient in observation for at least 30–40 min. In this case, you have time to clarify the diagnosis and take action.
- In case of a severe adverse event, do not panic. Be prepared. A bottle of hyaluronidase is a "safety equipment" and should be available in all offices of physicians who work with HA fillers.

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Hyaluronic Acid Filler for the Lips and Perioral Area

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Abstract

Beautiful lips have always been desired for the harmonization of the features. They represent sensuality, happiness, sadness, competence to retain food, verbal communication, and youth, as they are affected by aging process. Lips are hold as a key aesthetic feature, and therefore considered as an issue of great importance in cosmetic dermatology. As long as people get older, the lips lose their fullness, their proportions and become wilted, pale, and thin. One of the most useful ways to improve their characteristics and to mold them is the augmentation and correction through the right use of the available soft tissue fillers. Since this field grows fast and new techniques are constantly developed, the aim of this chapter is to hold forth about how the specialist can get the best results. The hyaluronic acid (HA) fillers have been proved to be a good choice, since there are no rejection reactions, they are easily obtained, and their effects, as well as their complications, can be minimized with the hyaluronidase injection, making them a safe product even for beginners. More viscous HA aim to increase the volume of the lip, whereas the softer HA is injected through serial puncture technique to redefine the vermillion of the lip. The most common adverse effects are temporary bruising, itching, edema, erythema, induration, tenderness and pain at the injection site. The most serious adverse events are vascular occlusion with necrosis and embolization, mostly avoided by pulling back the plunger syringe before injection looking forward any blood reflux. Equally important to know how to deal with the fillers is to be well and readily prepared to treat their early and late complications.

Keywords

Lip augmentation · Hyaluronic acid · Fillers · Lips

Introduction

Ever since globalization spread beauty concepts universally, the perfect lips are great subject of desire between human, especially for women. The lips have always been seeing as a symbol of sensuality, health, and youth besides other important functions as food intake, articulation, facial expression, and a tactile organ with erogenous function. Seen by men and women as a sexual attractive, the search for impressive and well-shaped lips is rising in dermatologist appointments. The importance of the lips can be illustrated by an analysis of the United States market research in 2001, which showed an appreciable increase of sales of lip sticks despite the economic crisis reflected in the other sales sectors in the same period, fact called the "Lipstick Index" by Leonard Lauder. Beautiful lips were considered a way to keep up with beauty and fashion without spending much on other luxury items (Sarnoff and Gotkin 2012).

The aging process progressively affects the lips and the perioral area. The upper lip vermillion gets thinner and lose volume, while the skin over it gets wider and wrinkled, with a substantial loss of support and degeneration of collagen and elastic fibers (Brandt and Cazzaniga 2008).

The philtrum is also affected by aging, as it becomes progressively flatten and looses its shape. Pillars for the upper lip, the philtrum columns are essential for the aesthetics of the lips,

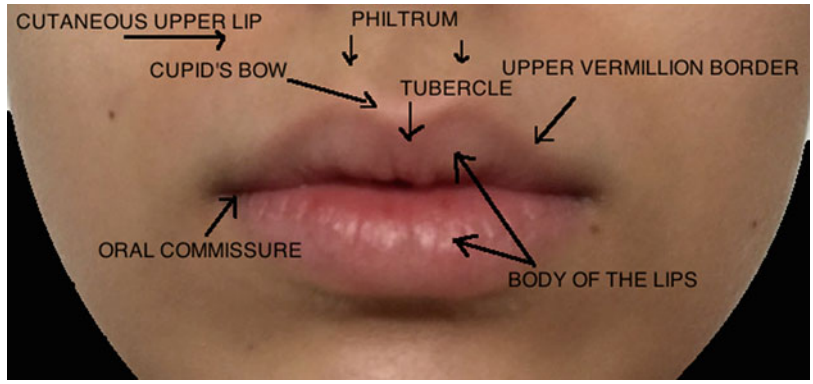


Fig. 1 Lips structures

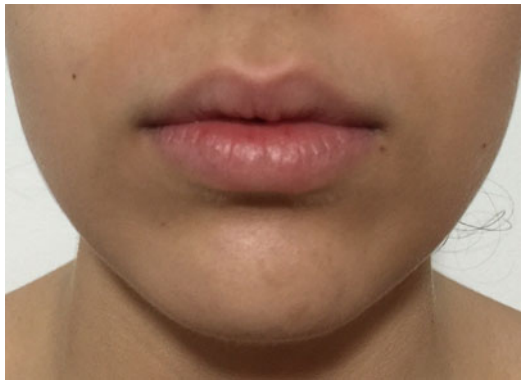


Fig. 2 Youth lips: the 17yo daughter – front view

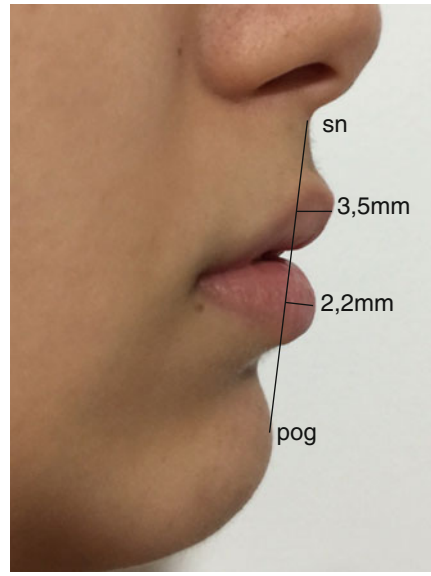


Fig. 3 Youth lips: the 17yo daughter – side view. Drawing a line from the sub-nasion (*sn*) to the pogonion (*pog*), the upper lip projects 3.5 mm anterior to the line, and the lower lip projects 2.2 mm anterior to this line, reinforcing the 1.6:1.0 proportion

and their reconstruction needs very often to be done together with the lip correction itself (Perkins and Sandel 2007; Wollina 2013; Vent et al. 2014) (Figs. 1, 2 and 3).

In addition to the evident genetic influence in skin and lips aging, lifestyle also interferes directly in this process, and practices like smoking and sun exposure are good examples of accelerators. External factors such as gravity and extreme weather conditions also play a role. Furthermore, bone resorption of maxilla and mandible, dental changes, loosening of ligaments and muscle weakness are intrinsic events that pave the way to lip disfigurement. Lastly, ethnicity and gender determines different anatomical patterns and, consequently, characteristic alterations throughout the years (Perkins and Sandel 2007) (Figs. 4 and 5).

Men have a thicker skin and more subcutaneous fat surrounding hair follicles in the upper lip area, making them less susceptible than women to rhytides formation in this area. Afro descendants have more melanin and, therefore, are protected against sunburn and elastosis, making perioral rhytides a rare finding in this group. They also have naturally more bulky lips, so their thickening throughout the years is discreet. (Sarnoff and Gotkin 2012)

Back in the early sixteenth century, Leonardo DaVinci models of the human body reinforced the proportion proposed by the ancient Greek, where the Fibonacci numbers leaded to a Golden Ratio called Phi ($\Phi = 1.618\ 033\ \ldots$). This proportion

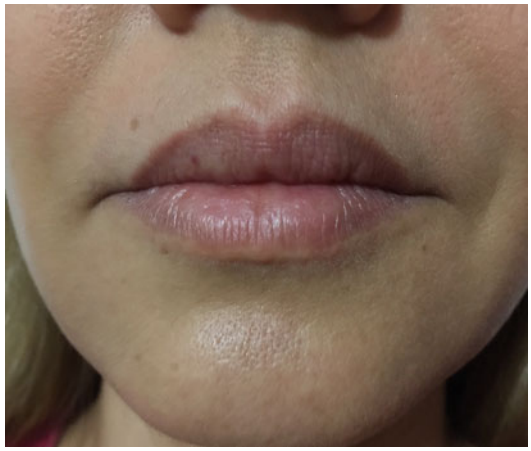


Fig. 4 Mature lips the 48yo mother – *front view*

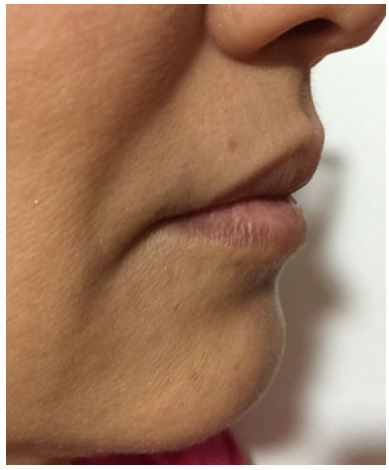


Fig. 5 Mature lips the 48yo mother – *side view*

has been, for a long time, used to produce objects of great beauty, like the Greek temples and some Michelangelo's work of art. In Caucasians, the ideal vertical height ratio of the upper lip to the lower is, indeed, 1:1.6 (Figs. 3, 6 and 7). Women can frequently ask their dermatologist to increase their upper lip, but proportions are to be maintained, and the physician needs to firmly reinforce this balance in order to avoid an overcorrection, resulting in the anterior projection of the upper lip, called "duck-like appearance," or the "sausage" lip.

The aim of treating the upper lip is to harmonize it with the patient's age and ethnicity; considering one's facial proportions and features. The goal for the lower lip is to improve the vermilion projection, making it naturally prominent and lush. As already mentioned, sometimes the professional analysis of the patient's needs does not represent his real expectations, but the physician must regard his experience and anatomy notions to produce harmonious results.

Even temporary fillers, like the HA, can cause persistent alterations on tissues, and therefore there is no predetermined time to new injections. Sometimes the patients return to the office just because it has been a long time since they had their procedures done, but the result of the correction is still kept. This is where the photographic documentation proves its importance, so you can show the before and after pictures and discuss with the patient that no more filler is needed by that time. It is also very important to show the lateral aspect of the mouth and its projection, explaining why the procedure must be done so carefully. (Sarnoff and Gotkin 2012)

Anatomy of the Lips and the Perioral Area

It is essential for the physician who intends to work with lip correction to know the anatomy of the lips, the origin of its shape and curves, as well as its innervation and nutrition.

The beginning of the upper lip formation starts around the fourth embryonic week, with a pair of structures derived from the neural crest, called pharyngeal arches, responsible for the facial prominences. Within weeks, the maxillary prominences migrate medially towards the nasal prominences, funding to form the upper lip. The philtrum and the medial part of the upper lip are formed by the fused medial nasal prominences, while the lateral parts are a result from the fused maxillary prominences. The philtrum columns are not parallel to each other but form an inverted V shape, closer to each other near the nose and getting further away towards the vermilion border. The lower lip, on the other hand, is formed by a simple fusion of the mandibular prominences, explaining its homogenous shape.

The vermillion of the lip is demarcated by the white roll of the vermilion border, clearly separating labial mucosa and perioral skin. This border is

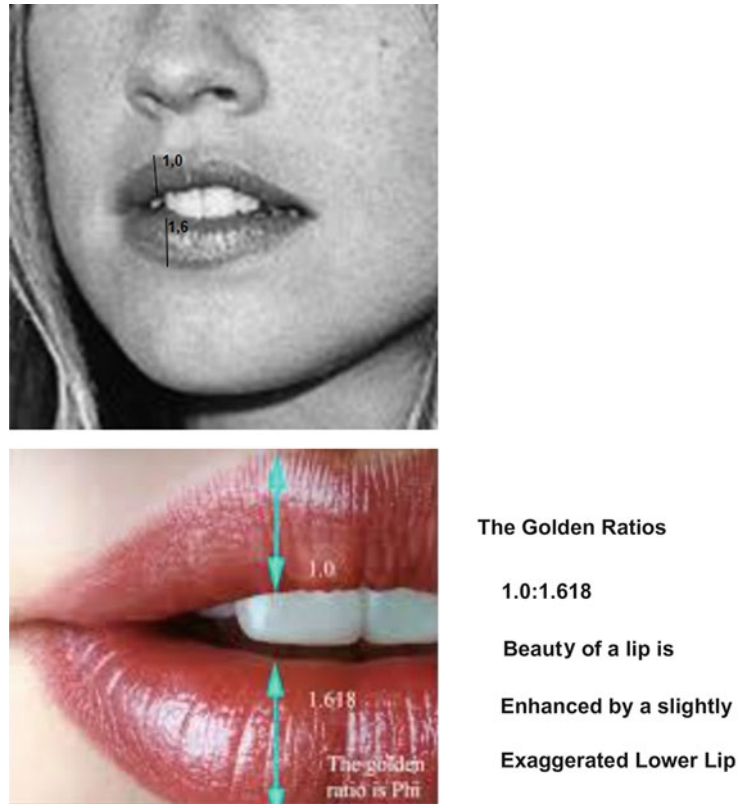


Fig. 6 The gold number and the proportions of beauty for the lips – static lips

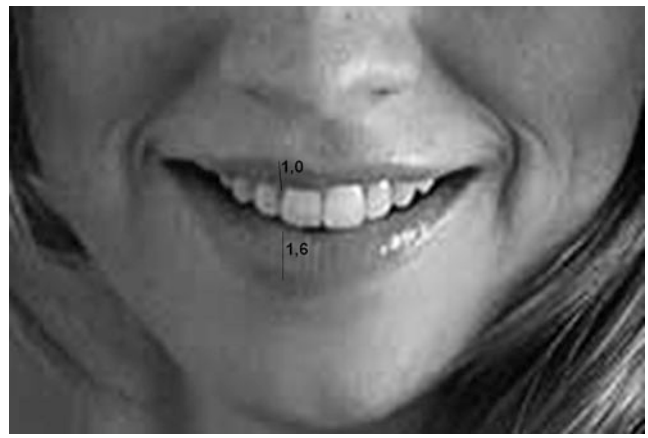


Fig. 7 The gold number and the proportions of beauty for the lips – smiling lips

very important aesthetically, and even an inconspicuous misalignment caused by scars or medical procedures is noticeable. On the upper lip, it draws a curly line like a "M", called the Cupid's bow, where the maxillary and nasal prominences funded. It is known buy the artists as the "the finger print of a face", making every smile unique. The tubercle is the fleshy protuberance located in the center of the upper lip (prochilo, "tuberculum labii superioris," "labial tubercle").

When the lips are closed, it is possible to define the end of the inner projection of the lip, called the red line, which separates the buccal mucosa and the lip vermilion. In contrast to the buccal mucosa, the lip vermilion has no minor salivary glands, giving its drier aspect. (Perkins and Sandel 2007)

The mandible, maxillary bone, and teeth are the hard tissue pillars for the shape of the mouth and perioral area. The perioral muscles are disposed in layers, the superficial and the deep part, the last consists of *pars peripheralis* and *marginalis*. The intimate connection between the *orbicularis oris*, the perioral muscles, and the submuscular aponeurotic system where the perioral muscles anchor is responsible for vital actions like smiling, speaking, and whistling. Coming from the top, the *levator labii superioris* insert into the upper lip and the oral sphincter. Laterally it is inserted to the *levator anguli oris* and both *zygomaticus* muscles. The *risorius* and the depressor *anguli oris* muscles insert at the lateral corners of the lips. The latter is the most superficial mimetic muscle. The lower lip is inserted by the *depressor labii inferioris* and *mentalis* (which also insert into chin dermis), and both interlace with platysma fibers. (Penna et al. 2015)

Facial fat is divided into deep and superficial layers. The deep perioral fat is located beneath *mentalis* and *orbicularis oris* muscles. The small lobuled superficial fat of the lips is superficial. The lipodystrophy of the aging process affects this fat tissue distribution. The philtrum is a fat cleavage surrounded by membranes related to its particular vascular anatomy.

Since the injection of soft tissue fillers may be painful, a short description of the innervation and anesthesia of the lips is to be made.

Innervation and Anesthesia

The trigeminal nerve is the great responsible for the sensory innervation of both lips through different subdivisions, the second (V2) and third (V3).

The second division (V2) is in charge of the upper lip. It emerges from the inferior orbital foramen, bilaterally. To reach it and produce anesthesia of this area, it is needed to place a needle under the lip, in the alveolar prominence of the first maxillary premolar, pointing directly to the pupil, and insert the anesthetic fluid (lidocaine without epinephrine, mainly) 4–5 cm in depth onto bone (Fig. 8).

The third division (V3) innerves the lower lip. It exits the parasymphysis at the mental foramen. It is reachable beneath the second mandibular premolar, between the lower border of the buccal mucosa and the alveolar prominence. It is required to block the mental foramen nerve bilaterally to a good anesthesia of the entire lower lip (Fig. 9).

Another possible and shorter-lasting way to obtain lip anesthesia is to inject into the labiogingival fold.

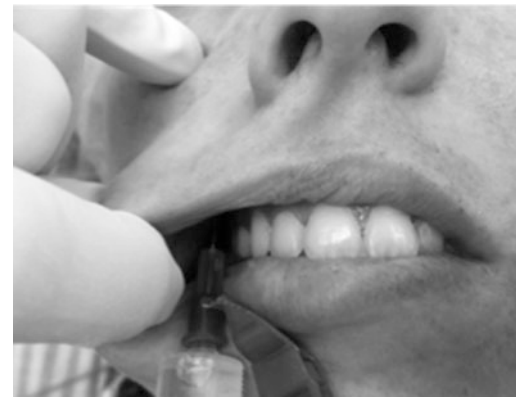


Fig. 8 Infraorbicular intraoral anesthesia of the upper lip

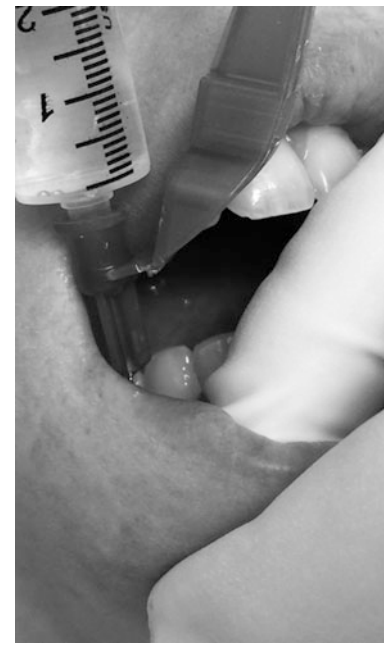


Fig. 9 Mentual intraoral anesthesia of the lower lip

The fillers that contain lidocaine in their formula might need only topical anesthetics or local anesthesia on the entrance spot of the cannula when it is the choice of the doctor.

Vascularization

The facial artery is the most important nourisher of the lips and perioral area. It is a branch of the external carotid artery and emerges from the anteroinferior portion of the masseter muscle to the superficial layers. A branch of the inferior alveolar artery and the submental artery also supplies the lower lip.

Histology

The lips are highly sensitive as the sensory cortex innervates the mucous membrane. The skin is a stratified squamous epithelium, the layers of the upper and inferior lips includes the structures of the normal skin but without the *extratum corneum*, and this is why it does have a red characteristic color, the color of the numerous capillaries. There are also minor salivary glands. Under the skin, in layers, from superficial to deep, come: the subcutaneous tissue, the orbicularis oris muscle and the mucosa. The arteries are observed between the orbicularis oris fibers and the mucosa (Bailey 1998).

Aging Process

It is crucial to understand what happens to the lips during the aging process to plan fillers injection at this region. Increasing the volume, reducing fine lines, restoring a symmetric ratio of all four lip quadrants, improving the dryness are issues that challenge the physician when we do perform the aesthetic cheiloplasty (Fagien et al. 2013).

Upper Lip

Up to the age of 45 years-old, the lips lose the tonus and the volume, and the vermillion undergoes the aging process elongating the length and widening the height of the lip, leading to the thinning of the exposed vermillion, the lateral corners of the lips move downward (Fig. 10A line) as well as the superior lip's lateral portion (Fig. 10B line).

Vertical wrinkles around the mouth occur as a result of the *orbicularis oris* contraction along the years, leading to a thinly folded skin, and these wrinkles appear around the lips in the beginning and can extend until the nose and inferiorly to the nasomental fold (Fig. 10C line).

A folded and downward commissure (down turning mouth corner or frown mouth) is a typical picture of a patient with a weakening dental support to the buccinator muscle and indicates the loss of facial height (vertical dimension and occlusion) with an anteriorization of the jaw. The distance between the columella of the nose and the upper lip grows 1 mm every 10 years. It does let us feel like the patient is bitter, sour, or disappointed (Carruthers et al. 2005). A thin and inward upper lip, a bulging, and downward nose can be a result of mimics muscles support, specially the *orbicularis oris*, worsened by an intense superior vestibular border alveolar resorption without protein replacement (Fig. 11).

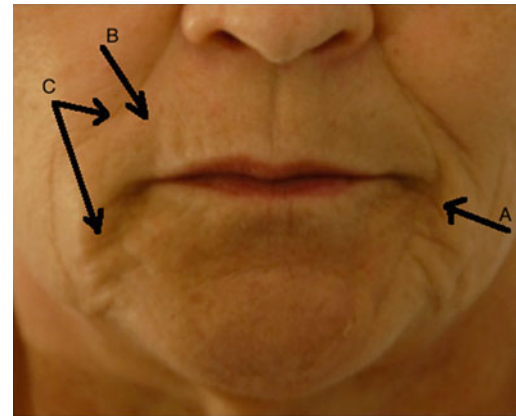


Fig. 10 Severe aging of the lips and the surrounding area. The lateral corners of the lips moves downward (*A line*) as well as the superior lip's lateral portion (*B line*). A thiny folded skin and these wrinkles appear around the lips in the beginning and can extend until the nose, inferiorly to the nasomental fold (*C line*)

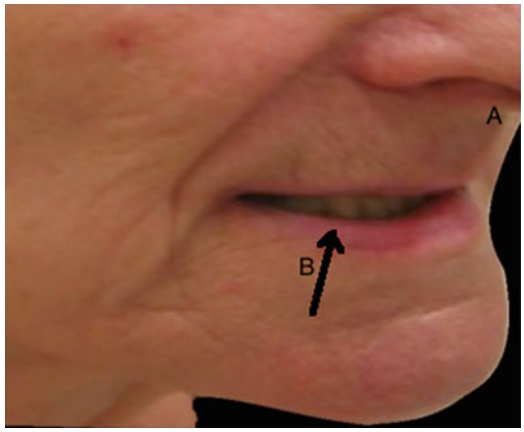


Fig. 11 Lateral "punchinello-like" profile. A thin and an inward upper lip, a bulging and downward nose can be a result of mimics muscles support specially the orbicularis oris worsened by a intense superior vestibular border alveolar reabsorption without protein replacement (*A*). The lower lip muscle tonus also become thin and moves inward as the lower dental support diminishes during the years and the severity leads to a dental exposition (*B*)

Lower Lip

The lower lip muscle layer also becames thin and moves inward as the lower dental support diminishes during the years and the severity leads to a dental exposition (Fig. 11).

Lateral "Punchinello-Like" Profile

The so-called punchinello-like profile occurs with a bulging nose, an inward mouth with the lips backward, a pronounced and upward chin due to the bone, and muscular natural aging process (Fig. 11).

Approaching the Patient

Analyze each patient very carefully understanding his desires and our professional experience and skills. One of the most-used description for lips aging is based on clinical features as follows: young patients with all structures preserved and a very thin lips (type I); aging of the lips with only few radial wrinkles (type II); aging lips with radial wrinkles and loss of volume (type III); aging lips with radial wrinkles, loss of volume through bone absorption, muscle and fat changes (type IV), or even if the patient does have a gummy smile (type V).

Kane et al. (2012) have also described different patterns of lips; their scale would define different thickness of the lips as follows: very thin upper lip, thin upper lip, medium upper lip, very thin lower lip, thin lower lip, medium lower lip, full upper lip, very full upper lip, full lower lip, and very full lower lip. This assessment (Medicis Lip Fullness Scale) should help to describe the clinical initial view and further comparison, especially when patients forget about how their lips looked before the treatment.

Rossi et al. (2010, 2011) has also suggested a validation of a photonumeric grading scale for assessing lip volume and thickness. The grade should vary from 1 (very thin), from every 0.5 to finally grade 5 (very full), to the superior lip and the inferior lips divided in 9 photo grades but this measurement is only applied to Caucasians patients. Carruthers (Carruthers et al. 2008) validated a scale between 0 and 4, 0 for very thin lips, 1 for thin lips, 2 moderately thick, 3 thick, and 4 full. Type I patients might need fillers at the nasolabial fold if there is not yet the need to repositioning the malar fat pad. On the other hand, a type IV might need plastic surgery.

Proportions are meant to be respected although beautiful lips might be not exactly those that fit the most famous proportion ratio (the Fibonacci's ratio were the upper lip would measure 1 in proportion to 1.6 to the lower lip), but this rule can help us many times when analyzing means to rejuvenate an aging lip. The vertical lines also help considering that normally the corners of the lips coincide with the line of the inner corner of the eyes.

Lips can be beautified enhancing its contour, filling them up discretely and even remodeling the philtrum. Fine lines can be corrected injecting the filler very superficially. Depending on the type of the filler, there are different techniques nowadays. Botulinum toxin can always be an interesting pre filler treatment, and the aim is to relax the *orbicularis oris* to obtain a better result.

Few years ago filling the lips would sometimes require anesthetic blockage as patient referred the procedure to be very painful. If still needed, the infraorbital and the mental nerve must be anesthetized, the first when treating the upper lips and the second the lower lips. Nowadays almost all good fillers do have lidocaine added to the formula giving a great relief leading to an almost painless procedure. If the patient does have any history of herpes simplex infection, it should be prevented with antivirus prophylaxis beginning just before the procedure.

Another important issue is the antisepsis. It must be rigorous, taken seriously and never forgotten. There are new fillers and also long-lasting products that might at some point complicate with a granulomatous reaction, infection, and/or the so feared biofilm.

There are innumerous techniques, concerning where to begin the remodeling, the direction and the depth of the injection, different needle sizes or various sizes of cannulas. The site of the punctures, the amount injected and the perioral reconstruction are also planned to optimize the lower face rejuvenation.

Fillers for Lips

The Hyaluronic Acid fillers can be either "biphasic" (particulate) or "monophasic" (gel). Both of them can be used to enhance lips volume and to correct the aging damages, showing very good results and satisfaction index of up to 90% in the first month post procedure and up to 50–70% after 6 months (Glogau et al. 2012). The FDA (US Food and Drug Administration) hyaluronic acid fillers approved for lips augmentation and correction are numerous and everyday new brands are being launched. Collagen might also be used for lips augmentation but by far HA is yet the best choice.

Injection Technique

Lips are not easy to treat and bad outcomes are not rare. The excessive lips augmentation leads to a bad marketing and patients do question if the results will really look natural. Although few authors contraindicate intramuscular injections, we agree with a lot of others that it is not contraindicated and sometimes filling it to give an effective natural looking lip augmentation is inevitable, not to mention the challenge to determine whether the filler is, for sure, restricted to the submucosa. We understand that it is not about treating only the lips themselves, but all the structures around the mouth need to be reconstructed to achieve a good global peribuccal result.

Outlining the contour of the lips might need patience and training. Most of all the times a retrograde fine line of filler is injected all along the margin of the vermillion with a linear, horizontal underlay technique (Fig. 12). Other fillers allow a very different technique: insert the needle under the skin and over the muscle and just inject the filler slowly. The filler slides along the vermillion border smoothly, from one oral commissure to the other and it is visible to bare eyes (Fig. 13).

The philtrum might be delineated carefully, but if the aging process already led to an elongation of the upper lip (distance from the columella to the margin of the upper lip), we do avoid filling it up as

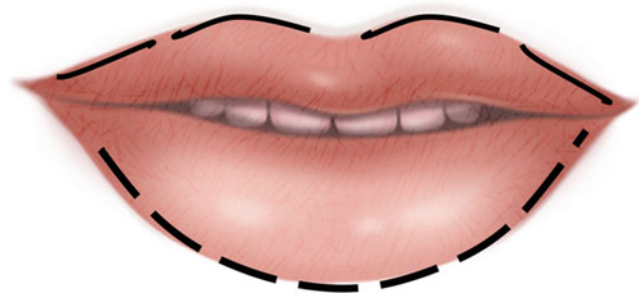


Fig. 12 Most of all the times a retrograde fine line of filler is injected all along the margin of the vermillion with a linear, horizontal underlay technique

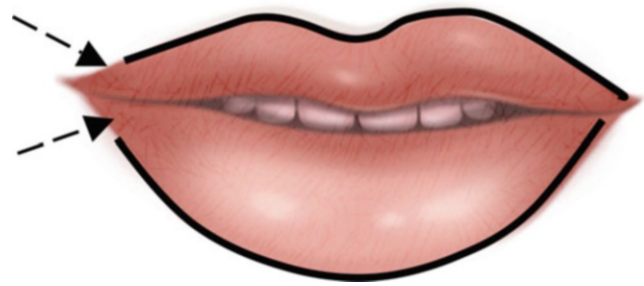


Fig. 13 Other fillers allow a very different technique: insert the needle under the skin and over the muscle and just inject the filler slowly. The filler slides along the border smoothly from one oral commissure to the other, and it is visible to bare eyes

the filler itself might elongate even more the superior lip and we focus on others perioral aging losses as the upper corner of the lips, creating a triangle hollow. When filling the philtrum, the filler can be injected through the vermillion or the skin above the vermillion. We prefer to inject through the vermillion in order to deliver a little amount exactly at the division of the mucosa and the skin to create a prettier Cupid's arch. The philtrum is molded with a retrograde injection at the dermis. The Cupid's arch can be enhanced with a tiny amount of filler injected at the border of the vermillion added to this little tiny amounts injected as bolus at the end of the philtrum. In the middle of the Cupid's bow, at the tubercle, we inject HA in a stamp injection technique to give support for the projection of the middle of the upper lip (injecting a deep depot, lifting the needle through the tissue to the surface while injecting, creating a vertical depot) (Fig. 14).

The superior hollow triangle can be filled with the same technique of the inferior mouth corner hollow. The fan technique is simple and enough to the upper lip hollow (Fig. 15A), and the needle can be directed upward and/or downward (Fig. 15B). We fill up the inferior mouth corner hollow with a fan technique crossing in different directions (Fig. 15C) injecting little bolus drops under the lateral vermillion border and also at the basis of the labiomental fold to lift the commissure might be necessary. Directing the needle laterally through the mucosa exactly at the angle (Fig. 15E), we inject about 0.3 mL to add the reconstruction of the corner and we can also inject in a 90° angle (Fig. 15F) from the lateral skin crossing all the side of the commissure reinforcing the structure. Most of the time, we fill at the subcutaneous layer to literally reconstruct the fat and muscular loss at this area.

The fine lines that result from the orbicularis oris contraction might also be treated with a retrograde technique injection. In our experience, when the patient needs fillers at these wrinkles, he also need a botulinum toxin (BT) pretreatment at least 2 weeks before the fillers to achieve a better and long lasting result. We prefer injecting 2 Units of BT each side of the upper lips and 1U each side of the inferior lips. To start, we introduce the needle through the vermillion (there are authors that do not inject through the vermillion, but only through the skin) as we intend to correct the line at the lips resulting from the weakness of the skin above it. The dermis is the depth of the first layer of HA, and sometimes we use the needle to rupture the dermis (transcision) when introducing it and injecting a very tiny amount of filler when turning back (retrograde injection). We withdraw the needle and perform the injection of micro drops separately, very superficial at the rhytides one by one to fill the line.

Reconstruction of the modiolus area is crucial for a lifting of all lateral structures of the lips. When it is well done, we can notice that even the superior and the inferior lips are slightly exposed because of the repositioning of the lateral mouth fat pad and muscle. We use parallel lines of fillers injected from the side to the middle and parallel to the rhytides of the nasomental fold (Fig. 16A). If using cannulas, we use the fan technique introducing it through one, two, or three points as shown at the Fig. 16B.

Finally, giving volume/projection for the lip: there are many techniques and we are discussing

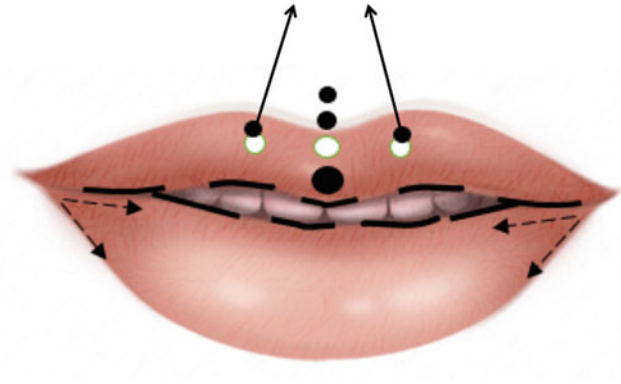


Fig. 14 The Cupid's arch can be enhanced with a tiny amount of filler injected at the border of the vermillion added to this little tiny amounts injected as bolus at the end of the philtrum and at the middle of the Cupid's bow; at the tubercle, we inject HA in a stamp injection technique to give support for the projection of the middle of the upper lip

Fig. 15 The fan technique is simple and enough to the upper lip (A) and the needle can be directed upward and/or downward (B) and a cross fan technique at the corner of the mouth (C) adding little bolus drops and also at the basis of the labiomental fold (D) to lift the commissure might be necessary. Directing the needle laterally through the mucosa exactly at the angle (E) we can inject 0.3mL to add the reconstruction of the corner and we can also inject in a 90-degree angle (F) from the lateral skin crossing all the side of the commissure reinforcing the structure

Fig. 16 Reconstruction of the modiolus area is crucial for the lifting of all lateral structures of the lips and when it is well done, we can notice that even the superior and the inferior lips are slightly exposed only because of the repositioning of the lateral mouth fat pad and muscle. We use parallel lines of fillers injected from the side to the middle and parallel to the rhytides of the naso-mental fold (*A*). If using cannulas, we use the fan technique introducing it through one, two, or three points as shown at the (*B*)

only few that are mostly described and added by our experience, depending on the rheological characteristics of the HA. We give volume for lips injecting fillers at the division of the dry mucosa and the wet mucosa of the upper and inferior lip. The filler is deposited inside the lip, around the middle of the lips thickness. When working with cannula, it is injected at one of the corners of the mouth and the filler is placed deeply between this limit, from one corner to the other, placing smaller amounts of fillers at the corners and greater at the middle aspect of the lips, touching and feeling within two fingers, grabbing the cannula and the filler between them to mold and quantify the filler that is being injected.

Using needle: fan technique. When volumizing lips with needles, using general HA we can also use the fan technique. Inserting the needle from the corner to the medial part of the lips, at the corners injecting in two or three different directions throughout its length, and at the end of the first injection towards the middle, in one or two directions in the body of the lip and finally a line at the middle of the lip, controlling the amount of HA injected. The same technique is performed both for the upper and lower lip (Fig. 17).

The other technique that we can use with a very modern much fluid HA is the bolus injection. For the lower lip volume/projection to achieve the 1 per 1.6 proportion between the upper and lower lip we insert the needle at the skin just below the middle of the lower lip, directing to the medial line and in a fan technique, also moving the needle again and directing to the sides as its length allows, inject another bolus of HA a bit less volume than the medial bolus for the both sides as shown in Fig. 18. If there is asymmetry, only control the amount of HA injected. To reconstruct a much sensual Cupid's bow, we inject with the stamp technique a small amount of HA at the middle of the upper lip (Fig. 14).

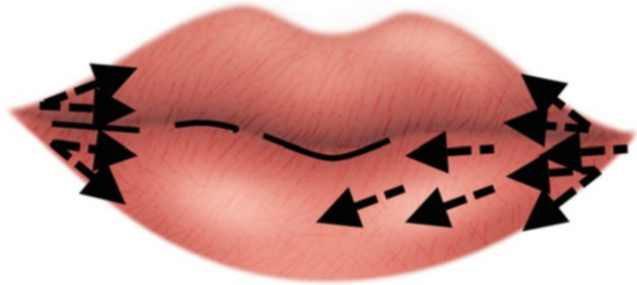


Fig. 17 Using needle: fan technique. Inserting the needle from the corner to the medial part of the lips, at the corners injecting in two or three different directions throughout its length, and at the end of the first injection towards the middle, in one or two directions in the body of the lip in the body of the lip and finally a line at the middle of the lip, controlling the amount of HA injected. The same technique is performed both for the upper and lower lip

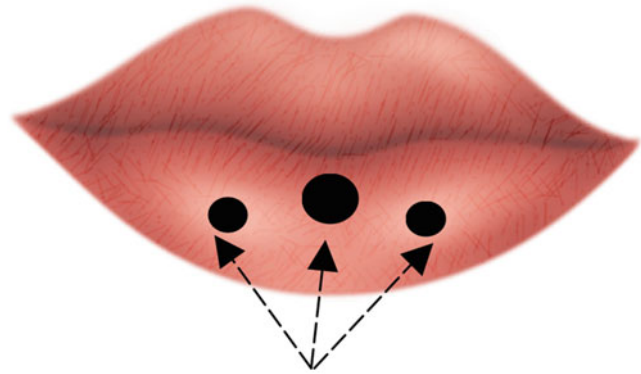


Fig. 18 Directing the needle to the medial line and in a fan technique, also moving the needle again and directing to the sides as its length allows, inject another bolus of HA a bit less volume than the medial bolus for the both sides

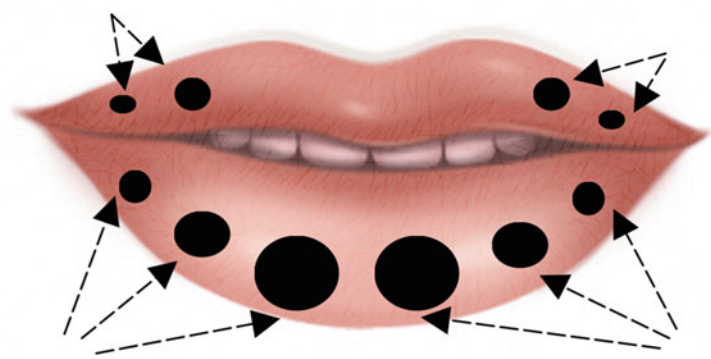


Fig. 19 The technique is in bolus for the lower lip: we insert the needle at the lateral quarter of the lip and with the same fan technique inject three to four bolus, always with decreasing amounts from the middle to the lateral part of the lips. The same for the upper lip followed by a molding massage along the length of the lips

When the lips are very thin, we suggest refilling it in parts, some amount injected in a first appointment with the restructuring of the perioral area and the final master filling to be performed at a second appointment, between 2 and 4 weeks later. The technique is also in bolus, but this time, for the lower lip, we insert the needle at the lateral quarter of the lip and with the same fan technique inject three to four bolus, always with a decreasing amount from the middle to the lateral part of the lips. The same for the upper lip followed by a molding massage along the length of the lips (Fig. 19).

Case Reports: Patients before and after Different Treatment Techniques

Adverse Effects

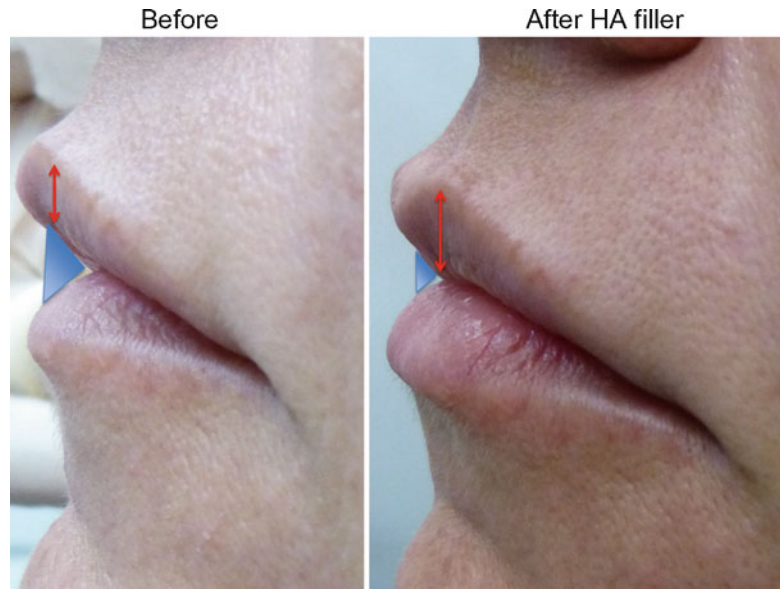
The adverse effects attributed to the use of HA fillers can be categorized in mild, moderate, or severe, according to the perception of the patient. The most related are pain, bruising, swelling, erythema, and tenderness, mostly described as mild (88%) or moderate (11%) and tolerable, with spontaneous resolution within a few days without the need of a prescription (Glogau et al. 2012).

Nodules and lumps are also described, but they are very rare in lips augmentation and can be avoided with the use of several microdroplets to increase the volume of the vermilion instead of the injection of strands, which can be compressed by the muscular movements into pearls and form noticeable lumps if the patient keeps nibbling the fillers. These lumps can be treated with hyaluronidase injections, injection of corticoids (triamcinolone), or by surgical excision.

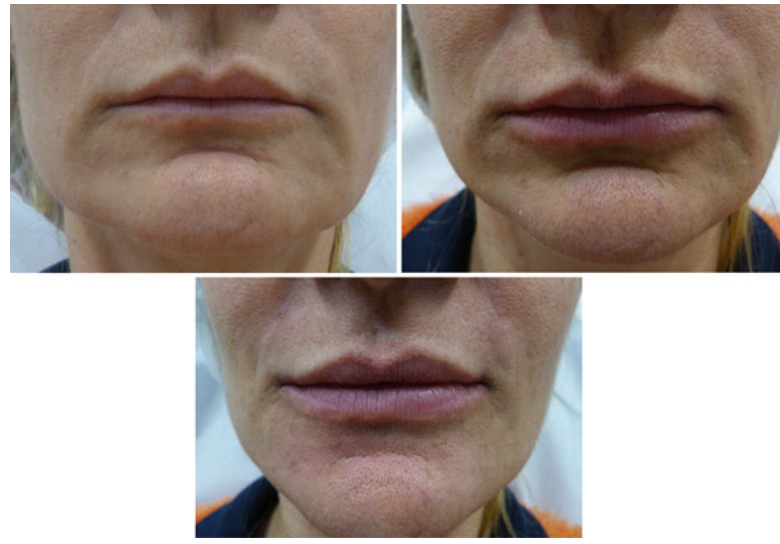
Serious Complications

Serious complications are described as less common or rare side effects of the HA fillers, according to the FDA. Among them are: infections, open or draining wounds, sore at the injection site, allergic reaction, and necrosis (tissue death). The rare side effects reported are: severe allergic reaction (anaphylactic shock) that requires immediate emergency medical assistance; migration or movement of filler material from the site of injection; leakage or rupture of the filler material at the injection site or through the skin (which may result from tissue reaction or infection); the formation of permanent hard nodules in the treated areas; vision abnormalities, including blindness; stroke; injury to the blood supply, and damage to the skin or the lips.

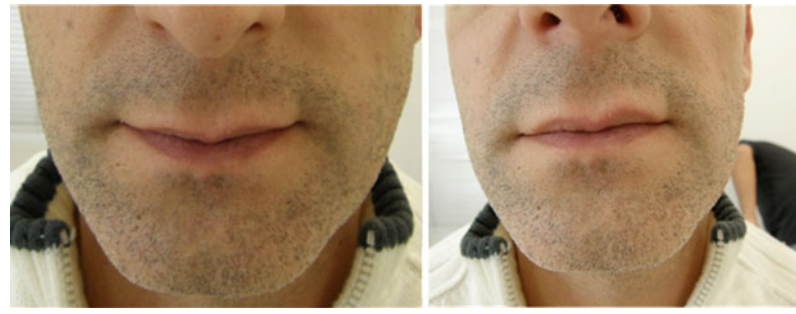
The ischemic complications can be avoided by the use of cannulas instead of needles, and with a previous knowledge of the anatomy of the approached area. They start within the early hours after the procedure and can be treated with the injection of hyaluronidase, preferably guided by an ultrasound scan of the arteries involved. A nitro patch and warm dressings can also be used to dilate the occluded artery.



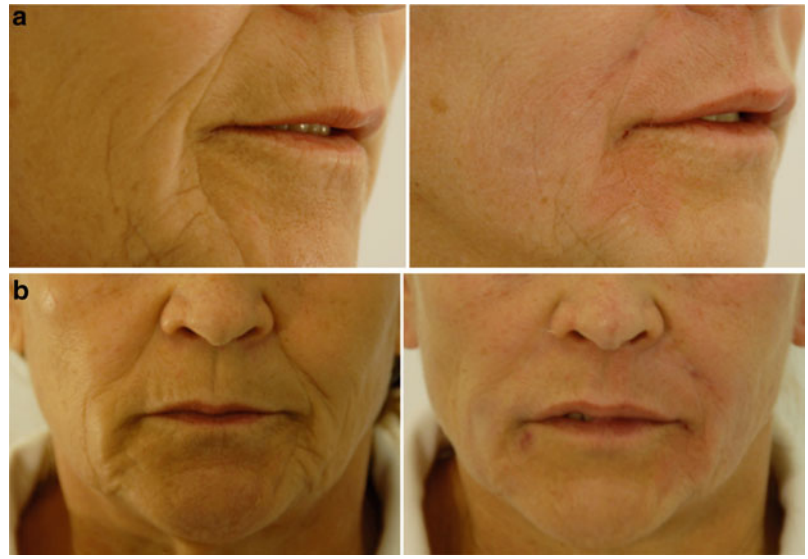
Case 1 HA to volumize the body of the superior lip, correcting the countour projection. Courtesy by Dr. Maria Issa



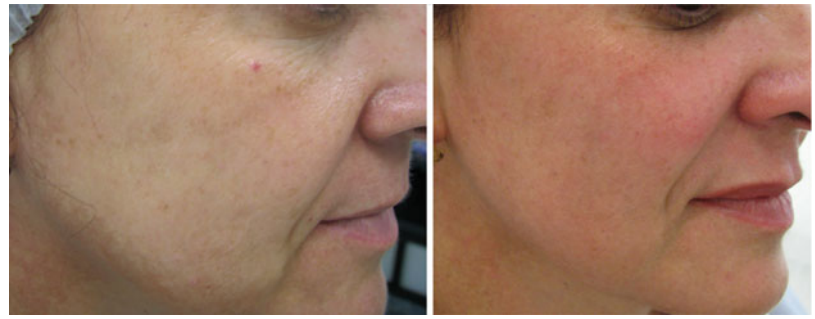
Case 2 Before and after volumizing superior and inferior lips, maintaining the proprortion, and below, after filling the metual region. Courtesy by Dr. Maria Issa



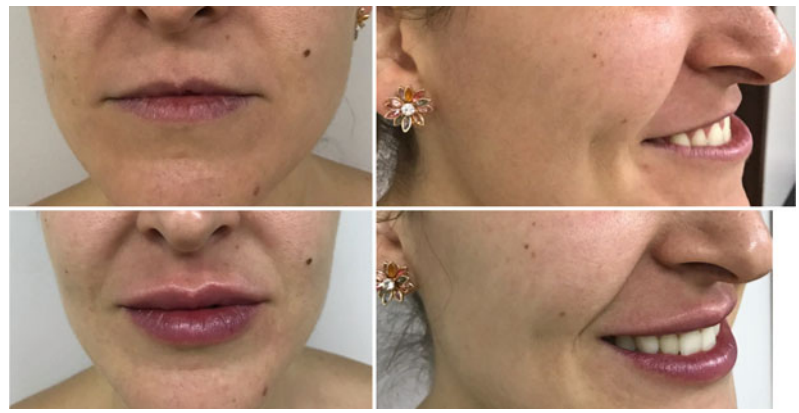
Case 3 Volumizing male lips with HA. Courtesy by Dr. Bhertha M. Tamura



Case 4 (**a**) Lateral view of a full peribuccal and lips rejuvenation. Before and immediate post HA fillers. Courtesy by dr. Bhertha M. Tamura. (**b**) Frontal view of a full peribuccal and lips rejuvenation. Before and immediate post HA fillers. Courtesy by Dr. Bhertha M. Tamura



Case 5 Lateral view before and after malar filler, mouth corners and lips correction with HA. Courtesy by Dr. Bhertha M. Tamura



Case 6 Volumizing superior and inferior lips with HA. Observe the improvement of the smile in the lateral view, with less exposure of the gum. Courtesy by Dr. Thales Bretas

Infections can be avoided with a meticulous sterile procedure and can be treated with antibiotics, such as clarithromycin. Late granulomas can be treated with early intralesional steroid injections: triamcinolone 20–40 mg/ml; betamethasone 5–7mg intralesionally; methyl-prednisolone undiluted 20–40mg; or triamcinolone 10mg/ml + 5-fluorouracil 5mg/ml. (Gottfried et al. 2006)

Take Home Messages

- It is essential for the physician who intends to work with lip correction to know the anatomy of the lips, the origin of its shape and curves, as well as their innervations and nutrition.
- The aim of treating the lip is to harmonize it with the patient's age and ethnicity, taking into account facial proportions and features.
- The physician should avoid an overcorrection, resulting in the anterior projection of the upper lip, called "duck-like appearance," or the "sausage" lip.
- Even temporary fillers, like the HA, can cause persistent alterations on tissues, and therefore there is no predetermined time to new injections.
- The photographic documentation is important to show the patients before and after pictures when they have doubts and even for the physicians' legal protection.

Final Considerations

Lips are very complex to be treated. Younger patients require simpler techniques but elderly, especially those that had never treated the lips and surroundings, are very tricky. There are dozens of techniques, and as many techniques, many different doctor's view concerning where, when, how, the amount of fillers, the type and quality of the filler, width of the needles, classification of each stage of lips aging, the ethnic patterns and personal, social, and medical concept of beauty.

Adding all these, we need to understand the complexity of the local anatomy, the dynamics and mimics of the patient if he does not have asymmetries, accidental scars, and neural impairment. Doctors must know the science deeply and have a real beauty sense when the matter is mouth rejuvenation.

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Hyaluronic Acid for Mental and Mandibular Contour

Débora T. S. Ormond and Paulo R. Pacola

Contents

Abstract

Nonsurgical dermatological procedures such as the use of hyaluronic acid (HA) are part of the therapeutic and preventive armamentarium against facial aging. Several intrinsic and extrinsic factors interfere with facial aging, many modifying the youthful anatomy of the face. In this process, alterations of bone, muscles, and face and skin fat together transform the standard face from convex to concave. The purpose of this chapter is to address the use of HA for rejuvenation and correction of imperfections.

Keywords

Filler · Hyaluronic · Mental · Mentum · Mandibular · Contour · Rejuvenation · Facial · Volume · Aging

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Introduction

Nonsurgical dermatological procedures have been gaining increasing importance in the therapeutic armamentarium of facial rejuvenation due to their safety and the reliability of the results. These less invasive procedures follow current trends, as well as being more preventive interventions for aging.

The process of facial aging is influenced by natural chronological factors (gravitational forces, subcutaneous fat loss, bone resorption), photo damage (breakdown of collagen and elastin, neoplastic changes), and traumas (diseases, inflammations, surgeries). Together, dentition alterations, bone remodeling, the SMAS (superficial musculoaponeurotic system), supporting ligaments, and dermal thickness, as well as facial fat loss and repositioning lead to loss of facial volume. These alterations cause the transformation of the young, convex face into the aged, concave face, forming face shadows (Fig. 1). The aged aspect is accentuated by the emergence of

M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_22

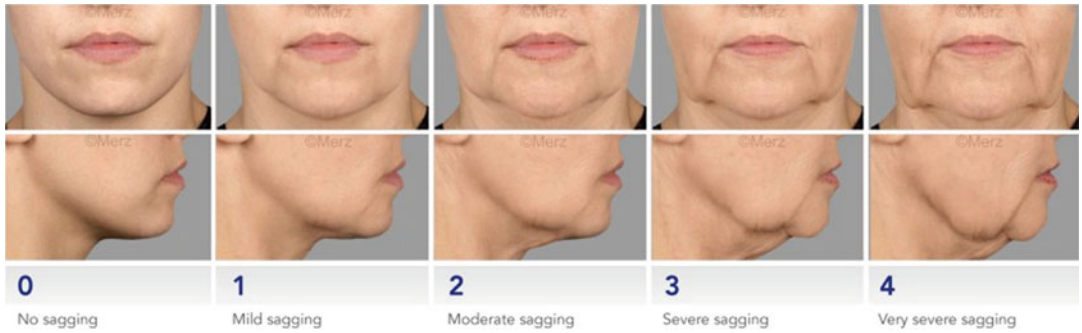

Fig. 1 Merz classification: typical changes from a youthful appearance (convexity of the face) to an aged appearance (flattened and concave face)

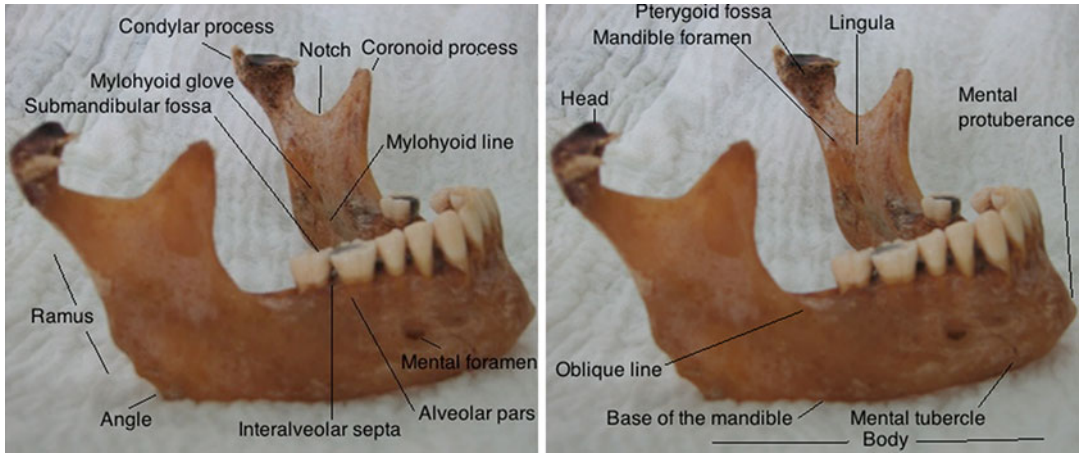

Fig. 2 Mandible anatomic structures

dynamic wrinkles, resulting from the kinetic activity of the facial mimetic muscles throughout life. Hence the importance of using fillers at the mentum and mandibular level, in isolation or in association with other techniques (neurotoxins, peeling, laser, radiofrequency and microfocused ultrasound), to restore facial contours.

Anatomy

In-depth knowledge of the middle and lower third of face and neck anatomy is of fundamental importance for the interpretation of the physiological and pathological alterations that resonate in the mandibular region, as well as to identify the anatomical structures that should be monitored during the procedure in order to prevent complications.

The mandible, the main representative of the lower third of the face, establishes the relationship with the structures of the middle third and neck. It is divided into a body (presenting as a "U" shape) and branch, which joins perpendicularly to the mandibular branch, forming an angle that may vary from 110° to 140°, with a mean value of 125°. The external surface of the mandible in the median line is marked by the faint ridge called the 'mandibular symphysis.' The space between the mentum and the mandibular angle is known as the mandibular line. The alveolar part of the mandibular region contains the teeth in the lower arch. Below the second premolar tooth lies the mental foramen (Fig. 2), which

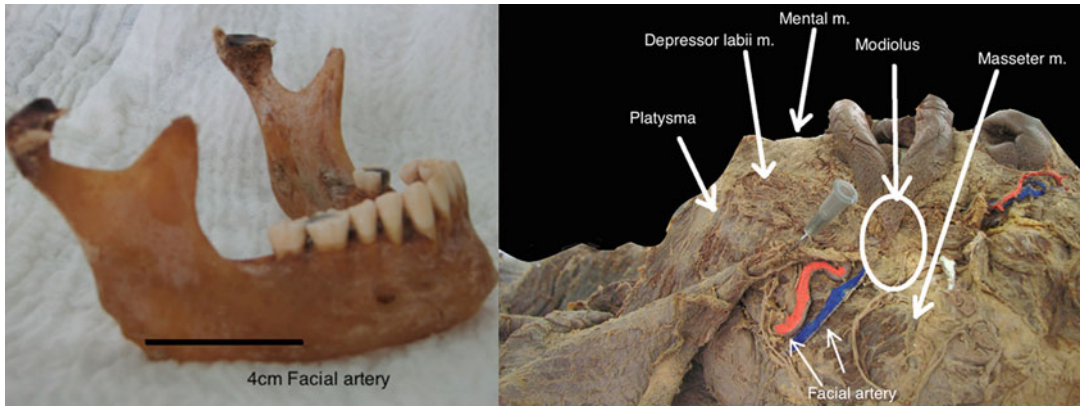

Fig. 3 Four centimeters before the angle of the mandible (this parameter might change in the same patient and in different subjects – always palpate and feel the sulcus to confirm the exact location): In the basis has the arterial sulcus through which the facial artery passes, where palpation is perceptible

Fig. 4 Bone alteration in the aging process: zygomatic arch with reduction of the curve and an increase in the mandibular angle

gives passage to the nerve and the mental vessels (Tamura 2010a), and is located in an approximately vertical line that passes through the limbus of the eyes, a little medially to the mid pupil. Neural blocking at mental foramen level anesthetizes the lower lip and part of the mentum.

Bone alterations as a result of resorption (Fig. 3) of the alveolar parts of the maxillary and mandibular bones, loss of the dental arch (Fig. 4), and vertical and horizontal maxillomandibular discrepancies are directly responsible for the improper positioning of the soft tissues, causing thinning and narrowing of their portions, reinforcing the impression that the face is "falling" and forming the famous "bulldog" formation (Fig. 5) and loss of facial contour.

The muscles that insert under the mandible are important in the treatment of the lower third of the face. These comprise the masseter muscle, platysma, depressor muscle of the angle of the mouth, depressor muscle of the lower lip, and mentalis muscle.

The masseter muscle is located in the parotideomasseteric region and is one of the masticatory muscles. The portion of the masseter muscle that is inserted all around the lateral branch of the jaw has the function of lifting the jaw. Treatment is indicated when there is pathological and

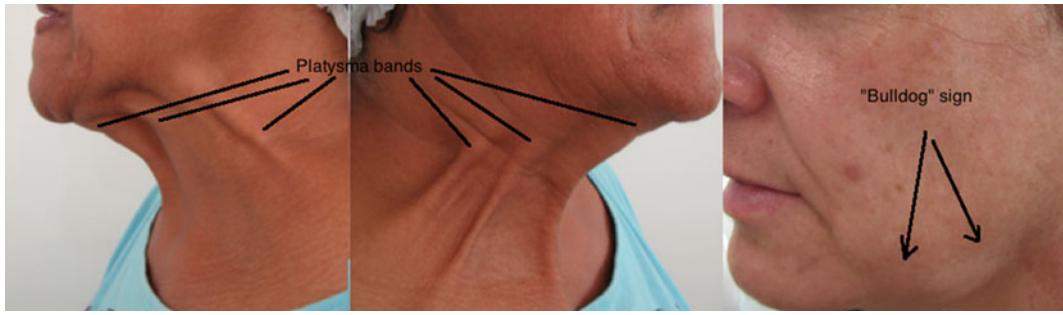

Fig. 5 Tissue looseness resulting from age and repeated muscle contractions: marionette sulcus, so-called "bulldog" formation, and platysma banding

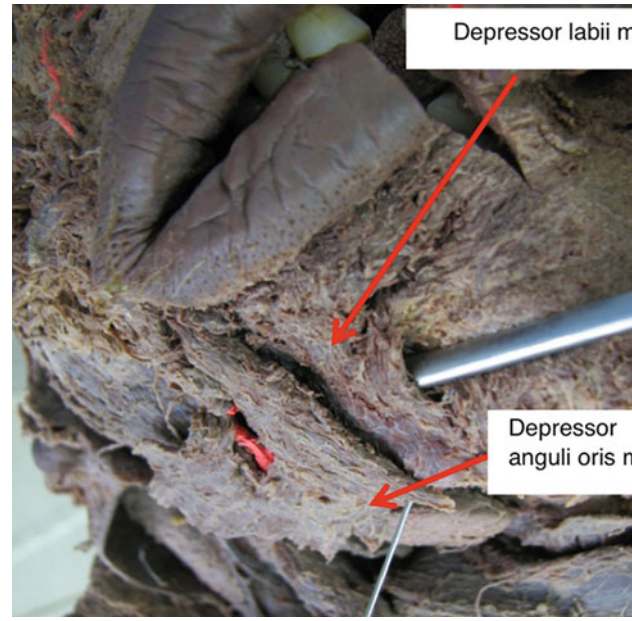

Fig. 6 Muscles in the depressor group: lip depressor and depressor of the angle of the mouth

functional hypertrophy, as well as to soften the facial contour.

The muscles considered to be depressors include the (Fig. 6):

- Depressor of the angle of the mouth
- Depressor of the lower lip
- Mentalis

The depressor muscle of the lower lip is inserted in the base of the mandible (over the origin of the depressor of the angle of the mouth) and in the lower lip. The mentalis muscle originates in the mental fossa and is inserted in the mentum skin; it has the function of wrinkling the skin of the mentum and everts the lower lip (Fig. 7). The depressor muscle of the angle of the mouth has its insertion at the base of the mandible and the angle of the mouth. It is the most superficial muscle of this group.

The platysma muscle (Fig. 8) originates in the sternoclavicular joint, clavicle, and acromion of the scapula and is attached to the base of the mandible and some of its fibers in the angle of the mouth. Its function is to distend the skin of the neck and pull latero-inferiorly along the angle of

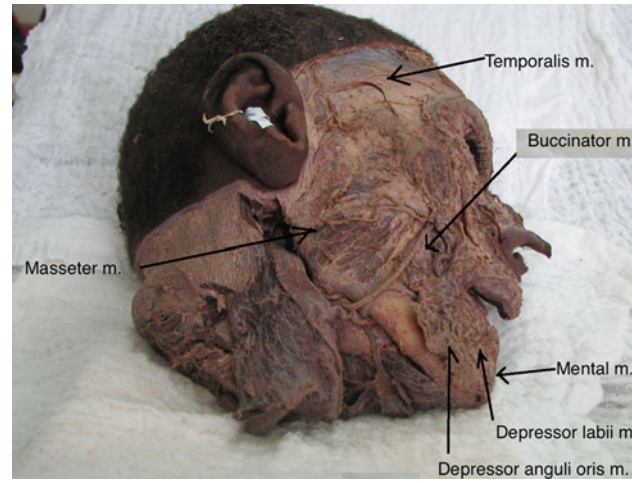

Fig. 7 Muscles with insertion in the mandible

Fig. 8 Platysma muscle showing its mandible insertion

the mouth. This muscle has a strong anterior portion, which moves in the anterior region of the chin towards the lip, meeting the complex called the modiolus (Fig. 9). It can also stretch laterally up to the angle of the mandible; however, not all individuals have this presentation (Tamura 2010b). With aging, its resting tonus increases and shortening of the vertical length occurs, leading to the formation of anterior bands, which eliminate the cervicomandibular angle. Under the jaw, contractions of the depressor muscle of the mouth angle stimulate the platysma muscle, discarding the deep fat anteriorly.

So-called "marionette" lines (Fig. 10) are formed because of the influence of the depressor muscle of the mouth angle and platysma, as well as because of flabbiness of the SMAS with aging.

The set of actions/functions of the facial mimetic muscles in youth has a curvilinear contour, presenting an anterior surface convexity. This reflects a curve in the underlying fat compartment to the deep surface of these muscles, acting as an efficient mechanical sliding plane. The amplitude of muscle movement is also higher during youth. The convex contour becomes rectilinear during the aging process and the underlying fat is expelled from beneath the muscles (Fig. 11), causing the superficial fat to decrease (Coimbra et al. 2014).

The combined actions of several muscles that are inserted in the mandible provide a balance of forces that keeps young faces harmonious. However, when an imbalance occurs in a muscle cluster of antagonistic forces, either an increase or decrease of the forces, the result is the loss of facial harmony. Hence, anatomical knowledge and a good aesthetic sense for the "lifting of the facial expression" is important to balance these forces.

Sensory innervation occurs through the mandibular branch of the facial nerve, which passes the medial portion of the mandible anteriorly. It is usually located in the mandible angle at the mandibular midlateral zone and its location is deep beneath the platysma until to approximately 2 cm lateral to the corner of the mouth where it surfaces (Zoumalan 2011).

The nerves of the infratemporal area – the masseteric, deep temporal, buccal, inferior alveolar, lingual, auriculotemporal, chorda tympani, and optic ganglion nerves – are involved in motor innervation.

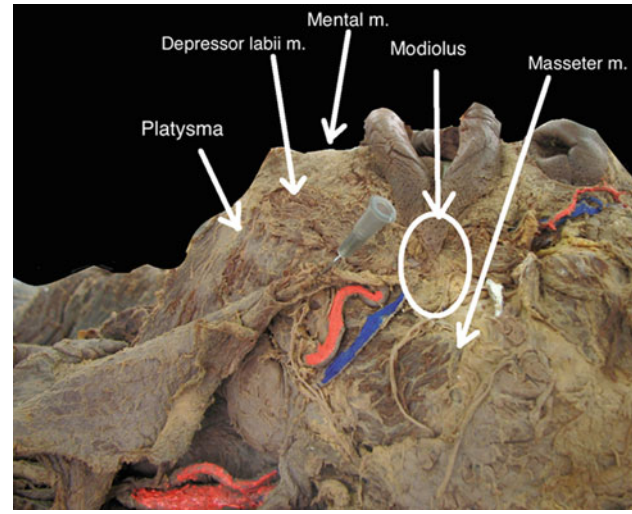

Fig. 9 Modiolus region

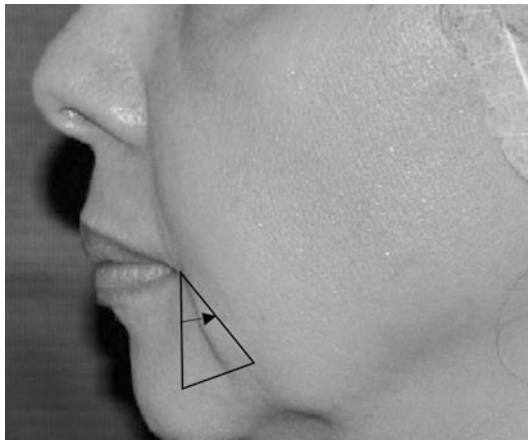

Fig. 10 Marionette lines

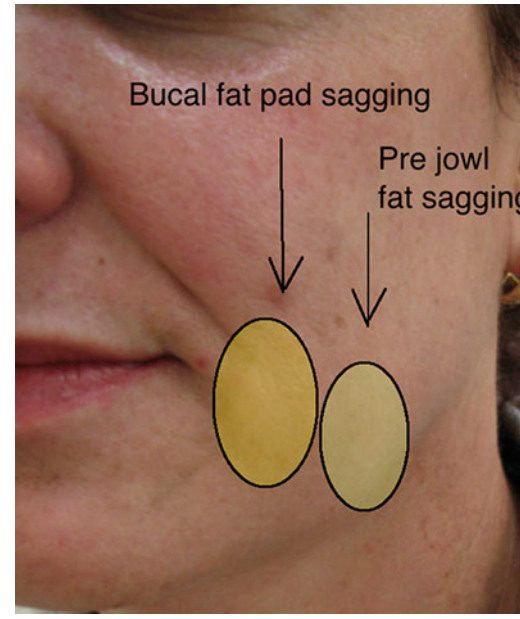

Fig. 11 Fat compartments and mandibular displacement

The buccal nerve (Fig. 12) is a continuation of the mandibular nerve, which is situated laterally between the bundles of the lateral pterygoid muscle and continues anteroinferiorly and medially to the fibers of the deep bundle of the temporal muscle. It runs through the buccal fat pad and distributes its fibers to the skin and mucosa of the cheek and the vestibular gingiva of the lower molars (and occasionally of the upper molars). The inferior alveolar nerve travels downwards, passing near the deep lateral pterygoid muscle region and then between the medial and lateral pterygoid muscles. It flows inferiorly down the medial region of the mandible branch, enters the mandibular foramen, crosses the mandibular canal, and subdivides into dental branches to the molars and lower premolars. After passing the mental foramen, it gives rise to the mental nerve (which innervates the soft tissues of the mentum and lower lip, vestibular gingiva incisors, canines, and lower premolars) and incisive nerve (which innervates the incisors, canines, and their respective periodontium).

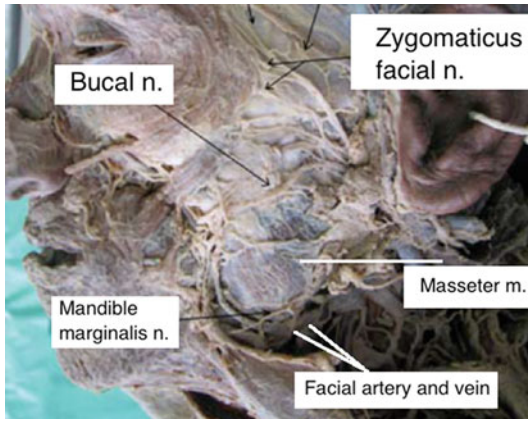

Fig. 12 Branch innervation of the trigeminal nerve in the face; anatomical relationship with the artery and facial vein: anatomical relationship with innervation of the masseter muscle

The motor nerves of the parotideomasseteric region are the terminal branches of the facial nerve that arise from intraparotid plexus (temporal, zygomatic, oral branches, marginal mandibular, and cervical branch) (Fig. 12). The oral branches are the motor nerves of the muscles in the upper lip and the marginal mandibular branch in the lower lip. They are considered to be high risk in relation to traumas and complications in thin patients. Therefore, like the zygomatic nerve (a facial nerve), one must be careful and delicate when injecting products 2 cm lateral to the angle of the mouth where the nerve is more exposed and prone to trauma (Goldberg 2008; Hirsch and Stier 2008).

Facial vascularization occurs mainly via the external carotid artery, and its main branches are the thyroid artery, lingual artery, facial artery (Fig. 13), occipital artery, posterior auricular artery, maxillary artery, and superficial temporal artery.

The facial artery is the most studied artery and its path follows the outer surface of the mandible, under the platysma, to the inner corner of the eye. It crosses the buccinator muscle and the maxilla, deep into the zygomatic major and elevator of the upper lip muscles. The facial artery branches off to the lip and lateral face of the nostril. The angular artery is the terminal part of the facial artery that runs along the nose to the inner corner of the eye to supply the eyelids.

In the mental region, the submental artery originates from the facial artery in the submandibular region, passes through the base of the mandible up to the mentum, and irrigates the mylohyoid muscle, the anterior belly of the digastric muscle, and the adjacent structures. The mentum is also supplied by the inferior alveolar artery branch of the mental artery, which emerges through the mental foramen. Venous drainage corresponds to the arterial supply. The mandible is supplied by the facial and inferior alveolar arteries.

Procedures in the region of the facial artery at the mandibular level performed on the skin or subcutaneously do not usually cause arterial injury; however, aggressive procedures carried out without anatomical knowledge may cause serious injure to the facial artery.

Facial lymphatic drainage occurs in a posterior and inferior direction, whereas the medial region (including the upper and lower lips) drains into the facial lymph nodes – the submental (including the central region of the lower lip) and submandibular lymph nodes – the side of the face, and scalp, in addition to the forehead on a diagonal line (infraorbital, zygomatic, and cheek region) up to the parotid lymph node.

The superficial fat compartments (Fig. 14) are separated by fascial septae, which are nothing more than pillars of the fascia that retain these compartments (Rohrich and Pessa 2007). The loss of this fat leads to alterations in the facial contour, especially in its lower third. This pseudoptosis of the face leaves an unsupported skin excess that contributes to a loss of submandibular contour and accentuation of the nasolabial folds (Coleman and Sengelmann 2009).

Coleman and Sengelmann (2009) described different compartments of fat, subdivided into regions: periorbicular, temporal, perioral, middle third of the face, cheek, and mandibular (Rohrich and Pessa 2011).

In a study of facial tomographies with contrast in cadavers, Gierloff et al. (2012) proposed a different classification of fat compartments to those already discussed. In their classification,

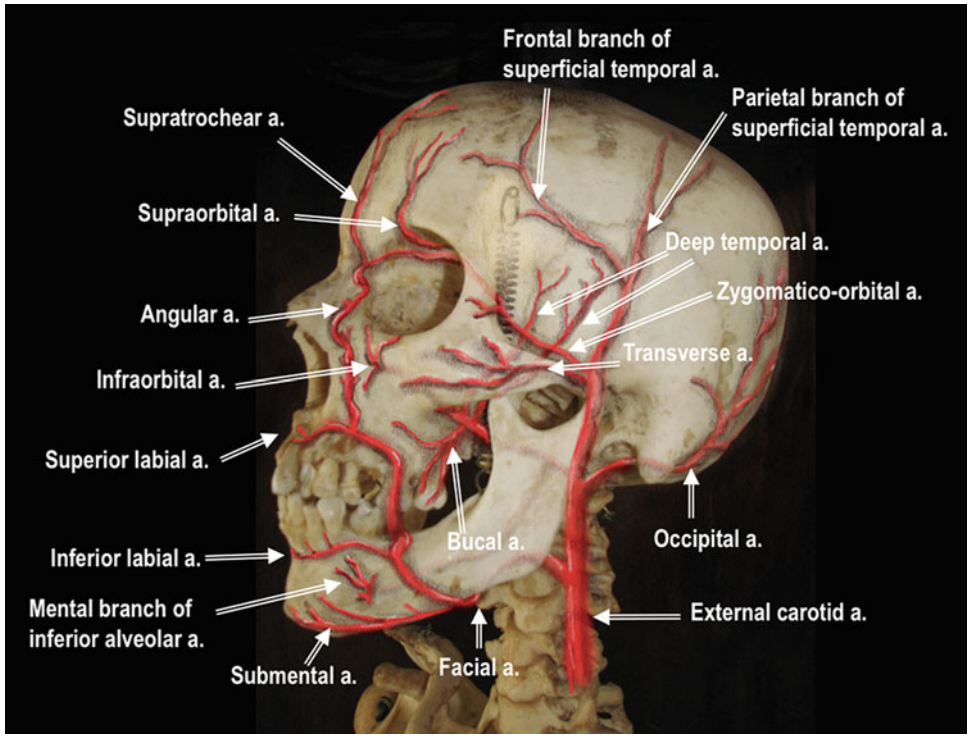

Fig. 13 Vascularization of the temporal, zygomaticus, and mandibular area

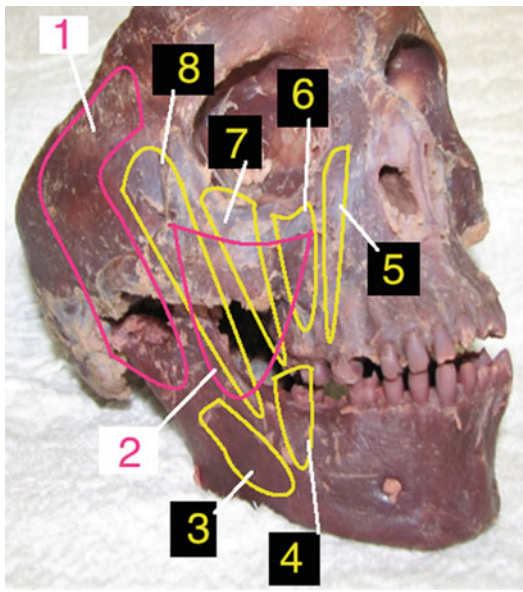

Fig. 14 Compartments of facial fat: (1) lateral temporal cheek fat; (2) deep medial cheek fat (lateral part); (3) inferior jowl fat; (4) superficial jowl fat; (5) nasolabial malar fat; (6) medial malar fat; (7) middle malar fat; (8) lateral malar fat

the compartments were divided into fat of the middle third of the face consisting of two layers (superficial and deep) and the paranasal region divided into three anatomically different layers.

Recently, Wan et al. (2013) analyzed 63 hemiface dissections on cadavers and observed three main alterations: (1) the adipocytes in the superficial fat compartments were bigger than the adipocytes of the deep fat compartments; (2) the size of the adipocytes in compartments of nasolabial fat (NLF) and deep medial cheek fat (DMCF) in males was significantly lower than in females; and (3) the size of the adipocytes in the nasolabial compartment (NLF) in patients with a normal body mass index (BMI) was significantly higher in females than in males. This supports the clinical and anatomical observations that suggest there are morphological differences between the compartments of superficial and deep fat, specifically selective atrophy in the deep fat compartments in the elderly. This finding may be clinically relevant for the effects of volumetric facial rejuvenation.

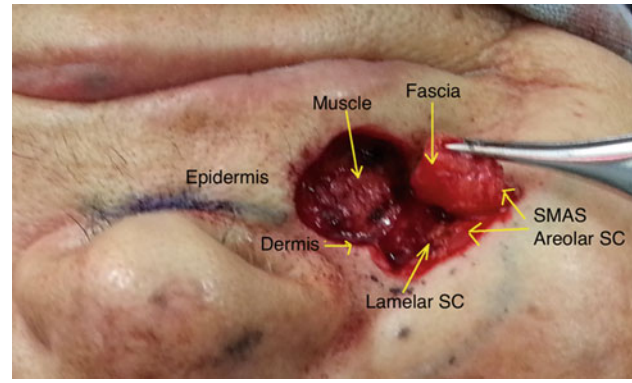

Fig. 15 Relationship of the SMAS (superficial musculoaponeurotic system) with subcutaneous tissue

In the maxillary region, the angle and the body of the mandible, with their overlying masseter and platysma muscles, define the inferior border of the inferior part of the face and create the mandible line. With aging, there may be remnants of fat deposits, which descend and deform the border of the mandible, reducing facial suppleness Tamura (2010a).

The fat on the cheek, in the nasolabial groove, and on the mandible is dense. The Bichat ball is located anteriorly to the masseter and deeper into the posterior fascia in the buccal region. The localization of these structures and the shape of the face must be considered when preparing to inject fillers with the purpose of lifting the malar and middle regions. It is necessary to avoid patients presenting with an artificial result, as if a prosthesis had been implanted.

In the parotideomasseteric area, the skin adheres closely to the fibers of the risorius and platysma muscles. The branches of the facial nerve (Fig. 3) and the parotid duct (Fig. 9) are located in a posterior position to the SMAS and anterior to the masseter and buccal fat. When carrying out treatment in the parotid region, it is worth remembering and being aware that the duct is beneath the line connecting the angle of the mouth to the tragus as there have been reports of traumatic fistulas.

The adipose tissue superficial to the SMAS (Fig. 15) in the mental region is firmly attached to the dermis via a fibrous septum, which makes the deep tissues very adherent to the skin at this level. Due to this adhesion, products injected in this area do not move easily with massage and, therefore, supraperiosteal injection is preferred for the reconstruction of the mentum and mandible with fillers. When a greater amount needs to be injected in the mentum region we might inject into the subcutaneous tissue as the mental muscle is tightly inserted to the bone, and the injection can be very painful for the patient.

At skin level, the changes and impacts that take place are the result of multiple interactions between intrinsic and extrinsic factors. The intrinsic factors, which reflect our genetics, influence the characteristics of the dermal collagen and the elastic tissue. With aging, the collagen starts to have increased cross-linking and its volume and elasticity reduces. The elastic fibers are more abundant in the dermis of the face than in the scalp and are therefore responsible for maintaining the static tension of the skin and for restoring the deformed collagen to its original status. Long-term sun exposure subjects the elastic fibers to structural and functional deterioration, gradually losing the ability to return to their original length, resulting in loss of skin firmness.

Extrinsic aging is caused mainly by sun exposure, but smoking, excess alcohol, and poor diet, among other conditions, also have an important role in skin damage over the years. In addition to extrinsic factors, it should be noted that the facial expression muscles are inserted directly into the skin, meaning there is continuous tension even while resting. Over time, collagen elongation occurs in the direction of the muscle contraction. Linear wrinkles result from the union of multiple fibers of the SMAS with the dermis, stretching the

skin and reducing the tension in the direction of the movement of the facial muscles. Reduction in tension, an increase in the stretch of collagen fibers, and the progressive reduction of the elastic tissue create lines that exacerbate with age and/or solar damage (Salasche et al. 1988). Thus, these factors together lead to increased cutaneous flabbiness and sagging of the face and neck skin.

Combined, these changes result in vertical and horizontal maxillo-mandibular discrepancies, which have a significant effect on facial harmony. The mentum is a prominent component of the face that, along with the associated musculature, has great importance in the perioral function and aesthetic facial balance (Wolford and Bates 1988).

Vertical harmony of the inferior third of the face is characterized by equal division into thirds, as the distances between the subnasal craniometric (Sn) and the stomion (St) points, the St points and the labiomental groove, and the labiomental groove and the lowest point of the soft mental tissue (Me) must be compatible. There should also be similar measurements between the Sn points and the mucocutaneous junction of the lower lip and between this and the most inferior point of the soft tissue of the mentum. The distance from the Sn to the St corresponds to half of the distance between the lower St and Me (Fig. 16).

In turn, cephalometric analysis plays a key role in evaluating the relationship between the mentum and other bone structures and with the soft tissue, enabling a tri-dimensional analysis of the mentum region and more accurate aesthetic or surgical planning of the correction. Various analyses, such as those described by González-Ulloa (1987), Ricketts and Langlade (1978), and Steiner (2015) can be used to relate the pogonion (the most anterior point of the soft tissue of the mentum in the midline) with other facial structures. According to González-Ulloa and (1987), the soft tissue of the nasion must be perpendicular to the soft tissue of the pogonion. Ricketts and Langlade (1978) believe that the upper lip must be 4 mm and the lower lip should be 2 mm posterior to the line that goes from the tip of the nose to the soft tissue of the pogonion. Steiner (2015) recommends that the upper and lower lips should border a line through the central region of the columella and the soft tissue of the

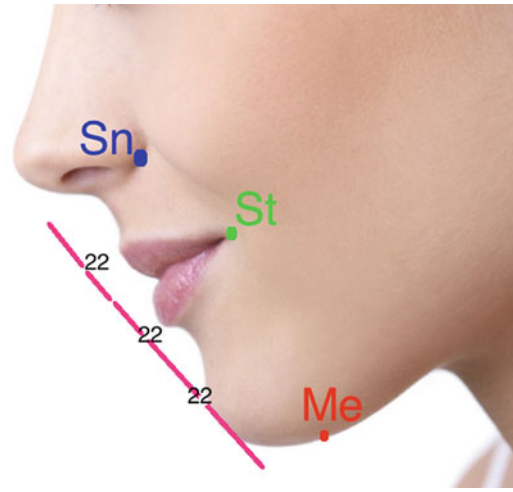

Fig. 16 Harmony of the inferior third and between the thirds of the face. *Me* the lowest point of the soft mental tissue, *Sn* subnasal, *St* union point between the upper and lower lip

pogonion (Fig. 17). It is important to observe that the various analyses do not allow a complete evaluation in isolation, since each one gives a relationship considered to be ideal between the bone and the soft tissue of the mentum.

As described previously, cephalometry is a very important diagnostic tool in planning mentoplasty; however, it is important to remember that for the evaluation of the soft tissues, tri-dimensional clinical examination of the patient is of more value in informative terms than conventional cephalometric analyses, which are bi-dimensional in nature (Freitas 1999; Pacheco et al. 2010).

Hyaluronic Acid

Hyaluronic acid (HA) is an absorbable substance that has been used in Europe since 1996 and received US FDA approval for cosmetic treatments in 2003 (Restylane®).

HA is produced using two techniques:

- Extraction from rooster combs
- Nonpathogenic bacterial fermentation (*Streptococcus equi* or *S. zooepidermis*)
- Biotechnology.

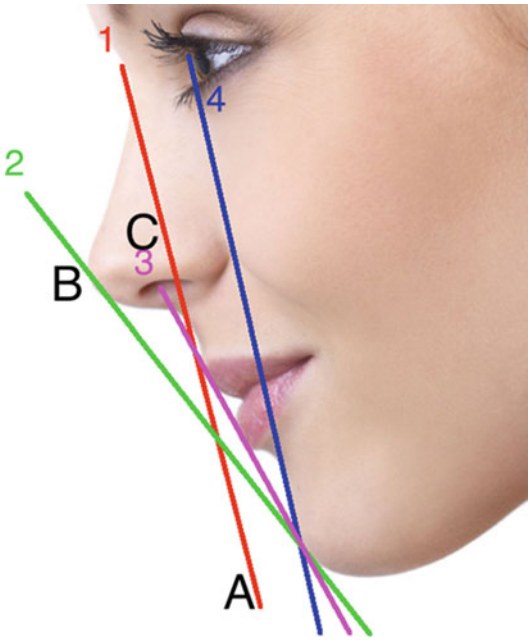

Fig. 17 Cephalometric tracing of a 20-year-old woman: (1) nasion; (2) nasal tip; (3) central region columella; and (4) pogonion (most anterior point of the mentum soft tissue midline). Analysis through the methods of González-Ulloa (1987) (line *A*), Ricketts and Langlade (1978) (line *B*), and Steiner (2015) (line *C*). In the tracing in question, the application of all analyses shows that this a retrognathic patient with a poorly positioned anterior to posterior mentum

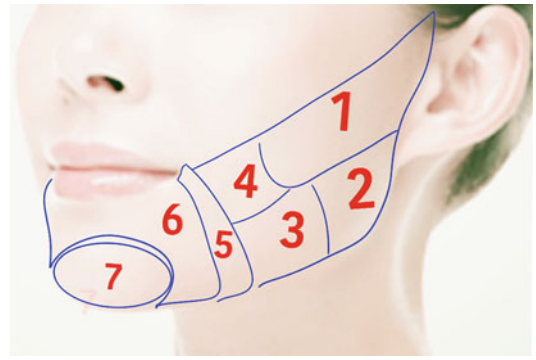

Fig. 18 Facial topography: emphasis on the lower face of the injection zone: (1) malar area; (2) posterior mandible region (between the anterior border of the masseter and the mandible angle); (3) anterior mandible region (between the mental lip sulcus and anterior border of the masseter); (4) buccal area; (5) mental lip sulcus; (6) inferior lip; and (7) mental region (Tamura 2013)

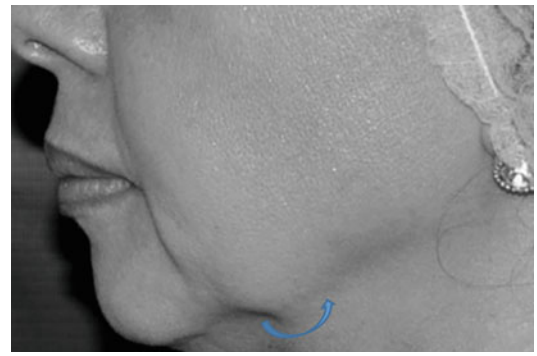

Fig. 19 *Blue arrow* indicates the ptosis area in the mandibular line, which should not be filled Lenza et al. (2015)

The most commonly used type of HA on the market is that obtained using biotechnology due to its lower risk of hypersensitivity. The different versions of HA available differ in their concentration, ability to provide volume, cross-linking, and resistance to degradation (free radicals and enzymes), allowing correction from surface wrinkles to volumization. Treatment for the lower third region is through fillers that promote volumization and redefine facial contours.

Considering the anatomical location in which the filler should be placed (subdermal and supraperiosteal) as well as the noble structures that can be injured, the use of microcannulae is crucial due to the safety that they provide. The cannulae recommended for this procedure are as thin as possible, with 21G and 22G being the preferred choices. Longer cannulae (40 mm and 50 mm) are also advantageous as they produce fewer punctures and therefore less pain and swelling for the patient. Being blunt, the cannulae does not progress into the dermis, contributing indirectly to reaching the ideal level of HA injection.

According to Tamura (2013), we need to consider topographical areas to be potentially risky zones, e.g., the mental foramen in the mental region, through which nerves and vessels pass, and the risk of hematomas and ecchymoses at the labiomental sulcus (arterial branch of the lower lip and the venous system). At the posterior mandible region, near the anterior border of the masseter, there is a depression in the mandible bone where the facial artery is located, which is

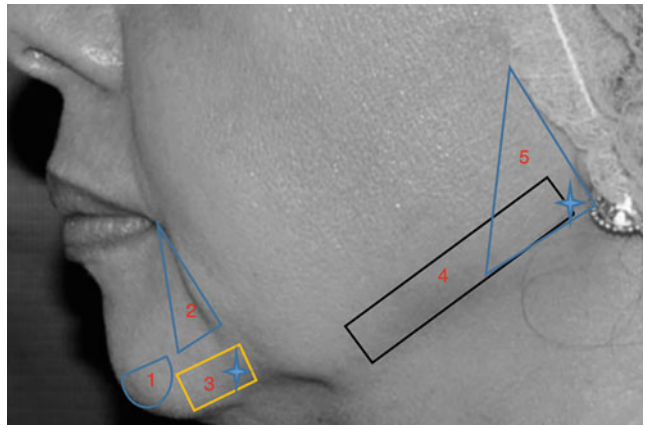

Fig. 20 (1) 1.0 ml of hyaluronic acid was injected via anterior access to the mentus using a 21G needle. Better results can be achieved when associated with botulinum toxin in this region. Places to insert the 21G needle to overcome the fibrotic adherences of dermis for the introduction of the microcannula are as follows: In the paramental point of insertion, the microcannula was introduced to fill the region and the marionette sulcus. (2) 0.5 ml of hyaluronic acid with lidocaine was applied per marionnete sulcus; (3) 0.3 ml of hyaluronic acid injection; (4) mandibular lines were treated using hyaluronic acid 0.5 ml each side; (5) mandible angle treated with 0.5 ml of hyaluronic acid each side in the subcutaneous plane via retroinjection. 0.3 ml in total was used in the region of the inferior lip (above the mentus)

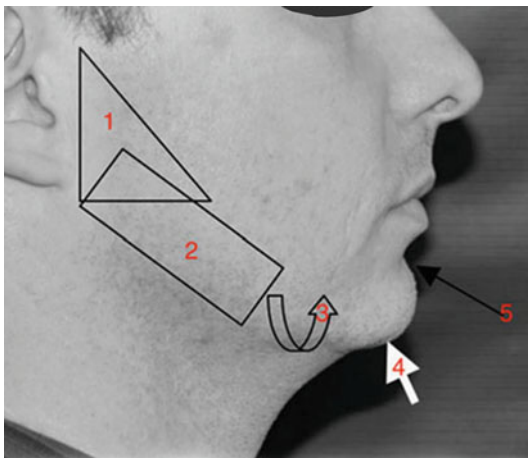

Fig. 21 (1) 1.0 ml applied in the mandibular angle region to each hemiface using 22G 50 mm microcannulas in the subdermal space. (2) 1 ml applied in each side of the mandibular branch. (3) Ptosis area. (4) 1 ml applied in the mental region. (5) 0.5 ml of hyaluronic acid with lidocaine applied in the inferior lip region and to acne scars next to the marionnete line with a 30G ½″ needle

the result of blood pressure on the bone throughout life. There is a risk of worsening the local sagging at the anterior mandible region due to an excess of the injected product (Fig. 18).

The reported general adverse reactions are less than 2% and are similar to those of other products that can be injected, characterized by erythema, edema, ecchymosis, acneiform eruptions, and reactivation of herpes simplex.

Injection Technique

Corrections can be performed with fillers for lip augmentation, attenuation of the labiomental groove, mentum volumization, redefinition of the lateral line to the mentum and the mandibular line, as well as mandibular contouring (mandibular angle reduction) (Fig. 19).

The technical approach is to use 22G or 25G needles and cannulae of 38 mm or more in length, depending on the corrections to be made and extension. The use of needles allows the injection of HA using the bolus or fan technique, as they are small in length. However, because they have a cutting edge, the risk of neural and vascular injury, hematoma, and ischemia and thrombosis/embolism may occur. Thus, special attention should be given to the mental foramen region, labiomental groove, and facial artery path (premasseteric,

identified on palpation as mandibular body depression).

The use of cannulae enables, in lower third volumizing situations, larger areas to be filled using a single access. With a blunt end, the cannula is positioned into a safe layer, it is easier to fill the subcutaneous area, and there is a slightly lower chance of vascular or nerve injuries.

In the posterior and anterior mandibular region, access may be made via the mandibular angle to treat the branch of the mandibular, the mandibular angle, and the mandibular body using the fan technique. Medial access to the mandibular body has been shown to address the entire mandibular line.

The mental region can be filled with side access into the center of the mentum direction using a cannula or bolus injection centrally using a cannula or needle.

When the groove of the marionette line and the supramental wrinkle is filled at the dermis, needles are normally used; however, but if it is filled under the skin it is better to use a cannula for the procedure.

For the lips, the use of cannula or needles is possible, and the choice will depend on whether the aim is to volumize or contour (Fig. 20).

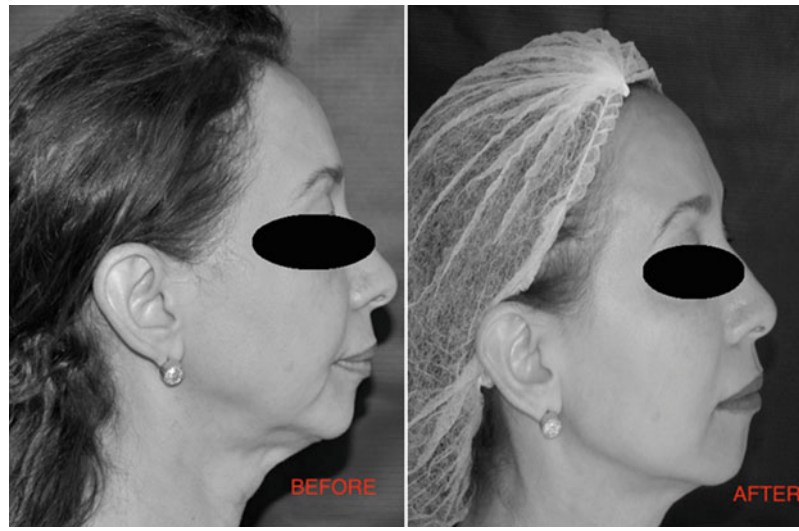

Fig. 22 Before and after

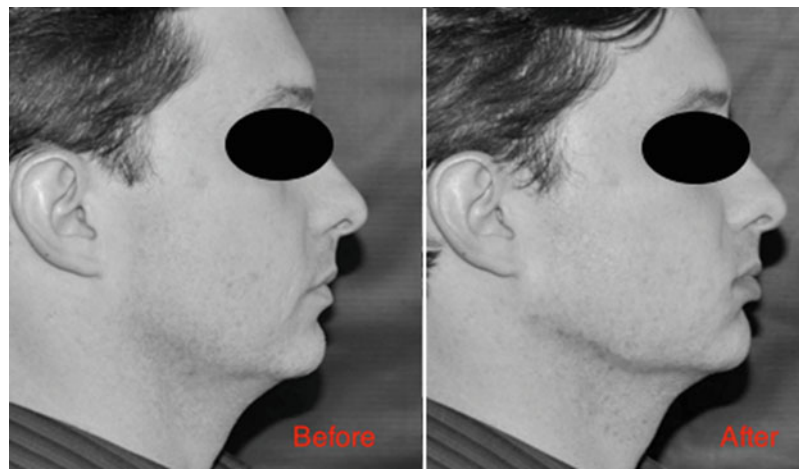

Fig. 23 Before and after

We usually inject high-viscosity HA developed for subdermal or supraperiosteal application using a 21G 40 mm cannula in the subdermal space after topical anesthesia with anesthetic cream (lidocaine + tetracaine); however, anesthetic injection (lidocaine 2%) could be used for the cannula insertion point and create the hole. Alcohol 70% or chlorhexidine should be used for asepsis in areas to be corrected and the anesthetic point is marked with the patient sitting at 45° under adequate lighting to gain a better idea of the sagging and contour of the face (Figs. 21, 22, and 23).

Take Home Messages

- Typical changes to the face during the aging process require therapeutic care such as the use of hyaluronic acid to restore youthfulness.
- Evaluation of changes in the mandibular and facial contours is important for selecting the filler and application sites.

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Hyaluronic Acid for Skin Booster on the Face

Sylvia Ypiranga and Rodrigo Fonseca

Contents

Abstract

Dermis consists mostly of protein fibers and extracellular matrix. Hyaluronic acid (HA) is an abundant glycosaminoglycan, natural compound of dermal extracellular matrix, with high affinity to water. This characteristic is determinant of skin viscoelasticity, hydration, structure, and firmness.

During aging process, collagenesis and elastogenesis are diminished, there are disorganization and degradation of dermic fibers and, finally, it is observed reduced glycosaminoglycans. These phenomena result in reduction of elasticity, density, and resistance of the skin.

Skin booster is a new concept of treatment which promotes a global improvement of the skin, by HA injections in dermis. The objective of this approach is to maintain skin hydration, delaying or reversing aging process, reducing aging indicators associated with loss of mechanical properties, and using small quantities of HA. It can be indicated to young or elderly people, preventing or treating senescence signs.

It is known that, after injected in dermis, HA improve hydration and stimulate collagen production, by mechanical tension, consequent to stretched fibers.

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_23

In this chapter, some aspects of physiological behavior of HA and how it takes part in aging process and skin booster treatment will be discussed.

Keywords
Skin hydration · Hyaluronic acid · Aging · Senescence · Collagenesis · Elasticity · Skin booster · Extracellular matrix · Rheology · Hydrobalance

Introduction

Once fillers and toxins are recognized as antiaging treatments, a new concept emerges – the global improvement of the skin or the skin "booster."

This perception involves rehydration induced by hyaluronic acid dermal injections with fibroblast activation and consequent neocollagenesis.

Hyaluronic Acid and Skin

The dermis consists mostly of protein fibers and extracellular matrix. This combination of fibers and extracellular matrix gives to the skin the viscoelastic properties and its consequent strength and resilience (Distante et al. 2009; Reuther et al. 2010). Types I and III collagen are found at the dermis, but the major structural protein is type I. Photodamaged skin exhibits degradation of these structures and their precursors, by metalloproteinases produced by fibroblasts, keratinocytes, and inflammatory cells (Talwar et al. 1995).

The extracellular matrix at the skin and the connective tissue is constituted by some endogenous polysaccharides and glycosaminoglycans. Among them, hyaluronic acid (HA) is found in highest concentrations at the dermis, and they are not linked to proteins. Besides many functions, HA can bind water up to 1000 times of its volume (Williams et al. 2009), and this characteristic mantains the skin hydration and turgor and is determinant for the skin viscoelasticity and firmness (Wang et al. 2007; Reuther et al. 2010; Streker et al. 2013).

The global aging process – both photoinduced (extrinsic) and genetic (intrinsic) – involves diminished collagenesis and elastogenesis, dermic fibers disorganization and degradation, and, finally, decreased glycosaminoglycans. By this view, it is not difficult to imagine that the aged skin tends to be thinner, less dense, less distensible, and less resistant. An important concept is that once the mechanical tension tends to diminish, it leads to an improvement of collagen degradation, what contributes to the maintenance of de aging process. Comparing elderly to young skin, fibroblasts and collagen fibers are shown in different shapes, with a clear prejudice to their interaction in senescence, where fibroblasts are "collapsed" and fibers are fragmented reducing the collagen production (Wang et al. 2007). The inverse, when induced, also happens.

Once HA is injected into the dermis, with its consequent water binding, it is observed a mechanical tension in the extracellular matrix, stretching protein fibers and stimulating fibroblasts, with an improvement of the collagen synthesis, specially the type I (Wang et al. 2007). Possibly, this mechanical stretching of fibers enhances their interaction with the fibroblasts, raising their collagen production. As a consequence, cutaneous density tends to raise (Fig. 1), resulting clinically in a less roughness and more firmness skin (Distante et al. 2009).

Hydration might help to keep the volume and elasticity of the skin (Wang et al. 2007), but the challenge would be how to maintain the skin hydration with HA. Topical application of HA is not so effective, because there is not a proper penetration down to the dermis due to its large molecule size (Williams et al. 2009). An alternative way to effectively achieve a significant increase in HA concentration in the dermis would be injecting it into the skin within needle or other technique that can deliver the polysaccharide directly into the dermis, respecting its physical or rheological characteristics.

Rheology of HA

Despite its natural occurrence in tissues, HA can be synthesized by biological fermentation. It is necessary to induce some modifications on its

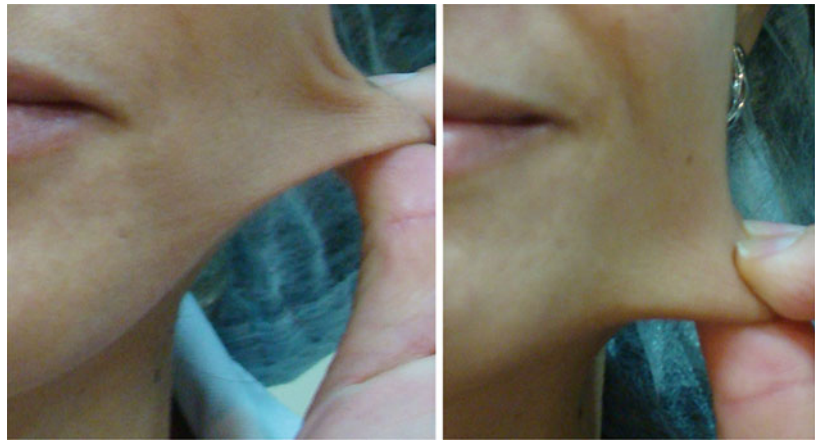

Fig. 1 During the aging process, skin tends to be thinner, less dense, less distensible, and less resistant *(left)*, due to diminished collagenesis and elastogenesis, dermic fiber disorganization and degradation, and decreased glycosaminoglycans, which most prevalent is hyaluronic acid. Because HA is characterized by its high affinity to water, its presence determines skin viscoelasticity, hydration, structure, and firmness. After HA injections, there is water binding, fibroblasts stimulus, and consequent improvement in collagen synthesis. Clinically, cutaneous density, elasticity, and firmness tends to raise (*right*)

structure to guarantee its stability for a period as long as possible, improving its mechanical properties and duration in vivo. Indeed, to reduce the natural degradation by hyaluronidases, there are chemical methods to introduce some cross-links between its chains to obtain a tridimensional network, more stable and still biologically compatible. The final product may differ due to different methods applied by each enterprise, resulting in different products, with physical differences (see chapter ▶ "Hyaluronic Acid Dermal Filler: Physical Properties and Its Indications").

To induce the cross-link formation, it is necessary to bind 2 HA polymer chains using a chemical cross-linker molecule, in which the most used is 1.4-butanediol diglycidyl ether (BDDE). BDDE induces strong covalent bonds and they are irreversible; thus, once stabilized, HA structures is modified permanently (Edsman et al. 2012). Binding these chains, they tend to constitute a three-dimensional network, resulting in a firm gel which shape is identical to the container in which it was formed. After this modification, the gel has to be fragmented into variable-size particles in a size that allows it to be pushed through a needle. The particles are separated by their sizes creating a distinct final product with different physical characteristics, strength, indications, and plan of injection (Edsman et al. 2012).

Rheology is the branch of physics that studies how materials react to forces applied against it, specifically for HA gel; it is focused on its capacity of resistance to deformation. This resistance is directly related to cross-link gradation, concentration, and size of HA particles (Kablik et al. 2009).

- The cross-link gradation is related to density of the gel. It is possible to calculate a ratio of cross-link formed by the total BDDE molecule incubated with HA. As much cross-link is present, denser and consequently stronger is the gel.
- The concentration has to be high enough to retain water, with minimum edema induction. This features may be tied to cross-link gradation, as much cross-link is present, HA molecule occupies less space in gel. Thereby, it is possible to find more or less HA molecule per volume.
- At last, the size of particles determines their capacity of projection or volumizing. Big sizes of HA gel induce bigger projection, which is the ideal, concerning fillers. HA gel with little particles might hydrate the skin without filling or volumizing the area to be treated. The goal, in this case, is to retain a good amount of water in dermis.

Knowing about these HA particularities is important to choose the best product of each indication and to proceed to the correct implantation. So, the bigger the particles are and the higher the density is, the deeper is the ideal plan of HA injection. While HA with smaller particles, less density and concentration should be injected more superficially, in the dermis. A misunderstanding of these details might have serious clinical consequences.

Hyaluronic Acids for Hydration

Understanding HA rheology makes clear how to provide a good HA gel for hydration purpose. Smaller particles may retain much more water, with no volume induction, than bigger ones (Reuther et al. 2010; Succi et al. 2012; Gubanova et al. 2015).

There are few commercial presentations available for hydration of the skin. All of them are made up of small particles of HA, and their concentration ranges from 13.5 to 20 mg/mL. Some of them offer no cross-linked HA and might be combined to another polysaccharide (manitol or glycerol) or not. Another presentation is a compound of cross-linked (stabilized) HA with no association with other products. These specificities imply in differences in techniques used, which will be discussed later.

Mechanisms of Action

Small volume aliquots of HA gel might be injected into the dermis, in multiple punctures; therefore the product should be distributed uniformly thru all the area to be treated. It is easily incorporated to the skin and interacts with native gel in matrix (Streker et al. 2013).

Once injected into the dermis, HA draws water into the matrix and induces it to swell, restoring the skin hydrobalance, creating some volume, increasing skin turgor, and improving its structure and elasticity. (Ribé and Ribé 2011). This also might improve dermal elasticity by stimulating collagen production (Kerscher et al. 2008). Initially there is an enhance of the stratum corneum hydration and the decrease of the transepidermal water loss, related to the water recruitment. After then, cutaneous elasticity improvement is noted and comprehended to an increased production of collagen, noted in 4 to 13 weeks after the injection (Kerscher et al. 2008).

The implantation of HA into the dermis, with consequent water retaining, may lead to some stretching of the fibers. This distention may impose some mechanical tension on nearby fibroblasts, which interact with collagen fibers through cell surface integrin receptors. There are evidences of stimulation of a "de novo" synthesis of the type I collagen by those fibroblasts activated in the dermis (Wang et al. 2007). Hyaluronic gel can improve the hydration and elasticity of the skin, as well as its structure and firmness (Distante et al. 2009; Williams et al. 2009). Considering its stability and its resistance to enzymatic degradation, these treatments can act as a reservoir of long-lasting hydration, sustaining the process of "de novo" synthesis of collagen, resulting in a smooth, soft, more dense with less roughness skin while improving its quality (Fabi and Goldman 2012; Streker et al. 2013).

Both stabilized (with cross-links) and non--stabilized (with no cross-links) hyaluronic gel are effective to promote hydration, improving elasticity and reducing roughness. However, these effects last for a longer period in treatments with stabilized HA gel. The main reason for this is due to the fact that the cross-links achieved in the stabilization process prevent a quick degradation of the HA by physiological hyaluronidases in the skin. In this way, HA persists for a longer period interacting to the extracellular matrix, also stimulating fibroblasts for a longer period, acting as a reservoir of a long-lasting hydration and collagenesis stimulus (Streker et al. 2013).

Different concentrations and associations with other polysaccharides should be considered among different HA for hydration. Glycerol and manitol are polysaccharides mainly responsible for attracting and retaining water molecules. They might enhance the potency of HA, especially those with no cross-links, promoting longer-lasting skin hydration. Concerning

concentrations, it is expected that the higher the concentration of HA is, the more intense should be its biological effects. The amount of water retaining is proportional to the HA concentration. Thus, whenever the skin to be treated is too thin or when treating young people, low concentration presentation might be used. In the first case, the risk of papule formation or mild to moderate edema justifies the choice. Eventually, after few sessions, with global improvement of the skin, the same patient could receive higher concentrations of HA. Those young patients, which treatment objective is aging prevention, may benefit by lower concentrations, enough for hydration maintenance.

Indications and Contraindications

Skin booster treatments are indicated to prevent and treat global aging events. Indeed, every adult can be treated, usually between 35 and 75 years old. Among young people, it may be useful to prevent aging process, maintaining skin hydration and turgor, before roughness onset. For elderly people, its use may improve some already established aging effects, as laxity, wrinkles, skin thinning, and elasticity loss, in variable intensity. It is a good choice for those patients seeking a minimally invasive procedure to improve the appearance of the skin, as this approach offers gradual changes in skin.

Any area of the body can be treated, specifically:

- At face: chins, perioral area, periocular area, frontal area, lips, and acne scars (Fig. 2)
- Neck and décolletage
- Hands and arms
- Knees

It is possible, and even recommended, to associate with other treatments, as botulinum toxin, ablative or non-ablative laser, intense pulsed light, radiofrequency, focused ultrasound, peeling, etc. These treatments might reinforce the described effects of the skin booster treatment or act as complimentary, treating other necessary fields on photoaging, as dynamics wrinkles and pigmentations.

Fig. 2 Facial areas can be treated with hyaluronic acid for skin booster – schematic plan

As HA-based fillers, skin booster treatments are contraindicated in patients with any infection, active acne, and autoimmune disease. It is necessary to take an extra care treating areas where long last filler was injected and avoid to treat areas with any previous definitive filler.

- Presentations and techniques of injection

There are some different commercial presentations of HA gel for hydration and skin booster treatment. In common, they comprise small-size particles of HA, the special characteristic to guarantee the skin hydration. As previously said, they differ from each other in concentration of HA, presence or not of cross-links and if they are associated with other polysaccharides. Some of the presentations and their specifications are listed in Table 1.

Respecting these rheological differences, the injection layer is also different. Presentations with no cross-links might be applied more superficially, in the dermis, resulting in small transitory, visible papules. On the other hand, stabilized

Table 1 Presentations of HA for Hydration and skin booster treatment

Product	Manufacturer	Stabilized (with cross-links)	Concentration of HA (mg/mL)	Polysaccharide associated	Application level
Juvederm hydrate™	Allergan	No	13.5	manitol	Superficial dermis
Mesolis™	Anteis	No	18	glicerol	Superficial dermis
Teosyal Meso™	Teoxane	No	15	No	Superficial dermis
Vital light™	Q-Med	Yes	12	No	Middermis or deep dermis
Vital™	Q-Med	Yes	20	No	Deep dermis

presentations have to be applied deeper, regarding different concentrations, as shown on Table 1.

All of them are provided in prefilled disposable 1.0-mL syringes supplied with 30-gauge sterilized needles. It is possible to use thin cannulas (30-gauge or 27-gauge, p.e.), alternatively to needles, when using stabilized HA. As non-stabilized HA has to be placed at superficial dermis, the only way to achieve this level is with needles.

Once treatment had been indicated, it should be recommended to take pictures of the patient in advance for documentation, concerning the fact that results occur gradually.

After topical anesthesia, with lidocaine 4% cream or lidocaine 7% with tetracaine 7% cream, p.e., the area to be treated must be cleaned and disinfected with antiseptic solution. When choosing stabilized HA, the injection technique might be as series of punctures or as retroinjection, placed approximately 1 cm apart. It is important to deliver small volume aliquots, approximately 0.02 mL per puncture (Kerscher et al. 2008). Retroinjection is safer, once it is easier to control the level of application, avoiding papules formation; furthermore, it permits a better distribution of the product.

The injection should be oriented perpendicular to the "broken lines" of the skin or forming cross shapes, always delivering very small quantities of product. If skin laxity is not so intense, it should be difficult to visualize such "broken lines"; thus, it is possible to perform a movement pushing and sliding the skin against gravity, identifying less resistant areas assuming the position of the "future broken lines", where the product should be injected, in the same way (Fig. 3).

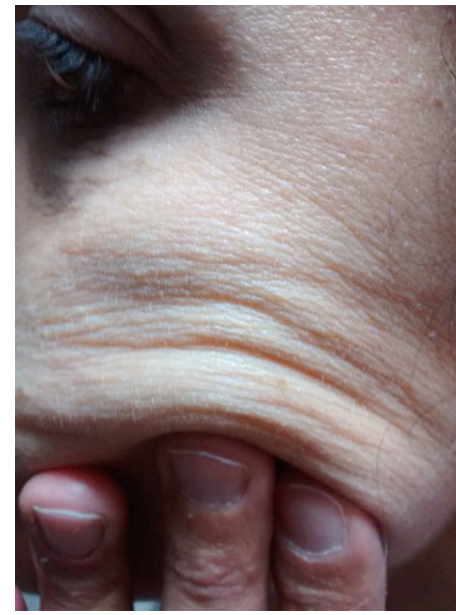

Fig. 3 Maneuver to identify "broken lines", to inject hyaluronic acid for hydration

With non-stabilized HA, the chosen technique has to be the series of superficial punctures leaving as a result, translucent visible micropapules on the skin surface with very small quantities of the product. It is important to remember that these papules usually persist for 5–7 days.

It is recommended to delimitate the area to be treated prior to the injections to perform a good plan of application with a uniform distribution of product recovering the whole area. Usually, when treating facial area, both lateral sides and chin should be treated, with top-down and lateral-medial approach, with retroinjection or multiple puncture (Fig. 4). Frontal region approach might

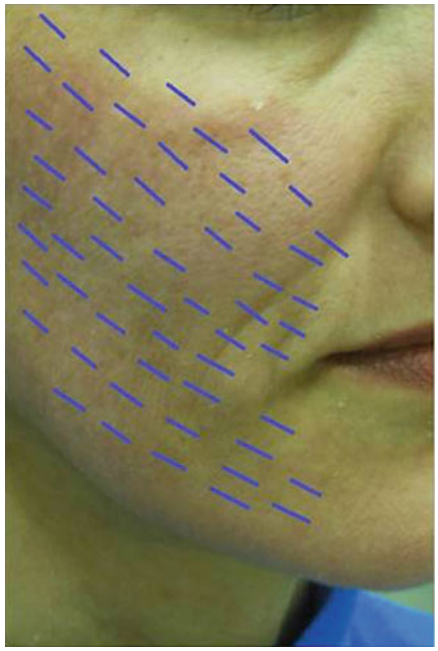

Fig. 4 Plan of application, recovering lateral and chin

be performed with serial punctures or retroinjections directly in lines, respecting application plans (Fig. 2).

Perioral area is another common and great area for skin booster treatment, as volume is undesirable at this site and it is a target for marked wrinkles. Because it is a painful region, it is recommended to proceed a locoregional block nerve anesthesia, few minutes earlier. The technique of injection is quite similar, regarding the deepness of application due to the elected type of HA. Once again, inducing papule formation, with non-stabilized HA, and deep dermis retro injection against lines, when using stabilized one, always in small amounts per puncture.

It is also important to use locoregional block nerve anesthesia to approach the lips. Aging process also involves lips, and, if there is no great loss of volume and no indication for fillers, hydration wit HA is a good option, especially with its stabilized form. Otherwise, if there is indication for fillers, they are best choice, because besides filling lips, they may act as boosters too. The injection technique is the same, placing very small amounts of product above the muscle and under the lips semi-mucosa.

Periorbital area comprises a very thin skin and should be treated with special care especially when using stabilized HA. As non-stabilized HA itself lasts for a short time, it can be used at this site, in the same way with multiple superficial punctures. However, stabilized HA persists for a longer period, and, if placed superficially, may lead to long-lasting visible papules or nodules. In this case, it is recommended to use a cannula to place the product deeper, even under dermis, with minimum risk of vascular occlusion accidents or bruising. At last, if periorbital skin in question is very thin, it is recommended to use a low concentration HA. Treating periocular area and lips is considered an advanced approach and should be performed after acquiring some experience with other areas techniques.

Cannulas should be used instead of needles, with less risk of vein or artery injuries. It is recommended to use 30 to 27-gauge cannulas performing an entry aperture with a little more calibrated needle. Using injectable local anesthesia prior to procedure is optional, but encouraged for patient comfort. As cannulas slide better in subcutaneous fat, in this technique HA is placed just above the dermis, in the superficial subcutaneous fat. That is the reason why its use is preferred when the skin is thinner, as periorbital areas, for example, whereas results of improvement are earlier evident in other areas that are treated with needle technique. Nevertheless they can be used for all facial areas taking these details in consideration. Whenever using cannulas, the product should be delivered slowly and still in small amounts, but with fan technique. It comprehends many retroinjections for each entry point. Usually, for a full face treated with cannula, up to four injection points might be needed, and it is necessary to take care with the HA amount delivered due its bigger length and gauge.

The use of cold packs at the injection area to avoid excessive redness and bruising is a good practice. In this field, it is important to check, when selecting the patient, if there is any clinical history of coagulation disease or use of anticoagulant medications. In these cases, cannula technique is the best option of approach.

There are some protocols suggested regarding best results and time for maintenance of the

effects. Initially, three sessions are indicated within 4 weeks apart. Once obtained the desired improvement, one session should be repeated, to maintain these results, every 3 to 6 months, for non-stabilized and stabilized HA, respectively. In severe cases of elastosis, extra sessions might be necessary to achieve good results, prior to the maintenance phase. It is possible to associate complementary treatments to improve the final result, as suggested in Table 2.

Skin booster treatment enhances global elasticity and firmness, turning the skin smoother with a better appearance. It may reduce the roughness and soften folds but does not replace a real volume (Figs. 5 and 6). In these cases, treatments with fillers should be considered after initial results of three-session protocol or even at same time. Combined treatment may improve results extending its effects for longer lasting (Ribé and Ribé 2011)

Table 2 Associated treatment protocol

Associated treatment	Protocol
Botulinum toxin	15 days apart
Superficial peeling	Alternate peeling and skin booster every 15 days Starting by the peeling
Medium peeling	20–30 days before first session of skin booster
Radiofrequency	15–20 days before first session of skin booster
Intense pulsed light (IPL) or fractional laser (FL)	Alternate IPL or FL and skin booster every 20 days Starting by the IPL or FL

Side Effects and Their Managements

Mild to moderate pain related to injection usually occurs but is well tolerated. It is recommended to use topical anesthesia to diminish this discomfort. Ice bags immediately previous each puncture may be helpful.

Edema may occur after each session and can last up to 7 days. It is common with non-stabilized HA treatment and is correlated to duration of papules. Clinical edema may occur, but it is less measurable when stabilized HA is used. Skin bruising and redness are frequent and usually resolve within 1 to 2 weeks after product administration. Once again, ice packs should be useful to preventing hematomas (Streker et al. 2013).

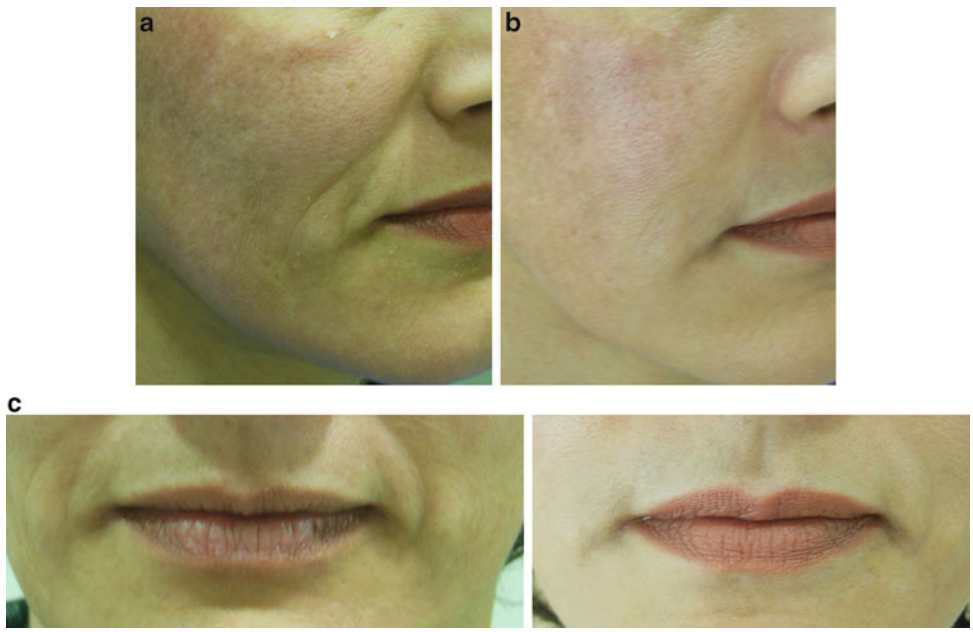

Fig. 5 Result 1 month after three session of HA acid for skin booster, with global skin improvement, restoring facial contour (**a** and **b**) and diminishing nasolabial folds (**c**)

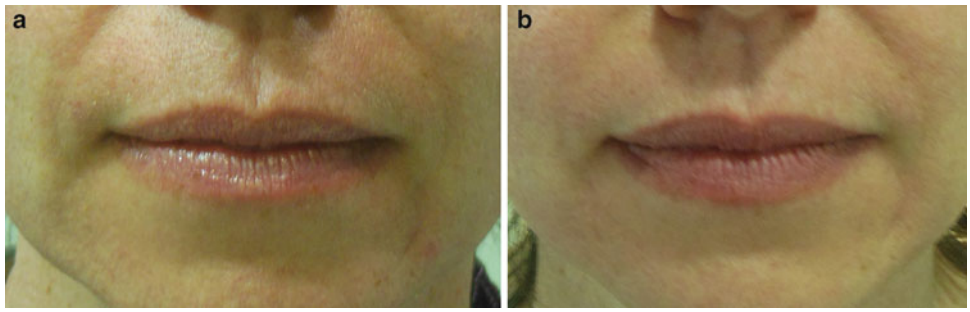

Fig. 6 (**a** and **b**) Result 2 months after three-session HA acid for skin booster associated to botulinum toxin and 1 month after nasolabial HA filler

Small- to medium-sized papules occur always after non-stabilized HA injection, and they are desirable, as part of technique. They might last for 5 days per session but with stabilized HA; these papules are considered side effects and should be avoided when stabilized HA is used. If they occur, they are related to the technique as a result of a wrong placement of product. Besides been visible they may last longer and for a variable period. If occasional lumps occur, immediately after injection, they have to be massaged. If they become persistent, they should be treated with hyaluronidase infiltration.

Like all injectable treatment, it is mandatory to respect anatomy of the involved area, especially those of higher risk. It is also important that prior to inject the product it is advisable to aspirate and check if there is a reflux of blood avoiding accidental intravascular injection. Because of the small amount injected per puncture per session, vascular occlusion or compression are not common.

At last and still important is to deal with unreal expectative. It is mandatory to explain exhaustively all details before treatment. Those explanations include indications, objectives, gradual results, and possible adverse events.

Take Home Messages

- Skin boosters are performed by HA, as a skin care treatment, not as a filler.
- It restores and maintains skin hydration, elasticity, and density, by stimulating de novo collagen synthesis. Sustained hydration leads to a mechanical tension and stimulates fibroblasts to produce collagen, type I, specially.
- It can be indicated to everyone between 35 and 75 years old. It can be used at the face, including periorbital and periocular areas, neck, *décolletage*, hands, and other areas.
- Both stabilized and non-stabilized HA promote hydration and enhance of elasticity, but stabilized ones trend to keep its effects for a long-lasting period.
- Respect rheological characteristics of HA chosen. Avoid papule formation when using stabilized HA, applying it in deep dermis. Whenever using a non-stabilized HA, apply it more superficially, in dermis.

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Hyaluronic Acid for Skinbooster® on the Neck and V Shape Neckline Area

Guilherme Bueno de Oliveira and João Carlos Simão

Contents

Abstract

The neck and "V" shape neckline area also undergo skin aging with dark spots, dilation of vessels, change of coloration with loss of brightness, copper appearance, and formation of vertical lines. There are numerous therapeutic options available to treat the region, and hydration or "skinbooster®" with uncrossed hyaluronic acid is of great value. Injection of uncrossed hyaluronic acid into the skin promotes a high degree of hydration from the inside out. They have been specially developed for skin hydration and are different from the fillers to hyaluronic acid base, which increase and replenish volumes. Skinboosters® do not increase volume or fill furrows, but they restore skin's luster, smoothness and hydration, and soften fine lines and special areas such as the neck, "V" shape neckline, and

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_24

eyelids. This chapter is going to describe the concept, indications, and skinbooster® procedure to treat the neck and V shape area.

Keywords
Hyaluronic acid · Skinbooster · Hydration · Wrinkles · Neck

Introduction

The skin is an organ where precisely regulated cellular and molecular interactions govern many of the aggressions from the environment.

The aging of the skin is a complex process, physiological, multifactorial, and progressive. It may be intrinsic, chronological, or extrinsic. The genetic material changes through enzymes, structural protein changes, and cell proliferation decreases. Consequently, the tissue loses elasticity, the ability to regulate nutrient and gas exchanges, and tissue replication becomes less efficient. Chemical and enzymatic oxidations involving the formation of free radicals accelerate this phenomenon of aging.

Free radicals are molecules made up of an unpaired electron in its outermost orbit. This situation implies high-energy instability, and, in order to remain stable, they must donate or withdraw an electron from another molecule. The formation of free radicals by environmental stimuli, such as exposure to UV rays, pollution, smoking, and metabolic processes, leads to oxidative stress, a process in which they initiate a chain of reactions, leading to changes in extracellular proteins and cellular modifications. These are expressed on the skin as degradation of collagen and elastin and decrease of glycosaminoglycans.

Hyaluronic acid is the most important glycosaminoglycan, possessing the ability to bind to water, giving a smooth and elastic texture to the skin (Stocks et al. 2011). Thus, its decrease in aging skin results in less firmness, greater dryness and pallor, increase in fine lines, and the degree of sagging.

All previously mentioned factors, such as photodamaged and chronologically aged skin, could be recovered with uncross-linked hyaluronic acid. The hydration of the skin is extremely important for the prevention of wrinkles, improvement of coloration, brightness and flaccidity. Maintaining tonus, elasticity, and firmness implies a youthful appearance.

The region of the neck and "V" shape neckline area also undergoes skin aging with the formation of spots, dilation of vessels, change of coloration with loss of brightness and copper appearance, and formation of vertical lines and checkered appearance on the spot. There are a number of therapeutic options available to treat the region, the hydration treatment with uncrossed hyaluronic acid or skinbooster® being of great value (Bertucci and Lynde 2015).

Skinboosters®

Boosters can be understood as "intensifiers." They are special products based on uncross-linked hyaluronic acid, with or without other substances in the composition, such as mannitol.

The concept of skinboosters® is to replenish the collagen and hyaluronic acid lost with aging, as well as other substances and fibers responsible for firmness, tonus, elasticity, and hydration.

Injection of uncrossed hyaluronic acid into the skin promotes a high degree of hydration from the inside out (Beer et al. 2015). They have been specially developed for skin hydration and are different from the fillers to hyaluronic acid base, which increase and replenish volumes. Skinboosters do not increase volume or fill sulcus, but they restore skin's luster, smoothness, hydration and soften fine lines and special areas such as the neck, "V" shape neckline area, and eyelids.

Presented in Table 1 are the main products used in the skinbooster technique.

Indications

The indications for hydration of the neck and V shape neckline area are summarized below:

Table 1 Main commercial products

Product	Company	Composition	Indication
Hydrate	Juvéderm®	AH = 13,5 mg/mL Mannitol (an antioxidant that prevents the accumulation of free radicals that degrade hyaluronic acid in addition to prolonging the effects of treatment)	All the areas
Restylane Vital	Galderma®	AH = 20,0 mg/mL	Mature skin
Restylane Vital Light	Galderma®	AH = 12,0 mg/mL	Young skin
Mesolis +	Anteis®	AH = 18 mg/mL e Glycerol 21 mg/mL (prolong treatment effect by having moisturizing effect) Note: it must be done in a more superficial plane	All the areas
Teosyal Meso	Teoxane®	AH = 15 mg/mL	All the areas
Stylage Hydro	Stylage®	AH = 14 mg/mL Mannitol	All the areas

For mature and photoaged skin:

- For vertical, horizontal, or figurative patterns of wrinkles of the region, fixed and dynamic wrinkles
- For thin, slightly elastic skin and with opaque coloring
- For dehydrated skin
- Adjuvant to technologies, being used 30 days before or 10 days after the use of technologies.

For young skin:

For prevention of wrinkles

For thin, dehydrated, slightly elastic, and opaque skin

To prevent the formation of stretch marks when used 30 days before the placement of a breast implant

Contraindications

The contraindications are few and are listed below:

- Active infection on site.
- Allergy to any component of the formula.
- Pregnant.
- Breastfeeding.
- Carriers of autoimmune or mucinous diseases.
- Patients with behavioral disorder.
- It is not recommended for patients who use anticoagulant or who have coagulation disorder due to the high chance of bruising in the place but can be performed if the patient is not anticoagulated at the time of injection. This contraindication is relative.

Method of Application

Anesthesia

Topical anesthesia with lidocaine 70 mg/g with tetracaine 70 mg/g 15 min before the procedure is sufficient, as it is a simple and painless procedure.

Application Techniques

Each professional prefers a different method to perform the application of AH as skinbooster in the neck and "V" shape neckline area (Brandt and Cazzaniga 2008).

The techniques described are:

- Micropunctures or micropapules (Fig. 1): 30G needle with 90 degree angled entry and 1 cm distance between the points. The application layer is dermal.

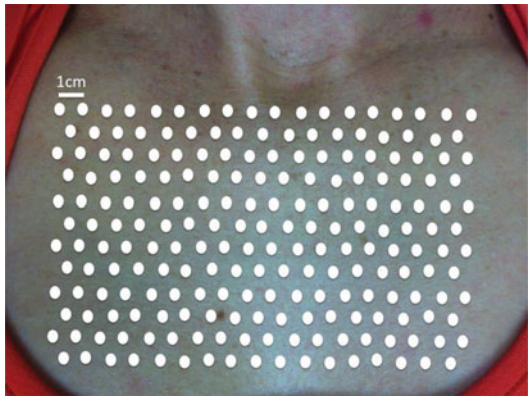

Fig. 1 Micropapules technique

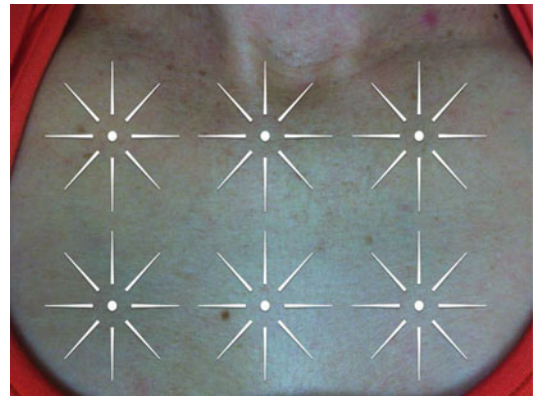

Fig. 3 Microcannula technique

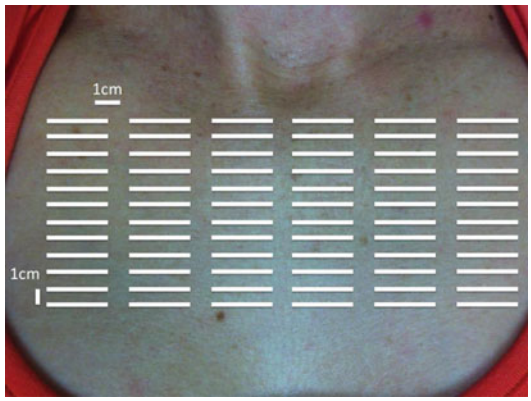

Fig. 2 Toothpick technique

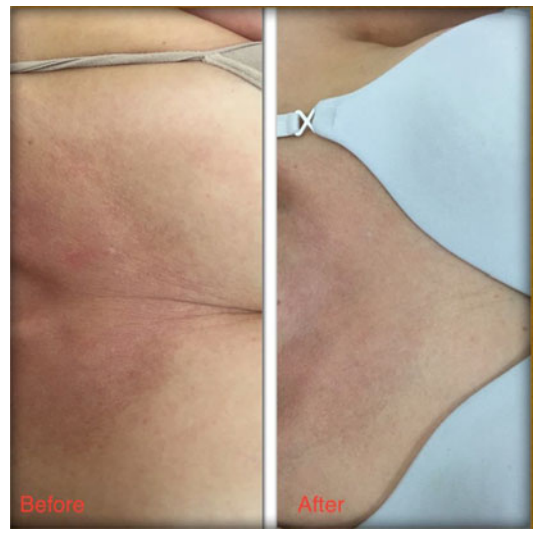

Fig. 4 V shape neckline area: *before* and *after* 1 month of the last session. Treated with three sessions with 30 day interval with two Hydrate® syringes in each session

- Toothpick technique (Fig. 2): 30G needle with dermal layer entry, which, in anterograde or retrograde injection, distributes AH in the region. The distance between the sticks should be 1 cm. The insertion of the needles should be perpendicular to the lines.
- Use of microcannula (Fig. 3): this can reach larger areas with a single point of entry into the skin. Through an orifice, the HA is placed with 25G or 27G microcannula and distributes it in the region. The distance between the holes must respect the length of the microcannula.

Marking the Area

The area to be treated with non-cross-linked HA should be labeled according to the choice of the application technique described above. Notice the differences in Figs. 1, 2, and 3.

Treatment and Maintenance Interval

The treatment protocols vary according to diagnosis and the degree of photoaging (Gold 2007). They can be performed every 15 days, totaling four sessions or even one per month, for 3 months. The final result can be seen after these sessions (Figs. 4 and 5).

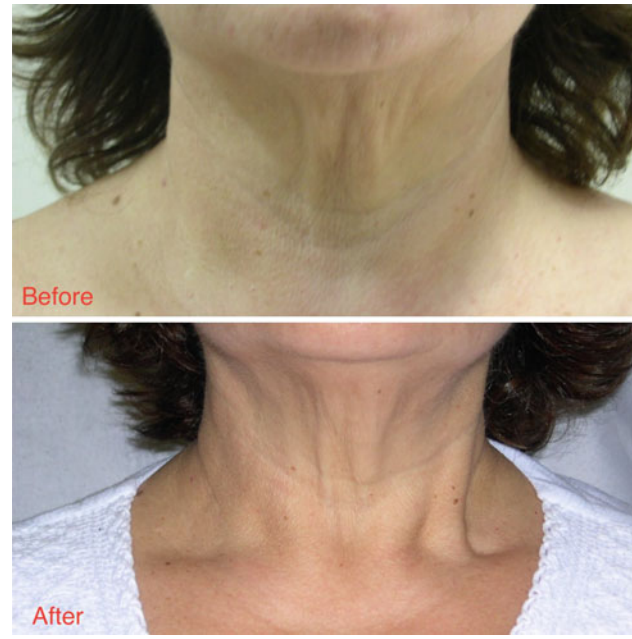

Fig. 5 Neck: *before* and *after* 1 month of the last session. Treated with three sessions with 30 days interval with two Hydrate® syringes in each session

The maintenance should be done every 4 or 6 months, with one or two sessions, depending on the degree of aging.

Side Effects and their Managements

Side effects do not differ from those produced during a mesotherapy session (Crocco et al. 2012).

Early Side Effects

- Erythema and edema: usually are immediate and observed in most cases. They occur by local inflammation and by the hydrophilic property of the product. They can be further aggravated by multiple injections, thick material, and incorrect application technique (Junkins-Hopkins 2010).
- Bruising: occurs by perforation of small vessels at the site of application or by compression and secondary rupture of vessels.
- Infection: probably due to product contamination or inadequate patient asepsis technique (Van Dyke et al 2010). It may be of bacterial or viral origin.
- Formation of papules and nodules: usually observed in the short and medium term, it manifests as whitish or normochromic papules, or nodules. They occur most often due to poor application technique by very superficial injection of HA. Because of the Tyndall effect, the papules may have a slightly bluish color.

Delayed Side Effects

- Granulomas: arise as non-painful palpable nodules in the application path of the fillers. It is believed that these reactions occur by the presence of impurities in the process of bacterial fermentation in the production of hyaluronic acid and not due to hypersensitivity to the product itself. The formation of granulomas after fillers can be deepened in the review article by Ghislanzoni.
- Allergic reaction: described in 0.1% of the cases, it starts between 3 and 7 days after the application of the product, however, which may extend up to one to 6 months. Clinically, there is edema, erythema, and hyperemia in the application path of the filler.
- Hypertrophic scar: it appears in the puncture sites of the skin.

Take Home Messages

- The region of the neck and "V" shape neckline area also undergoes skin aging with the formation of spots, dilation of vessels, change of coloration with loss of brightness and copper appearance, and formation of vertical lines and checkered appearance on the spot.
- Hyaluronic acid is the most important glycosaminoglycan, possessing the ability to bind to water, giving a smooth and elastic texture to the skin. Thus, its decrease in aging skin results in less firmness, greater dryness and pallor, increase in fine lines, and increase in the degree of sagging.
- Injection of uncrossed hyaluronic acid into the skin promotes a high degree of hydration from the inside out. They have been specially developed for skin hydration and are different from the fillers to hyaluronic acid base, which increase and replenish volumes.
- The indications of skinbooster® to the neck and "V" shape neckline area are summarized for vertical, horizontal, or figurative patterns of wrinkles of the region, fixed and moving wrinkles; for thin, slightly elastic skin and with opaque coloring; for dehydrated skin and adjuvant to technologies.
- The treatment protocols vary according to diagnosis and the degree of photoaging. They can be performed from applications every 15 days, totaling four sessions or even one per month, for 3 months.

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Calcium Hydroxylapatite to Treat the Face

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Contents

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Abstract

Face rejuvenation is a wide concept and involves not only, but mostly, volume restoration of mainly fat and bone. With aging, subdermal fat and dermis thickness diminish at the extremities, and in the face, the dermis

M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_25

thickens and loosens. Many different fillers can be used to restore facial volume, and each of them has advantages and disadvantages. In this chapter, we describe the use of calcium hydroxylapatite (CaHa) as a secure and effective product to be used to not only restore volume but also stimulate neocollagenesis.

Keywords
Calcium hydroxylapatite · Fillers · Volume restoration · Biostimulation · Neocollagenesis

Introduction

Face rejuvenation is a wide concept and involves not only but mostly volume restoration of mainly fat and bone (Fitzgerald and Rubin 2014). Although subdermal fat disappears and the thickness of the dermis diminishes at the extremities with aging, in the face, the dermis thickens and loosens (Pellacani and Seidenari 1999). Calcium hydroxylapatite (CaHA) is a mineral constituent of bone and has been used in various medical applications for more than a decade. Like hyaluronic acid (HA), CaHA is non-immunogenic. CaHA gel is more palpable than HA derivatives, especially if injected too superficially. To prevent bumps and lumps, injection is preferably performed subdermally or deeper according to the anatomic area. To avoid side effects, anatomy knowledge is crucial, and understanding anatomy of the aging process is even more important (Radiesse Datasheet 2006; Hirsch and Stier 2008; Casabona and Michalany 2014; Murray et al. 2005).

Basic Concepts

Calcium Hydroxylapatite

Calcium hydroxylapatite (CaHA) is a mineral constituent of bone and has been used in various medical applications for more than a decade. The only FDA and CE approved is Radiesse[R] manufactured by Merz Pharmaceuticals GmbH, Frankfurt, Germany. Like hyaluronic acid (HA), this naturally occurring substance is non-immunogenic. It is composed by a suspension of 30% calcium hydroxylapatite microspheres (25–45 μm) in a 70% gel consisting of 1.3% sodium carboxymethyl cellulose, 6.4% glycerin, and 36.6% sterile water for injection. CaHa contains a prefilled syringe with 1.5 cc of material. It should be stored at room temperature (15–32 °C) and expires 2 years from the date of manufacture (Radiesse Datasheet 2006; Murray et al. 2005).

The size of the particles and the particle surface are particularly important since it is described that particles smaller than 15 μm can be phagocyted and migrate to lymph nodes, and irregular surfaces are better recognized by the macrophage to be phagocyted (Hirsch and Stier 2008; Murray et al. 2005). No skin testing is required before use, as a CaHa implant is immunologically inert. A CaHA gel is more palpable than HA derivatives, especially if injected too superficially. To prevent bumps and lumps, injection is preferably performed subdermally. The product is radiopaque, so if the patient was injected with a large amount of the product, such as the patients injected for lipoatrophy correction, it could be seen in an X-ray, computed tomography (CT) scan or magnetic resonance imaging (MRI) (Fig. 1).

Histology

Histologically, CaHa stimulates almost no foreign-body reaction, but depending on the patient, it can occur. No granuloma reaction was shown after 6 months of biopsies (Casabona and Michalany 2014; Berlin et al. 2008; Marmur et al. 2004) (Fig. 2a, b). At 1 month after injection, fibrin and scant cellular tissue surround the microspheres, which appear smooth and uniform, without evidence of inflammation. (Fig. 3a) At 3 months, a fine outer capsule consisting of fibrin, fibroblasts, and macrophages surrounds the microspheres (Fig. 3b). The microspheres become deformed, appearing irregular, and start to be adsorbed after

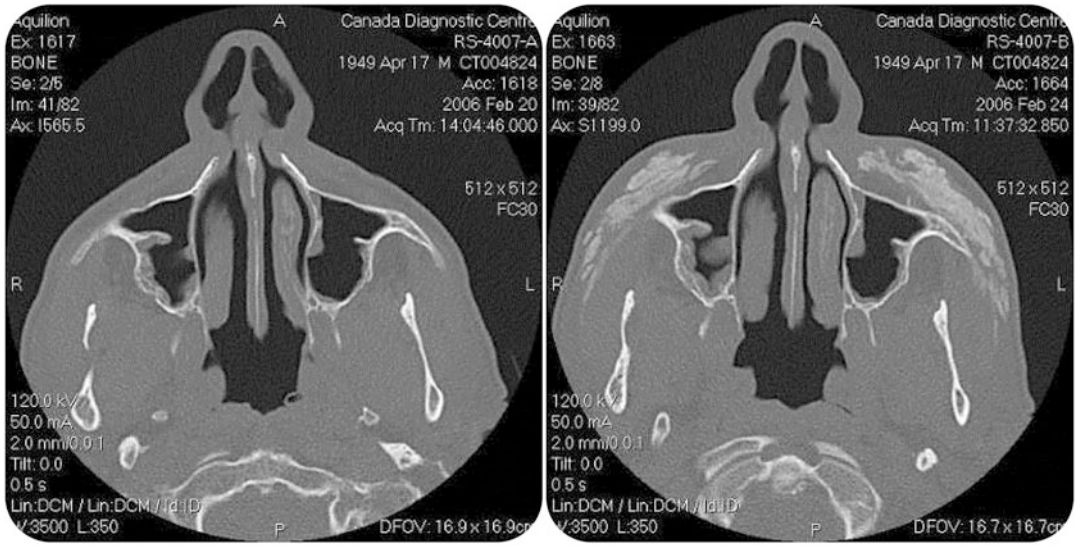

Fig. 1 Imaging of CT scan pre and post CaHa

9 months, likely because of enzymatic breakdown of the calcium hydroxylapatite (Fig. 3c); however, electron microscopy shows calcium particles extracellularly and microspheres within macrophages (Lemperle et al. 2003) (Fig. 4).

Biostimulation and Degradation Process

As mentioned above, the particles undergo an enzymatic breakdown, and macrophages around it start to phagocyte ions phosphate and calcium, following the same metabolic pathway as bone debris resulting from orthopedic surgery or common bone fractures (Drobeck et al. 1984) (Fig. 5). As a result of chemotaxis of macrophages, an inflammatory cascade starts bringing fibroblasts, as in a healing process, leading to collagen and elastin production (Murray et al. 2005).

Fibroblasts are found in all connective tissues, and CaHA microspheres are thought to elicit their activation and subsequent collagen production regardless of the level of injection. Macrophages are 25–30 μm and can ingest up to 25% of their volume per hour. Particle size is important in phagocytosis, but size is not the sole determinant of effective phagocytosis. In the case where the particle volume is greater than the volume of a macrophage, macrophage aggregation is required and foreign-body giant cells are formed, but it does not mean that it will lead to a granulomatous reaction (Lee and Kim 2015).

Animal studies have shown that this new collagen growth occurs as early as 4 weeks post-injection and continues for at least 12 months (Loghem et al. 2015a). Most of the collagen formed is type III collagen, and a fibrotic tissue can be seen in all surrounding areas. Then collagen type I gradually replaces type III (Yutskovskaya et al. 2014). In a study published in 2014, biopsies were taken a month after injection, and it showed a significant collagen and elastin formation (Fig. 6) (Casabona and Michalany 2014; Drobeck et al. 1984; Loghem et al. 2015a; Yutskovskaya et al. 2014).

Duration

The effects of Radiesse have been reported to last from 2 to 7 years, (Marmur et al. 2004; Narins and Bowman 2005), although the clinical effects can disappear as early as 6–9 months (Broder and Cohen 2006). Other articles showed duration of 12–24 months but suggest that in order to have a

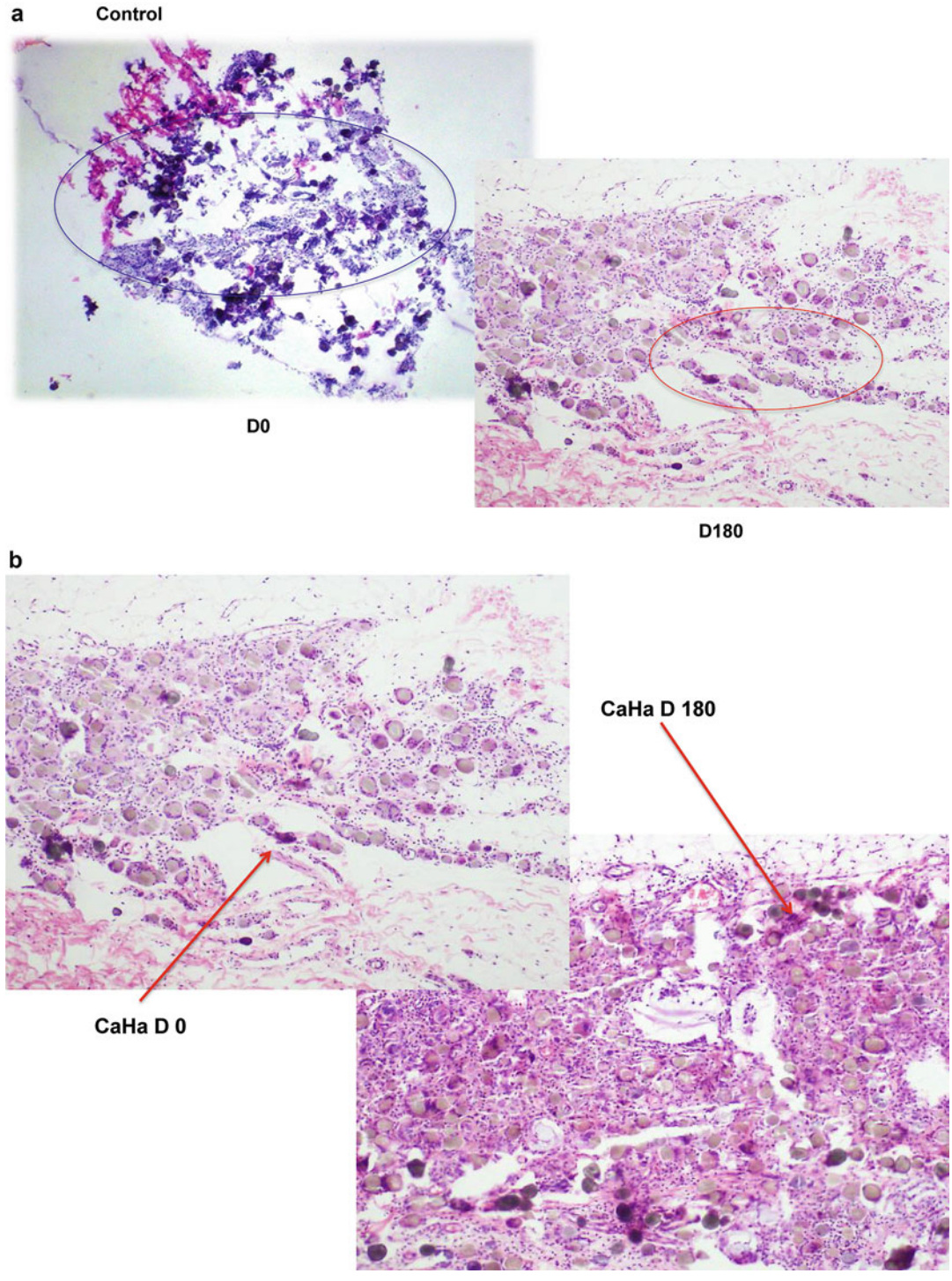

Fig. 2 (**a**) Follow up of 6 months biopsies of CaHa showing no granuloma reaction but some foreign body giant cells around the implant. (**b**) Follow up of 6 months biopsies of CaHa showing no granuloma reaction but some foreign body giant cells around the implant

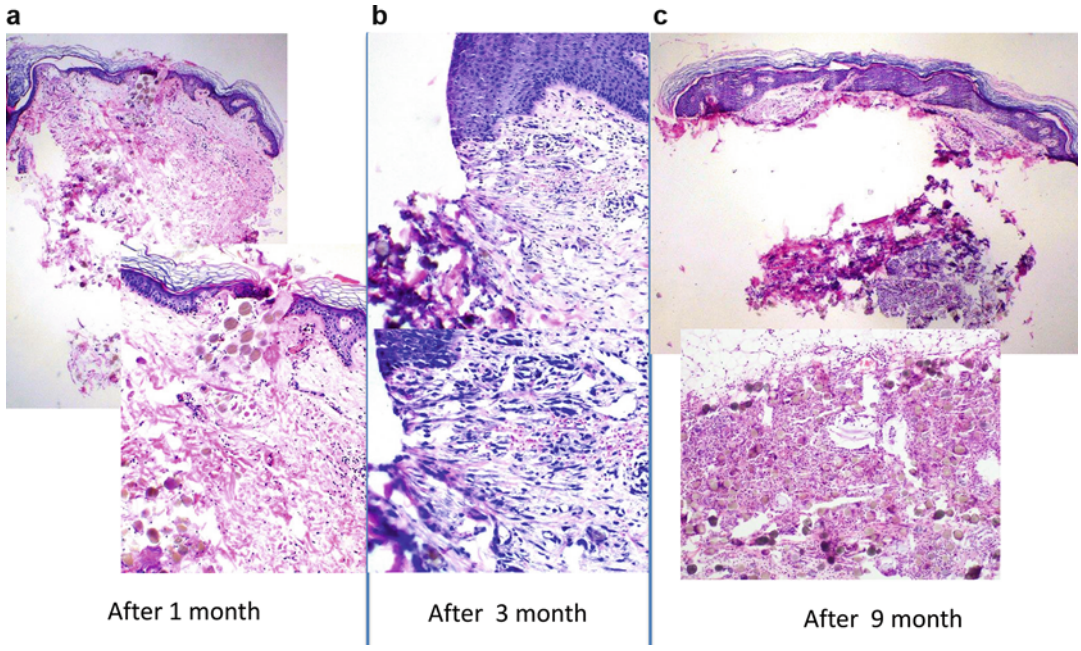

Fig. 3 (**a**–**c**) CaHa injection site. (**a**) Biopsy a month after, (**b**) Biopsy after 3 months after, (**c**) Biopsy 9 months after (Stained H&E)

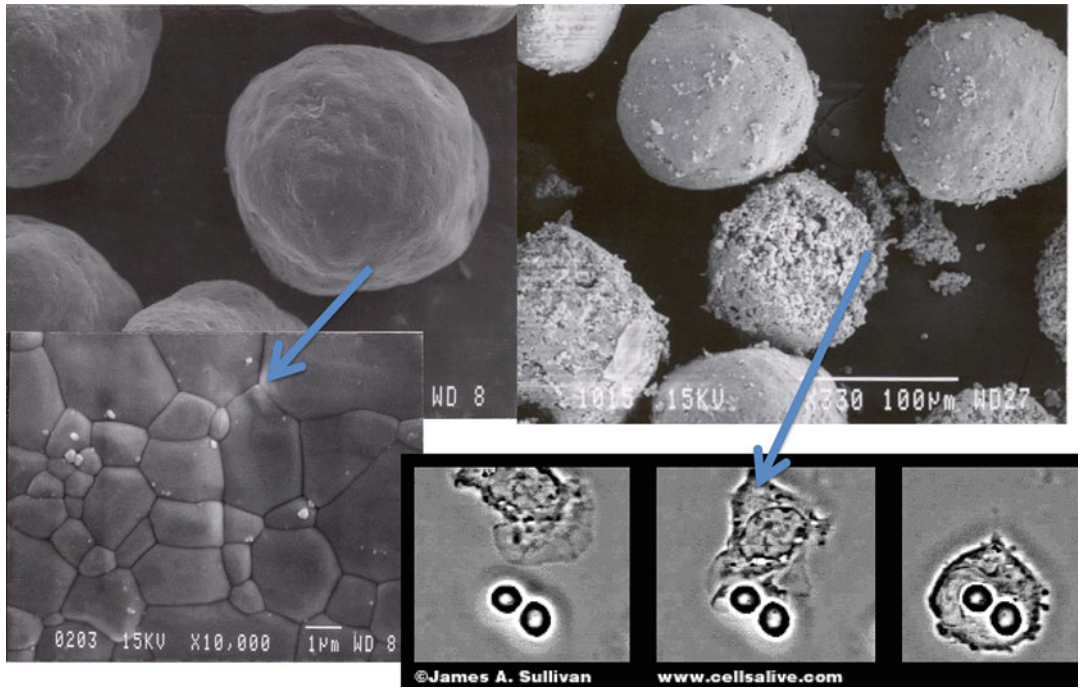

Fig. 4 Electron Microscopy showing CaHa surface and degradation process along 18 months

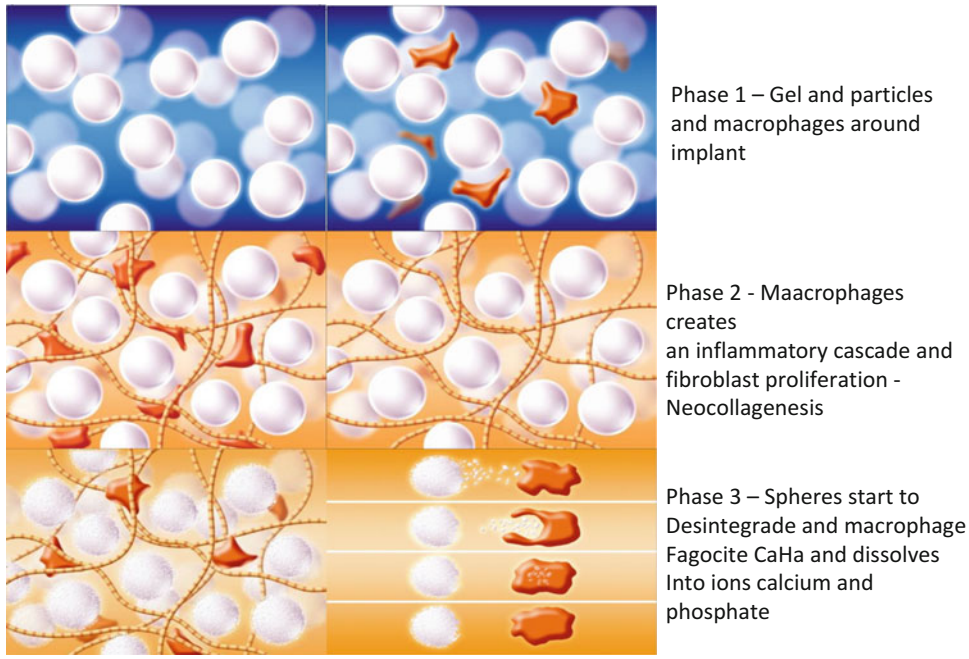

Fig. 5 Scheme of bioestimulation and degradation process of CaHa and cells envolved

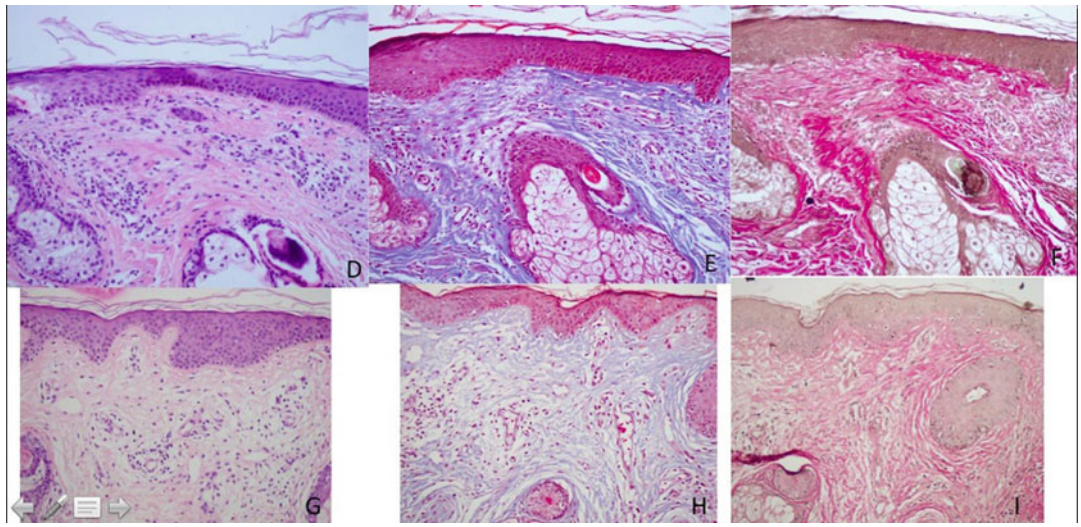

Fig. 6 Biopsy a month after CaHa injection site (**d**–**f**) versus an non injected site (**g**–**i**) stained with H&E, Masson T and Verhoeff showing a significant collagen and elastin stimulation on the injected site

better idea of the final amount, the session should be divided in two, 1 month apart (Jansen and Graivier 2006). Efficacy has been demonstrated, with 87% patient satisfaction within an 18-month follow-up period (Jacovella et al. 2006). In our experience of more than 1,000 injected patients, we recommend to tell the patients that CaHa implant may last around 9–18 months.

Fig. 7 Areas with CE and FDA approved indications

History

Prior to its use in the dermatology field, CaHa has been used in dentistry and reconstructive surgery with a well-established safety record. In 2003 CaHa [Radiesse®] (Merz Pharmaceuticals GmbH, Frankfurt, Germany) received FDA approval for soft-tissue augmentation, vocal cord augmentation, and correction of maxillofacial defects. The efficacy and favorable safety profile of CaHA in these soft-tissue indications led to the adoption of its off-label use in facial rejuvenation (Pavicic 2013).

In Europe CaHa received a Conformité Européenne (CE) certification mark (medical device class 3) for plastic and reconstructive surgery, including deep dermal and subdermal soft-tissue augmentation of the facial area in 2003. It may be injected into the deep dermis, the subcutaneous tissue, or supraperiosteally depending on the area of the face being treated. The European label includes, but is not limited to, the nasolabial folds, marionette lines, cheek hollows, cheekbone, jawline, oral commissures, chin, temple, bridge of the nose, and hands. In 2006, Radiesse received FDA approval for the correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds, and/or the restoration and correction of the signs of HIV-associated facial lipodystrophy (Loghem et al. 2015b; Funt and Pavicic 2013a) (Fig. 7).

Anatomy

In order to use CaHa to inject the face, anatomy knowledge is crucial, and understanding anatomy of the aging process is even more important. The concept of fat and bone loss was described by Lambros in 2006 (Lambros 2006). Rohrich in 2007 (Rohrich and Pessa 2007) described the importance of the fat pads loss in the aging process, as did Shaw in 2011 with bone loss and skeleton changes. Merz Pharmaceuticals developed scales of aging (Merz Aesthetics Scale) according to the anatomic areas of the face as demonstrated in Figs. 8, 9, and 10.

Fat Pads

There are the superficial and deep fat compartments and its fusions**.** Each one ages differently.

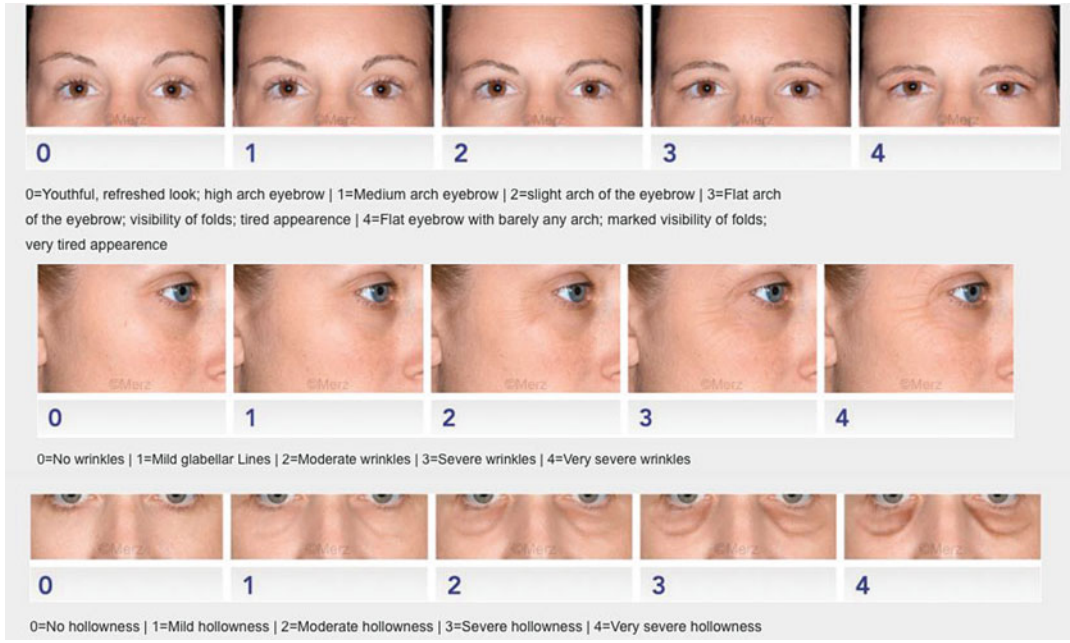

Fig. 8 Merz aesthetis scale for upper face (Brow/crow feet/inferior eyelid)

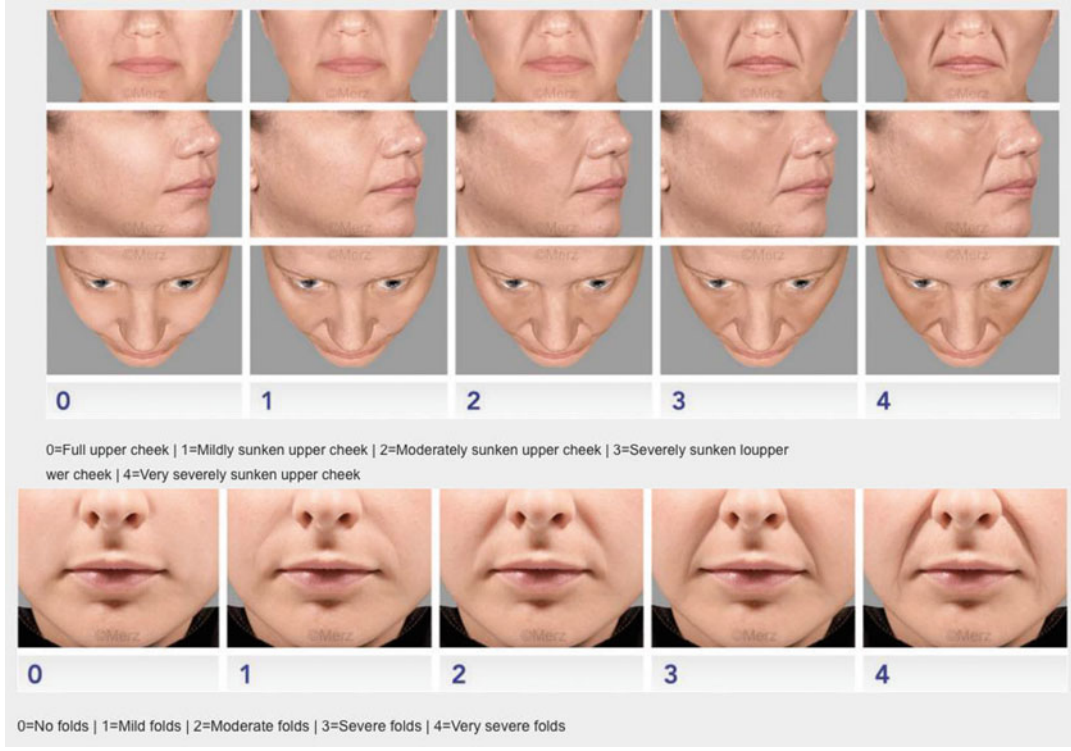

Fig. 9 Merz aesthetis scale for mid face (mid cheek/nasolabial fold)

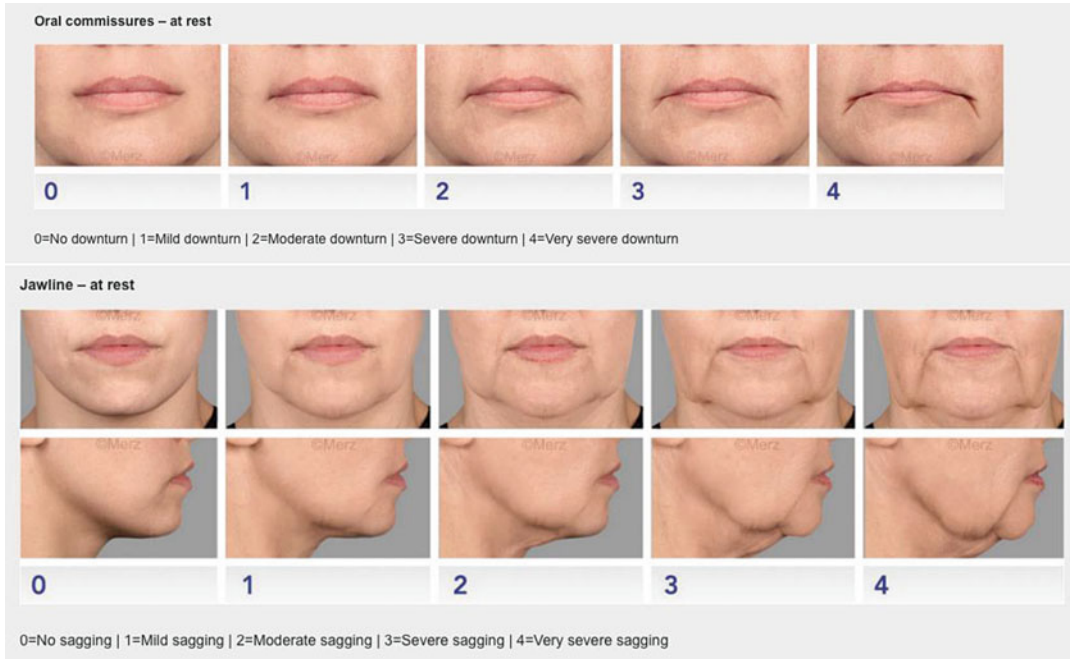

Fig. 10 Merz aesthetis scale for lower face

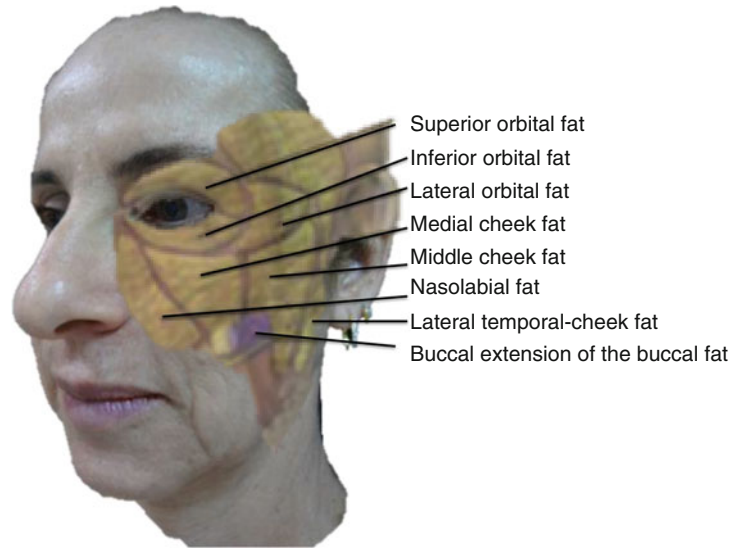

Fig. 11 Superficial fat pads compartments

The knowledge of compartmentalization of the face gave us a new perspective on volume loss assessment and its restoration (Rohrich and Pessa 2007). Fitzgerald in 2014 (Fitzgerald and Rubin 2014) well described an excellent correlation of fat pads and volume restoration (Figs. 11 and 12).

Bone Structure

The aging process has also been shown to affect the facial bones. Multiple studies suggest that the bony aging of the orbit and midface is a process primarily of contraction and morphologic change.

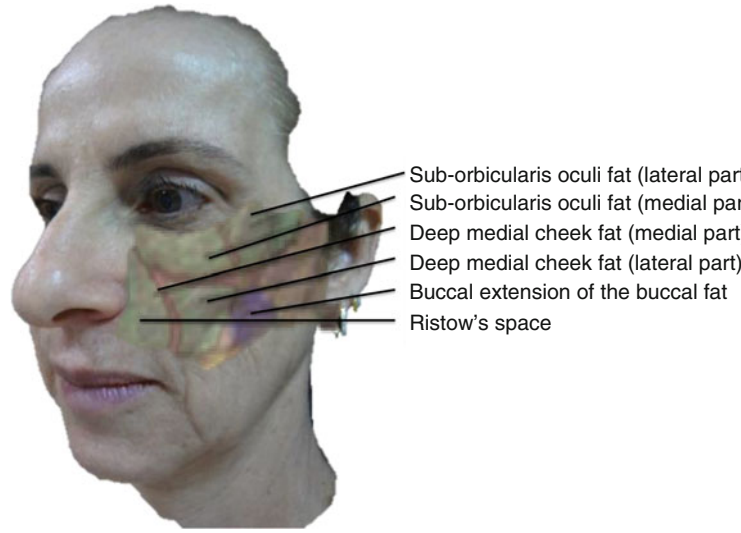

Fig. 12 Deep fat pads compartments

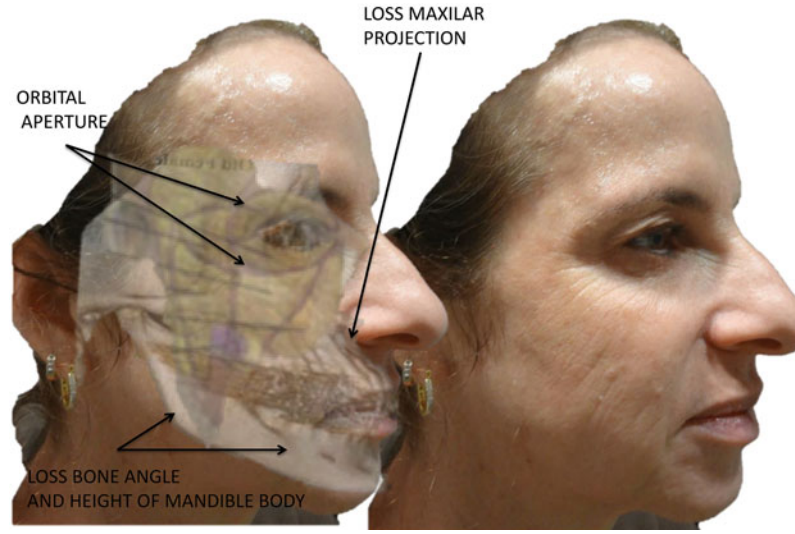

Fig. 13 Bone loss and relation to fat pads and aging appearance

The lack of bone support to facial fat pads leads to aging appearance such as below (Fig. 13):

Orbit The orbit aperture, not only in inferior margin but also the superior margin of the orbital rim, increase with age. That combined with the loss of glabellar projection generates a lack of support for the mid-brow and glabella and also the orbital malar region which leads to medial brow ptosis, inferior eye bags, and also worsening of crow's-feet wrinkles.

Maxilla Also there is an increase aperture in piriform aperture (nose) and a loss of maxillar bone projection which generates a lack of support to the tip of the nose, medial fat pad, and nasojugal groove leading to a droopy tip of the nose, inverted superior lip, inferior eye bags, and worsening of the nasojugal groove.

Jawline There is also bone aging in the mandibular area. There is an increase of mandible angle and a decrease of mandibular length

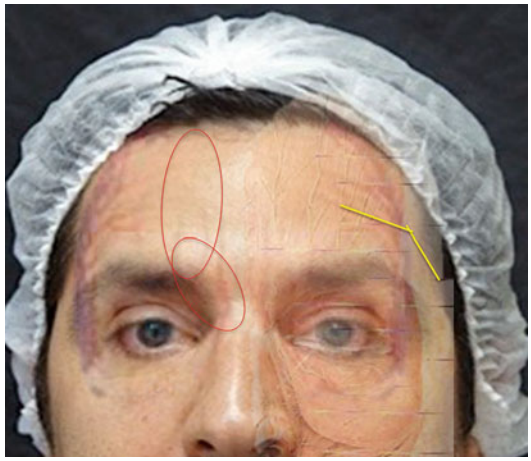

Fig. 14 Upper areas of concern: *red circle* are location of main artery branches and *yellow line* points to the most common area where the temporal and frontal branches of facial nerve sits

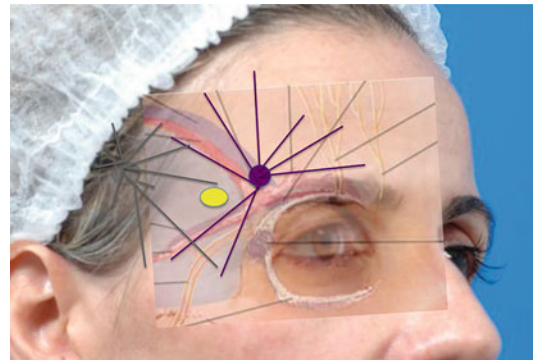

Fig. 15 Plan of application of CaHa with 25 G cannula for Volume restoration of lateral forehead, upper quadrants of temporal fossa. Deep correction (*purple* and *grey lines* cannula injection. The same plan can be used for superficial injection but the cannula goes to a more superficial plane.) (*Yellow dot* needle injection)

and height which generate a lack of support to the neck (skin and platysma), chin, and perioral area. That leads to an increase of prejowl sulcus, sagging neck, and an inverted inferior lip (Shaw et al. 2011).

Cosmetic Units and Plan of Application

Upper Third of the Face

- Forehead:

Structures of concern:

Facial nerve, supraorbital/supratrochlear nerve, and arteries (Fig. 14).

-Injection plane: Subgaleal/supraperiosteal plane.

-Injection techniques: Linear threading, microdrops.

-Cannula size: 25G cannula, 1.0″ (25 mm) or 1.5″ (38 mm) – cannula technique is advised starting from the temporal crest 0.5 mm above the brow (Fig. 15).

- Temples:

The temporal fossa is divided in four quadrants. If the temporal concavity is too deep, the two-plane correction is preferred: one deep and another one more superficial to the smooth transition of the temple area and forehead (Fig. 15).

-Structures of concern: Venous network, superficial temporal artery.

-Injection plane protocols:

1. Deep injection: Needle (23G). Subtemporal muscle injection protocol; one or more boluses are injected in the submuscular/supraperiosteal plane, with the needle tip gently touching the periosteum. The safest point of injection lies 1 cm above the orbital zygoma junction and 1 cm behind the lateral orbital rim. Inject low volume of bolus (0.1–0.3 mL per bolus).

: Cannula (22G). Below the superficial temporal fascia through an entrance 1 cm behind the hairline and another 0.5 cm above the brow just on the temporal fusion line

2. Superficial injection: Subdermal injection protocol with a blunt cannula 25G, but in a more superficial plane such as subdermal

- Brow:

-Structures of concern: Venous plexus, supraorbital artery and nerve, and intraorbital area.

-Injection protocol: A cannula is advised to avoid intravascular injection. If a needle is used, use a 23G and inject with (1) low volume and (2) low pressure; (3) always perform blood reflux test for at least 8 s each site – the dermal/subdermal plane of the area from the peak to

the lateral end of the brow; more medially from the peak, direct arterial connections to the intraorbital area are present (supraorbital artery, supratrochlear artery). Also avoid deep injection to prevent intra-arterial injection. Advocate no more than 0.1 mL of total volume to the brow in a single injection sitting.

Middle Third of the Face

- Middle cheek:

Structures of concern:

- Infraorbital rim: Stay well below the infraorbital rim when using needles.
- Infraorbital foramen: Avoid injection near the infraorbital foramen/nerve when using needles.
- Midface fat compartments: If a needle is used, always choose a 23G or bigger. Always perform a blood reflux test for at least 8 s if using needle injection to avoid the risk of intravascular injection. The product should be placed supraperiosteally, below the region of the suborbicularis oculi fat (SOOF) and medial cheek fat compartments to project these fat compartments.

Injection procedure: First find the cheek apex. There are many ways to find it. The most used is the one described by Hinderer in 1984 (Hinderer and de Rio Lagarreta 1984). Then from there you assess and decide which areas need volume restoration. Always start in the malar eminence and go to lateral areas then to the middle cheek (Fig. 16).

Injection plane: Supraperiosteal (zygomatic bone and malar/maxilla) or subdermal (lateral zygoma).

Injection techniques:

Needle 23G bolus or mini-bolus (0.1–0.3 ml per site).

Cannula: 25G, 1.0″ (25 mm) or 1.5″ (38 mm) fanning or microdrops.

Clinical results: Fig. 17.

- Nasolabial folds:

Structures of concern:

- Angularis artery: Too much product in the area of the alar triangle may compress the artery angularis and could cause necrosis. There is an anastomosis between the ophthalmic artery (angular artery branch) and the facial artery.

Fig. 16 Application plan for mid (*yellow*, entrance point; *green*, plan application) and perioral region (*blue*) on the face (cannula 25G, *right side*/ needle 23G, *left side*)

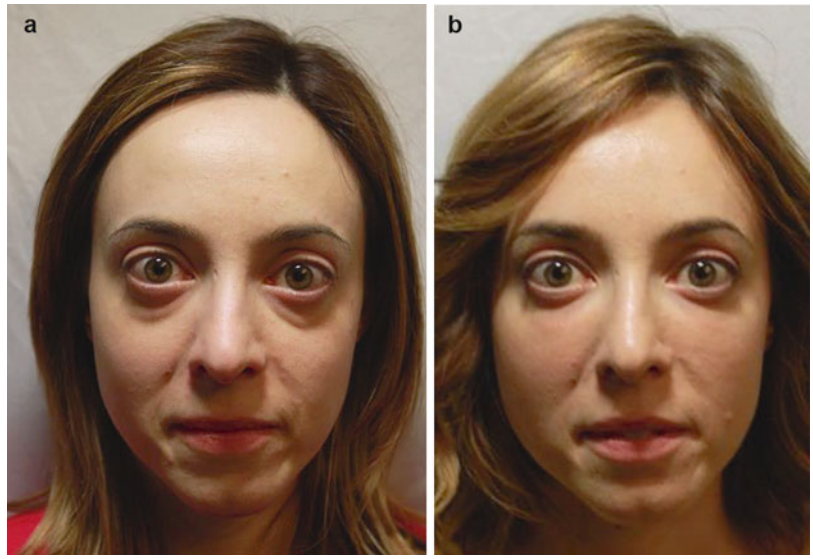

Fig. 17 (**a**, **b**) Pre and 6 months after CaHa injection – Cannula 25G, Dilution 1.5 CaHa: 0.5 ml Lidocaine 2% with epinephrin

- Musculus orbicularis oris: Perimuscular injection anywhere on the face can lead to product compaction/nodularity or even displacement (migration) of product by mimic activity of the affected muscle.
- Infraorbital foramen.

Injection Procedure:

Cannula: From the same entrance we do the middle cheek, we go toward the piriform fossa and the base of the nose deep to the muscular layer and start injecting a mini-bolus and filling with a fanning technique.

Needle: Use the microdrops technique creating bridges below the nasojugal groove toward the supralabial area.

Injection site: Injections should be given in the subdermal layer or supraperioteal when addressing the piriform fossa (Bass et al. 2010; Smith et al. 2007).

Needle or cannula: 23G needle, 25G cannula, 1.0″ (25 mm) or 1.5″ (38 mm).

Average volumes: May depend on the degree of correction needed (Bass et al. 2010; Smith et al. 2007).

- Submalar cheek hollows:

Structures of concern:

- Parotid gland: Found in the subcutaneous tissue of the face. The gland extends irregularly from the zygomatic arch to the angle of the mandible injection procedure.
- The facial nerve and its branches pass through the parotid gland injection procedure.

Injection plane: Subdermal and/or subcutaneous plane.

Injection techniques: Linear threading, fanning, microdrops, and cross-hatching.

Needle size or cannula: 23G needle, 25G cannula, 1.0″ (25 mm) or 1.5″ (38 mm).

Average volumes: 0.5–1.5 ml per side.

Lower Third of the Face

- Marionette lines:

Structures of concern:

- Orbicularis oris muscle: When injecting into the muscle, there is a higher risk of nodularity post-injection.
- Facial artery: Just lateral to the oral commissure, running lateral and inferior. Common cause of increased bruising in the area.

Injection Procedure:

Injection site: Injections should be given below orbicularis oris or in a subdermal layer to avoid intramuscular injection in this area or injection into the mouth.

Injection techniques: Linear threading, microdrops, and fanning.

Needle /cannula: 23G needle, 0.5″ (13 mm), 25G cannula, 1.0″ (25 mm) or 1.5″ (38 mm).

Average volumes: Maximum of 0.7–0.8 ml per marionette line.

- Mental crease:

Structures of concern:

- Buccal sulcus: Susceptible to product accumulation if injection is placed too deeply superior to the alveolar process. In this case, the product may take the path of least resistance.
- Orbicularis oris muscle: If you inject in the muscle, there is a higher risk of nodularity post-injection.
- Mental foramen: Pressure on the incisive and mental nerves may affect the sensitivity of the mandible and anterior teeth.

Injection Procedure:

Injection site: Supraperiosteal or deep dermal layer

Injection techniques: Linear threading, fanning, microdrop, and parallel line

Needle or cannula: 23G needle, 0.5″ (13 mm), 25G cannula, 1.0″ (25 mm) or 1.5″ (38 mm)

Average volumes: 0.2–0.4 ml total or 0.1–0.2 ml per side

- Prejowl sulcus:

Structures of concern:

- Orbicularis oris muscle: If the muscle is injected, there is a higher risk of nodularity post-injection.
- Facial artery: Just lateral to the oral commissure, running lateral and inferior; common cause of increased bruising in the area.

Injection Procedure:

Injection site: Subdermal/supraperiosteal layer

Injection techniques: Linear threading and fanning, bolus

Needle/cannula: 23G needle, 0.5″ (13 mm), 25G cannula, 1.0″ (25 mm) or 1.5″ (38 mm)

Average volumes: Maximum of 0.4 ml per PJS

- Chin:

Structures of concern:

- Mental foramen and nerves: Properly map the mental foramen, and avoid placing aliquots near this area. Keep the augmentation on the anterior side of the mandibular rim, and avoid volume placement above the mental crease, as this could manifest as a gingival sulcus nodule on the mucosal aspect.

Injection Procedure:

Injection site: Supraperiosteal plane

Injection techniques: Bolus and/or threading

Needle size: 23G needle, 0.5″ (13 mm)

Average volumes: Up to 1.5 ml

- Mandibular angle and jawline:

Structures of concern:

- Arteria facialis: Just lateral to the oral commissure, running lateral and inferior. Common cause of increased bruising in the area.
- Facial nerve: Do not inject too deep to avoid hitting the nerve.
- Mental foramen and nerves: Properly map the mental foramen, and avoid placing aliquots near this area.
- Masseter muscle.

Injection Procedure:

Injection site: At the supraperiosteal (needle) or at the subdermal layer (cannula).

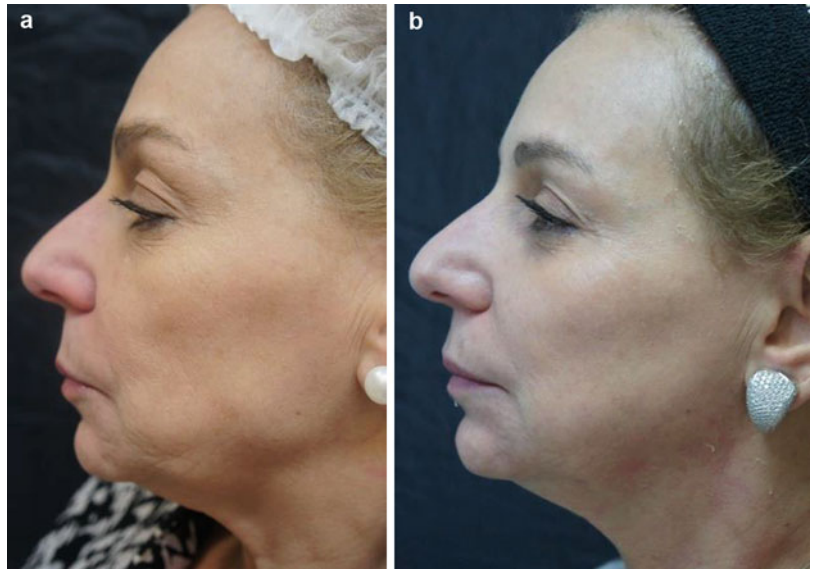

Fig. 18 (**a**, **b**) Before and 30 day after CaHa injection of mid face and lower face

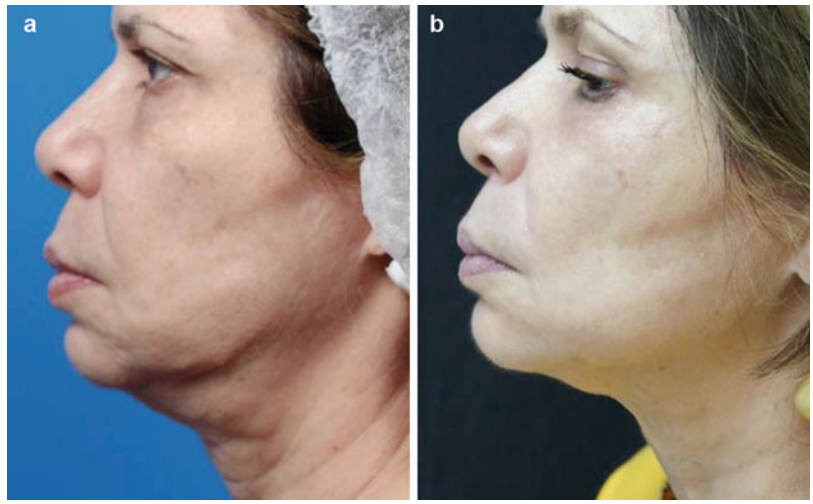

Fig. 19 (**a**, **b**) Before and 30 day after CaHa injection of mid face and lower face

Injection technique: Bolus, linear threading and fanning.

Needle size: 23G needle, 0.5″ (13 mm), 25G cannula, 1.0″ (25 mm) or 1.5″ (38 mm).

Average volumes: Linear threading – may depend on the degree of correction needed.

Bolus: An average volume of 1.0–3.0 ml is normally used for jawline/mandibular contouring

Clinical results: Figs. 18a, b, 19a, b, and 20a, b.

Classifications

In order to plan treatments with the patients, first the aging process of each area should be assessed. Carruthers and colleagues (Carruthers 2008; Carruthers et al. 2008a, b) published in 2008 a grade scale of aging divided by cosmetic areas. Grading the severity of each area, it is possible to estimate the amount of product needed in order to obtain realistic and satisfactory results. That could

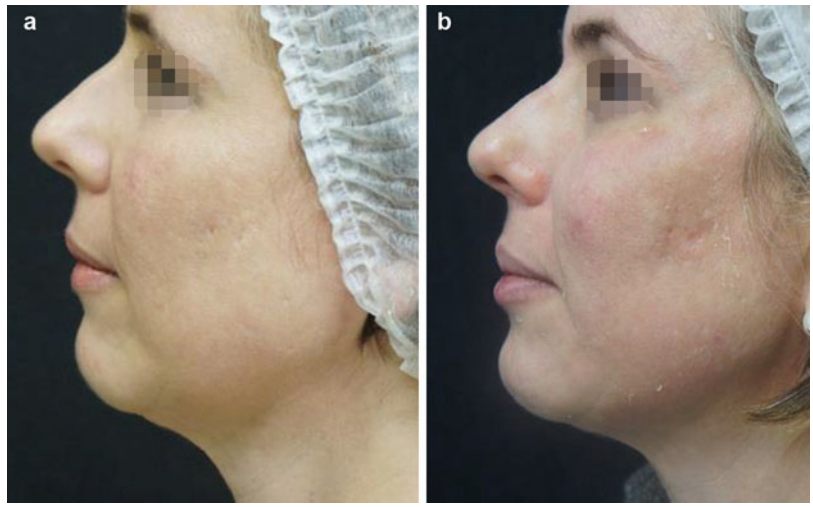

Fig. 20 (**a**, **b**) Before and 30 day after CaHa injection of mid face and lower face

be done in one or more sessions as planned with the patient always respecting the 1:1 correction regarding the endpoint (Marmur et al. 2004).

Indications and Contraindication

On-Label Use on the Face (Approved by CE and FDA)

The European label includes, but is not limited to, the nasolabial folds, marionette lines, cheek hollows, cheekbone, jawline, oral commissures, chin, temple, bridge of the nose, and hands. In 2006, Radiesse received an FDA approval for the correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds, and/or the restoration and correction of the signs of HIV-associated facial lipodystrophy (Loghem et al. 2015b; Funt and Pavicic 2013a) (Fig. 7).

Off-Label Use on the Face

In the last 4 years, the use of CaHa spread, and more off-label indications have been described such as nose reshaping; dark circles; forehead, brow, and temporal area augmentations; and acne scars. Stupak et al. (Dayan et al. 2007; Stupak et al. 2007) published their experience using CaHA in the nasal dorsum and radix with results persisting over 1 year. They have used CaHA for post-rhinoplasty deformities of the dorsum, supratip, sidewall, and ala. Becker (Humphrey et al. 2009; Becker 2008) reports correcting saddle nose and retracted columella deformities. These authors find that CaHa for nose injection is very useful, although we do not recommend it because most of the blindness cases were after nose and glabella injections and CaHa does not have an enzyme like hyaluronidase that we could use in case of an intravascular injection.

Bernardini and colleagues in 2014 (Bernardini et al. 2014) published a paper in which they show 63 patients successfully treated for hollow eyes and dark circles with the idea of using the white color to disguise the purplish color of the nasojugal area and also correct the hollowness and to enhance collagen formation which gives a better appearance to the inferior eyelid skin. Although it seems a safe procedure, still it requires a very experienced hand to do this procedure in order to avoid complications such as the accumulation of the product and yellowish area that can appear if injected too superficially. The study showed 17% of complications such as this last one but improved in 6 months at the most (Bernardini et al. 2014).

The brow, forehead, and temporal areas are very much related when it comes to eye frame appearance. This author has been using CaHa for volume restoration on these three areas in the last

4 years with minor complications and great satisfaction of the patients. The best indications for these areas are the ones with great volume loss in three areas but not a very hollow temporal area (for which hyaluronic acid is better because of its greater projection capacity).

Contraindications

Generally, CaHa should not be used in patients with bleeding disorders, severe allergies manifested by a history of anaphylaxis, a history of hypersensitivity to the components of CaHa, and active skin inflammation or infection in or near the treatment area. Other contraindications are areas in which many adverse events were described such as:

-The glabellar lines and nose due to intravascular injection that cannot be reverted

-Lips, perioral, and periorbital lines due to movement of the orbicularis muscle that can promote an accumulation of the product and late-onset nodule

-Over a permanent filler as has been described in the literature that any filler injected over a permanent one can stimulate a biofilm

Use and Doses

Dilution

CaHa can be used to restore volume or just to stimulate neocollagenesis.

Volume restoration: These authors recommend that the CaHa that comes in a 1.5 ml syringe be mixed with lidocaine 2% with epinephrine (Lido2%wE) for the use in the face. It can be mixed either with 0.25 ml or 0.5 ml of Lido2% wE. First one is for the areas we are seeking more projection, and the second one is for the use in areas with thinner skin. Because the gel component offers a 1:1 implant-to-tissue defect correction, no overcorrection is required (Marmur et al. 2004).

Biostimulation: We recommend CaHa to be mixed with 1 ml or 1.5 ml of Lido2%wE for the use in a subdermal plane.

Technique

Needle

The recommendation of the manufacturer is to use a 27G needle. A paper published in 2015 showed that in order to have a positive blood reflux test prior to injection, a 23G needle should be used. So we recommend the use of a 23 G needle especially on areas in the center of the face that have higher risks of intravascular injections that can lead to blindness (Casabona 2015).

Cannula

CaHa should be used with a cannula of at least 25G or larger.

Side Effects and Their Managements

All filler substances have an associated risk for both early and delayed adverse events[j] Table 1.

CaHa implant has demonstrated safety, with no evidence of systemic adverse effects or immunologic responses and has a 5% incidence of hematoma and ecchymosis. Complications, including ecchymosis and hematoma, are temporary. One of the most common side effects described in the literature is nodule formation, and normally it is due to superficial injection of the product in hyperkinetic areas, such as lips, and can lead to accumulation of the product when the gel starts to be reabsorbed in 3 months (Jansen and Graivier 2006). The majority of all adverse events reported are due to improper technique and not to the injected material. Early complications resolve

Table 1 Early and delayed adverse events

Early complications/ adverse events	Delayed complications/ adverse events
Bruising	Nodules
Tenderness	Granulomas
Swelling	Migration
Erythema	Infection
Asymmetry	Immunologic reactions
Lumpiness	
Infection	
Allergic reaction	
Vascular accident	

within 5–7 days. Delayed complications/adverse events (>2 weeks to years following injection) are managed as described below.

Delayed Adverse Events

Nodules

The word nodule is a general term used to describe the shape of a palpable induration. Possible causes are an undesirable accumulation of filler product, a hematoma overlying a seroma, or the formation of granulomatous tissue. Nodules may occur when the filler is unevenly spread under the skin, or too much is injected per site. They may be associated with inflammation, swelling, and infection. Generally, a nodule usually appears within a few hours or days of treatment. In clinical studies of CaHa, nodules reported on the lips were due to a filler buildup as a result of perioral muscle activity. CaHa is not recommended for treating the lips or the zone around the eyes, as repetitive muscle activity in these areas may lead to filler-based nodules. When used for lip augmentation, nodules that occur can be surgically excised (Jacovella et al. 2006).

Results of a large-scale clinical trial with 1,000 patients and a total duration of 4 years (Tzikas 2008; Sadick et al. 2007): Nodules occurred rarely and were mostly restricted to the lips. CaHa is not recommended for the lips. All nodules could be successfully treated using massage after injection of saline solution, needle puncture in case of early onset, or excision (Fig. 21a, b). In the case of nodules accompanied by an inflammation process, in our experience, the combination of 10 mg/ml intralesional steroid (Kenalog 40 mg/ml) with hyaluronidase and massage can resolve it. For persistent nodules, series of three injections of 5-FU, triamcinolone and lidocaine, or 5-FU and lidocaine may be considered (Funt and Pavicic 2013b). The risk of nodule formation with CaHa can be reduced by avoiding areas not approved for CaHa (e.g., the lips) and choosing the correct injection plane (not too superficial, not intramuscularly). Evenly distribute the filler by thoroughly massaging the treated area (Voigts et al. 2010).

Granulomas

A granuloma is an unwanted tissue response with proliferation of connective tissue and

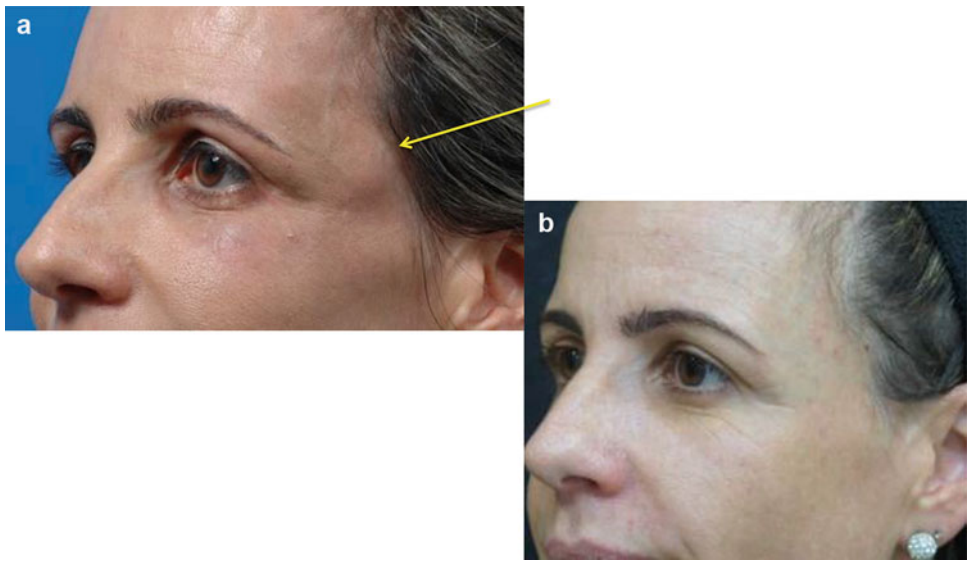

Fig. 21 (**a**, **b**) Nodule (product accumulated) 15 day post injection CaHa fronto-temporal area (*yellow arrow*); and 15 day after treatment with injection of saline and massage

immunoreactive cells. It may appear 2–3 months after treatment. A granuloma can only be distinguished from a simple accumulation of the filler by removing it and examining it under a microscope. It can be diagnosed by the presence of filler particles surrounded by immune cells and fibrous tissue. Since 2004, there have been only five reported and confirmed cases of granuloma in over five million syringes shipped (0.0005%). In 2009, a retrospective meta-analysis of studies dating from 1985 to 2005 showed lower granuloma rates with CaHA than with HAs or poly-L-lactic acids: 0.001%: CaHA; 0.04–0.4%: HAs; 0.2–1%: PLLAs.

A comparison of estimated granuloma rates from the literature, presented at IMCAS 2012 by granuloma expert Professor Gottfried Lemperle, showed that CaHa had the lowest granuloma rate (Voigts et al. 2010) (Table 2).

Standard treatment is with either oral or intralesional steroids (Sclafani and Fagien 2009).

Intralesional steroids require judicious use, as they have been associated with localized atrophy, erythema, and pigment changes, as well as systemic vascular events. Adding 5-fluorouracil to the intralesional steroid has also been advocated for granuloma treatment (Voigts et al. 2010).

If these treatments fail, surgical excision can be attempted as a last resort. In two of the largest studies performed with CaHa (Radiesse®) so far, neither granuloma formation nor severe infections were observed over a total study period of 39 months (Tzikas 2008) or 52 months (Sadick et al. 2007), respectively; observed adverse events were minor and mostly restricted to injection-related events. As of November 2014, over five million syringes have been shipped worldwide, and only in 5 CaHa (Radiesse®) cases has granuloma formation been reported by the company.

Table 2 Estimated granuloma rates after filler injection

Radiesse^{R} 1:5.000	Kollagen 1:2500	HA 1:2500	Artefill 1:2500
Artecoll 1:1000	Sculptra^{R} 1:1000	Acrylamide 1:1000	Dermalive 1:80

Skin Color Change

That adverse event normally occurs from 1 to 3 months after injection, and it is due to a very superficial placement of the material. Since CaHa is white, it gives a yellowish look to the skin. It is very easy to diagnose because it looks like a xanthelasma. In our experience, it can be easily treated with two monthly sessions of ablative fractional laser using low density but high energy and deep penetration of the laser.

Take Home Message

- Before injecting CaHa, the patient should be screened and given a written informed consent.
- The use of an anesthetic agent (e.g., lidocaine) is highly recommended.
- CaHa needs to be placed into the deep or subdermal tissue layer.
- Recommended injection techniques for the use of CaHa include linear threading, parallel lines, fanning, microdrops, and cross-hatching.
- CaHa indications include medial cheeks/lateral cheeks, submalar cheek hollows, nasolabial folds, marionette lines, mental crease, mandibular angle and jawline, prejowl sulcus, chin, hands, frontal concavity, temporal concavity, and brow lift.
- As with all filler substances, the use of CaHa may be associated with a risk of adverse events; however, the majority of reported adverse events are due to technique and are temporary.
- Proper injection technique, choice of injection site, and choice of filler and dilution can limit the risk of adverse events.
- CaHa has been extensively studied, and all studies confirmed the high safety profile.
- In two of the largest studies performed with CaHa so far, neither granuloma formation nor severe infections were observed.
- The use of CaHa is contraindicated in the glabellar lines and in the nose.
- The use of CaHa is not recommended on the lips.

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Calcium Hydroxyapatite to Treat the Hands

Carlos Roberto Antonio and Lívia Arroyo Trídico

Contents

Abstract

As time goes by, the appearance of the hands undergoes several changes due to the natural aging process. Once this body region is an open area that is usually in evidence, the search for aesthetic procedures that may ensure its rejuvenation has become a permanent concern. Because of the loss of volume and elasticity on the back of the hands, the vessels and tendons become more apparent as well as the emergence of wrinkles, which characterizes an aged hand. Dermal fillers guarantee good results considering the reversal of this process and the restoration of the volume loss. The calcium hydroxyapatite is biocompatible, non-antigenic, and biodegradable, and the fillers consisting of such material have characteristics that provide excellent results in the treatment of aged hands, besides presenting minimal side effects and ensuring an extended duration for more than 6 months.

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_26

Keywords
Hand · Skin aging · Hydroxyapatites

Introduction

The hands are one of the most exposed areas of the body, together with the face and neck. Thus, their aesthetic appearance has an important impact on personal self-esteem. Although cosmetic procedures in dermatology are mostly performed on the face and neck, when a patient undergoes a rejuvenation treatment in these regions, there may be a clear inconsistency compared with the back of the hands of such individuals. Therefore, in order to avoid the contrast of a rejuvenated face compared to the back of the untreated aged appearance hand, the demand for hand rejuvenation procedures has increased significantly.

Due to aging, the appearance of the hands changes on account of extrinsic and intrinsic factors. Extrinsic factors affect the most superficial layers (epidermis and dermis); occur due to sun exposure, contact with chemicals, and smoking; and are expressed in the form of actinic keratosis, solar lentigo, and marked hypopigmentation. On the other hand, intrinsic aging factors affect the deeper layers (dermis and subcutaneous), thus reducing the elasticity of the skin, the tissue volume (atrophy of the dermis and hypodermis), and the dermal vasculature. The signs of intrinsic aging include wrinkles, laxity, and thinning of the skin; prominence of veins, joints, and tendons (Kühne and Imhof 2012); and bone viewing.

Changes that occur in the hands due to the aging process can be observed in varying degrees according to the individual. Carruthers et al. (2008) have established a grading scale to determine the appearance of hands. The 5-point scale ranging from 0 to 4 is based on the lack of adipose tissue. The lower score means the existence of more adipose tissue and that the superficial veins are not easily observed. The higher score indicates less adipose tissue and the easy visualization of superficial veins.

0 point: no loss of fatty tissue; 1 point: mild loss of fatty tissue and slightly visibility of veins; 2 point: moderate loss of fat tissue and mild visibility of veins and tendons; 3 point: severe loss of fatty tissue and moderate visibility of veins and tendons; 4 point: very severe loss of fatty tissue and marked veins and tendons.

Rejuvenation of Hands

There are several treatment options for rejuvenation of hands. Most procedures currently available are intended to treat the changes caused by extrinsic factors as they seek to unify the pigmentation of the skin and renew the surface layers, such as the use of topical acids (tretinoin, vitamin C, and others), clarifiers, chemical peels, liquid nitrogen, laser, and intense pulsed light (Butterwick 2005). However, none of these treatments is able to recover the volume lost due to the aging process (Sadick 2011).

Dermal fillers are a good treatment option to recover the volume of hands because they are safe and effective, and the application is fairly simple and quick (Sadick 2011). Among many types of dermal fillers used for hands, the calcium hydroxyapatite has shown lasting results, besides presenting as a distinctive feature compared to other fillers, the ability to make veins and tendons less apparent due to its consistency and opacity (Shono et al. 2012).

Calcium Hydroxyapatite

The fillers, of which the basis is the calcium hydroxyapatite, are a synthetic product consisting of microspheres of calcium hydroxyapatite (30%) suspended in a gel vehicle (70% – consisting of water, glycerin, and carboxymethyl cellulose). Its formulation consists of two minerals that are naturally found in the bones and teeth (calcium and phosphate), thus being a biocompatible and nontoxic filler (Emer and Sundaram 2013).

The use of calcium hydroxyapatite was approved by the FDA (Food and Drug Administration) in 2006 as a facial filler. It was initially used for correction of moderate and deep wrinkles and for the treatment of lipodystrophy

in patients with human immunodeficiency virus. Due to the good results obtained with facial filling with calcium hydroxyapatite, the use of this filler for aesthetic purposes has expanded to other indications that are off FDA labeling, including lower face, nose, hands and other body areas, and also for acne scar treatment (Emer and Sundaram 2013; Kasper et al. 2008).

The use of calcium hydroxyapatite base filler for filling the back of the hands was first reported by Mariano Busso and David Applebaum in 2007 in Florida (Kasper et al. 2008). The result was effective and associated with little pain. Since then, several studies have shown good results using this type of filler for hands (4.8).

Mechanism of Action

The initial mechanism of action is the distribution of the microspheres of calcium hydroxyapatite by the soluble gel at the injection location. The spherical and uniform shape particles favor the emergence of space between them, avoiding that they are strongly adhered. The space that lies between the microspheres is initially filled by the gel vehicle. The gel is gradually dissipated, leaving the microspheres of calcium hydroxyapatite at the locations injected in order to induce the long term collagenesis. The calcium hydroxylapatite microspheres are anchored in the injection area, thus preventing its translocation and ensuring the long-term procedure duration with effects lasting up to 15 months, on average, and more than 30 months in some cases (Pavicic 2013).

Due to the histological examination carried out 9 months after the filling with calcium hydroxyapatite in the deep dermis, one can observe nearly none foreign body reaction. Thus, it is possible to conclude that the microspheres of calcium hydroxyapatite are gradually broken into calcium and phosphate ions that are eliminated by the body's natural process of excretion. All components of this type of filler are metabolized over time (Pavicic 2013).

The size of the calcium hydroxyapatite particles, considering it can be relatively large (25–45 Um), ensures that macrophages are unable to absorb them, thus promoting their durability. Therefore, the calcium hydroxyapatite fillers are able to initially promote the recovery of volume by simply injecting the substance in the location. The long-term effects may be assigned to the biostimulation that occurs in the location as the gel vehicle is dissolved and replaced by the collagen around the microspheres of calcium hydroxyapatite, which is synthesized by local histiocytes and fibroblasts (Emer and Sundaram 2013).

By analyzing the histological examination of the locations receiving the dermal filler of calcium hydroxyapatite in a period of 6 months before the biopsy, it is possible to see the collagen deposition around the calcium hydroxyapatite microspheres with tissue response of fibroblasts and histiocytes. In an immunohistochemical analysis, it was observed two types of collagen, 1 and 3, with the prevalence of collagen type 1 (Emer and Sundaram 2013).

Accordingly, we can conclude that the lasting result of calcium hydroxyapatite does not occur due to the presence of the microspheres at the injection site, but due to the collagen production at that place.

Antigenicity

Some fillers behave as foreign bodies and have the potential to cause a reaction of the body, which may range from a limited infiltrate of macrophages to an intense inflammatory reaction with fibrosis. The calcium hydroxyapatite is associated with a minimal inflammatory infiltrate around the injected particles, indicating nearly no foreign body reaction to this type of filler. The granulomas resulting from the excessive immune response to a foreign body rarely occur after filling procedures with calcium hydroxyapatite (Pavicic 2013).

Indications and Contraindications

The dermal fillers are intended for the replacement of volume loss in the back of hands, which causes the vessels and tendons to be visible. Calcium

hydroxyapatite base fillers present the ability to stimulate the neocollagenesis and also, through its opacity, help to reduce the visibility of vessels and tendons (Shono et al. 2012).

When performing an aesthetic procedure, the first step is to understand the desire of the patient and carefully discuss his expectations. It is also critical to evaluate the patient's history by paying attention to possible allergy stories, autoimmune diseases and connective tissue diseases, pregnancy and breastfeeding, once the procedure should be avoided in these cases. We shall also investigate the medicines used by the patient and evaluate the possibility to discontinue the use of drugs that may can increase bleeding and bruising, such as acetylsalicylic acid (Lizzul and Narurkar 2010).

It is very important to explain to the patient the procedure, the discomfort that occurs at the application site, and the possible adverse effects. Pretreatment photographs should always be taken for documentation purposes and comparison of results.

Application Technique

The knowledge on hand anatomy is primordial to obtain good results with fillers. Three adipose tissue layers are identified in the back of the hand (superficial, intermediate, and deep). The thickness of the superficial layer seems to be related to the body mass index, and such layer does not present vessels or nervous structures. The larger veins of the back of the hands and the sensory nerves are located in the intermediate layer, while the tendons are located in deeply. Theoretically, the ideal place to apply the filler would be the superficial layer once it is above the vessels and allows to hide them. However, effectively, this is technically impossible without avoiding the occurrence of the accidental puncture of the vessels, which leads us to the preference for the use of cannulas. Thus, the injection is carried out in the deepest layer above the metacarpal plan, and even though the procedure is successful in reducing the visibility of veins due both to the opacity and the compression of adjacent veins from the injected material (Bidic et al. 2010).

In 2007 Busso and Applebaum were the first authors to describe the technique of injection of calcium hydroxyapatite fillers for rejuvenation of hands (Kasper et al. 2008). They used calcium hydroxyapatite associated with 2% lidocaine injected subcutaneously between the deep and superficial fascia in the spaces between the wrinkles formed from the fist to the metacarpophalangeal joints (Busso and Applebaum 2007). According to the technique described by Busso and Applebaum, it shall be added from 0.1 to 0.2 ml of lidocaine to a 1.3 ml of calcium hydroxyapatite syringe (Radiesse®; Bioform Medical Inc. San Mateo, California). To this end, it is used a Luerlok connector (Baxa, Englewood, NJ) that attaches the syringe with lidocaine to the syringe with calcium hydroxyapatite; thus, the mixture of both substances goes from one syringe to the other for approximately ten times in order to mix the two substances and to ensure an homogeneous appearance to the solution. Once the association between lidocaine with calcium hydroxyapatite is ready, the skin on the back the hand is pinched between two fingers and raised to a level above the vessels, and then it is applied the injection in bolus. After that, it is necessary to have an on-site massage to spread the filler. To ensure a better distribution of the filler, the patient should close the fist after application, so the doctor is able to work at the filled area (Busso and Voigts 2008; Busso and Applebaum 2007).

Although this type of application was the first one described, it is also possible to carry out the lidocaine application in bolus prior to the injection of the filler (Busso and Applebaum 2007; Busso 2008; Grunebaum et al. 2010). In this case, a 1% lidocaine 2 ml bolus is injected into the back of the hand with a syringe of 3 ml or 5 ml and a 30 gauge needle. Caution should be taken so the application is intradermal and not deep. After the injection, a blister is immediately formed on the back of the hand. Once the skin is stretched, the injection of calcium hydroxyapatite is to be applied directly to the blister with the help of a 27 gauge needle. In the place where the blister is formed after the injection of the anesthetic, it should be introduced by the filler needle, but in a level above the tendons and vessels by injecting 1.3 ml of standard

formulation filler (Radiesse®). The next step should be the massage for a better distribution of the filler (Bank DE 2009). The authors of this chapter prefer the injection with cannula due to the rare risk of embolism.

Nowadays, the technique that we prefer is as follows: asepsis, marking the area to be filled, marking with a different color pen the vessels, nerves, and visible tendons, small anesthetic point, mandatory application with a 22G cannula of 90 mm to reach all distances and injection in lines to give a uniform and natural result. We avoid massaging a lot and we also ask the patient to avoid massages. We have also noticed a greater comfort and less edema in patients who did not move, massage, or work in the day following the procedure.

However, after the application, the patients may frequently present an edema and erythema that lasts up to a week or a local pain, although the latter is less common (Shono et al. 2012). The edema can be mitigated with ice on the location, as well as by keeping the hands raised for the first 24 hours after the procedure (Nijhawan et al. 2012). Rest is recommended for 2 days following the procedure.

Durability and Safety

The duration of the calcium hydroxyapatite filler on the back of the hands is over 6 months. In our experience, it lasts at least 18 months. This property is probably related to neocollagenesis (Figs. 1, 2, and 3). When we evaluate the patients 1 year after the procedure, 60% of them report the maintenance of a clinical improvement and in general the rate of satisfaction is high (75%) (Sadick 2011; Shono et al. 2012; Lizzul and Narurkar 2010). Laboratory studies show that the neocollagenesis stimulated by the calcium hydroxyapatite filler can be extended for up to 72 weeks (Berlin et al. 2008; Edelson 2009). The duration of the correction depends on several factors including the patient's age, its ability to produce collagen, and the individual's metabolism.

The biocompatibility of the calcium hydroxyapatite with human tissue ensures that the risk of an inflammatory reaction is extremely small (Pavicic 2013). Thus, side effects are minimal and include transient erythema, ecchymosis, and edema that can last from days to weeks. Cases of granuloma formation are rare (Marmur et al. 2009).

Conclusion

Following the constant concern about the rejuvenation of several areas of the body, hand has been a target of various therapeutic technologies that seek a good aesthetic appearance. The filling procedure on the back of the hands aims to recover the volume loss with the aging process. Calcium hydroxyapatite is an excellent option for filling the back of the hands once it has an appropriate consistency that ensures its dissemination among

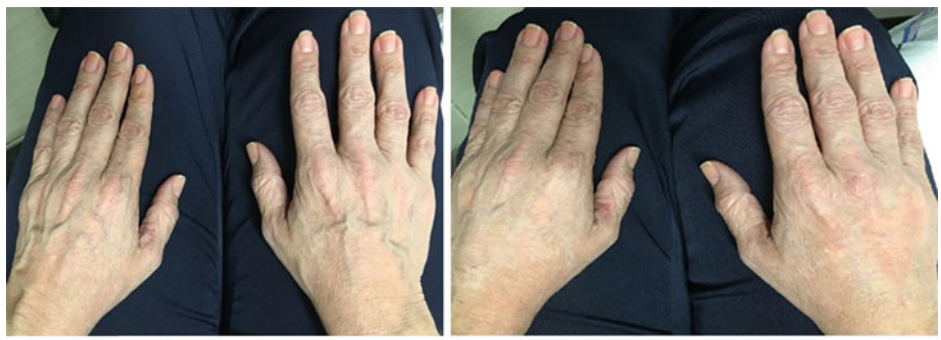

Fig. 1 Before and after treatment with calcium hydroxyapatite filler on the back of the hands

Fig. 2 Before and after treatment with calcium hydroxyapatite filler on the back of the hands

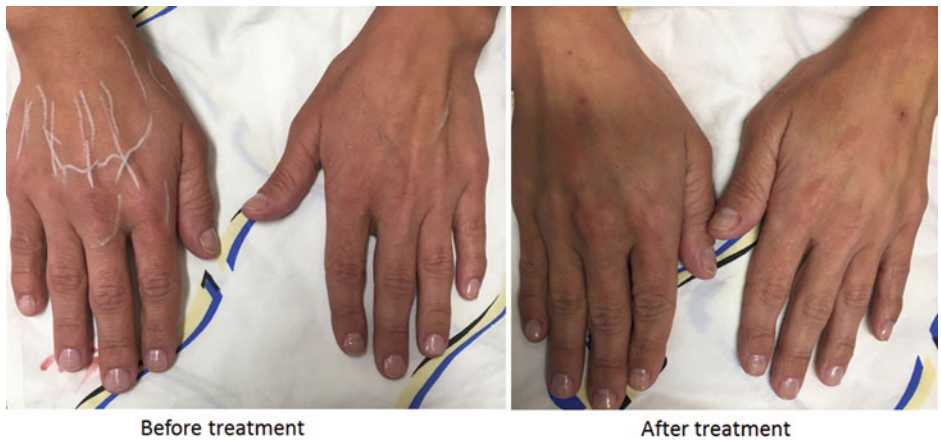

Fig. 3 Before treatment: Highlighting the veins before the procedure (right hand) and after treatment with calcium hydroxyapatite filler on the back of the hands

the tendons and vessels. Moreover, its injection is easy and ensures immediate effects with a longer duration due to its neocollagenesis capacity, thus ensuring the existence of few side effects. Therefore, it is an effective and advantageous procedure associated with high levels of satisfaction among patients.

Take Home Messages

- Clinical findings of aged hands include wrinkles, pigmentation, loss of elasticity, and loss of volume on the back of the hands.
- There are several treatment options for rejuvenation of hands. Most procedures currently available are intended to treat the pigmentation and to renew the surface layers. However, none of these treatments is able to recover the volume loss due to the aging process.
- Dermal fillers guarantee good results considering the reversal of this process and the restoration of the volume loss.
- The calcium hydroxyapatite is biocompatible, nonantigenic, and biodegradable, and the fillers consisting of such material have characteristics that provide excellent results in the treatment of aged hands.
- It has minimal side effects with an extended duration for more than 6 months.
- The microspheres of calcium hydroxyapatite are gradually broken into calcium and phosphate

ions that are eliminated by the body's natural process of excretion.

- Lasting result caused by fillers of calcium hydroxyapatite does not occur due to the presence of the microspheres at the injection location, but due to the collagen production at such place.

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Poly-L-Lactic Acid for Facial Treatment

Maria Helena Lesqueves Sandoval

Contents

Abstract

Since its approval for cosmetic use, injectable poly-L-lactic acid (PLLA) has become increasingly the choice for restoring a youthful appearance to the aging face. This minimally invasive procedure involves the creation of long-lasting volume in the region where it is reinjected without treating the wrinkle itself. However, due to the side effects which can ensue from the improper application of the product, it is essential that physicians follow consensus recommendations to obtain optimal patient results. The present article provides an overview of the history and instructions for injecting PLLA and specifically focuses on its use for facial volumization. Based on the large body of medical evidence available and 11 years' clinical experience, the author also provides details for preparing,

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_28

injecting, and reinjecting the product, using retrograde linear threading and depot injection techniques as well as a treatment plan with effective results avoiding complications and side effects.

Keywords
Poly-L-lactic acid · Biostimulators · Facial aging · Cosmetic techniques · Cosmetic · Injectable agents · Injectable PLLA

Introduction

Aging is a complex process that takes place through interdependent changes in the tissues of the face. These changes are gradual and can be seen in the skin, fat compartments, muscle, and bone structures that lead to the overall appearance of facial aging (Fitzgerald and Vleggaar 2011).

Aging in the mid-face region is caused by multiple factors, described in a three-dimensional aging process that involves the loss of fat pad volume, the dropping of this volume, and changes in the skin. The entire anatomical component of the mid-face region is affected. The changes of the proportions during facial aging led physicians to research on bone augmentation techniques and injectable agents. Understanding how volume is lost, where it is lost from, and the optimal place to reposition it has increased our ability to achieve natural-looking results using biostimulators such as poly-L-lactic acid (Fitzgerald and Vleggaar 2011).

History Poly-L-lactic acid (PLLA) was first introduced commercially in Europe in 1999 for the cosmetic correction of wrinkles and scars under the name of New Fill® (Narins and Rotunda 2006; Valantin et al. 2003). The original usage guidelines were inadequate due to incorrect dilution and incorrect injection techniques, and this, coupled with a lack of clinical experience, led to adverse side effects such as nodules and areas of subcutaneous hardening (Lowe 2006). In 2004, PLLA was approved by the US Food and Drug Administration (FDA) under the name of Sculptra® for the treatment of facial lipoatrophy associated with human immunodeficiency virus (HIV/AIDS) (Mest and Humble 2006; Valantin et al. 2003). Five years later, in 2009, it was approved for cosmetic indications to treat lipoatrophy in immune-competent patients (Vleggaar et al. 2014a).

Over the years, the demand for facial rejuvenation has increased and consequently has the number of studies on this particular product. Medical evidence and practical experience with PLLA over the last decade have contributed to a greater understanding of the clinical, technical, and mechanistic aspects of this agent and led to many improvements in patient results. We now have consensus recommendations regarding the usage, storage, and optimal injection techniques (Vleggaar et al. 2014a).

Indication and Satisfying Patient Expectations

PLLA is primarily indicated for the restoration, recuperation, and replacement of volume loss and contour due to facial lipoatrophy, making it a good choice for the treatment of patients between 40s and 50s (Fig. 1a, b). However, it is also appropriate for younger patients wishing to maintain healthy, youthful and firm skin. A recent consumer survey conducted on behalf of the American Society of Plastic Surgeons found that a consistent number of patients would rather have a facial injectable treatment than a surgical treatment (American Society of Plastic Surgeons 2006; ASDS Survey 2014a, b; Vleggaar et al. 2014b).

As we have observed in our daily practice, the results obtained with PLLA injections are prolonged and can be maintained for over 2 years (Mest and Humble 2006). According to a comparative study (Brown et al. 2011; Narins and Rotunda 2006) which tested the efficacy and duration of PLLA and collagen injections when applied on the nasolabial folds, PLLA had a longer duration, lasting over 25 months which was longer than the collagen. This differentiates the product from other fillers, despite being considered better as a biostimulator than a filler itself.

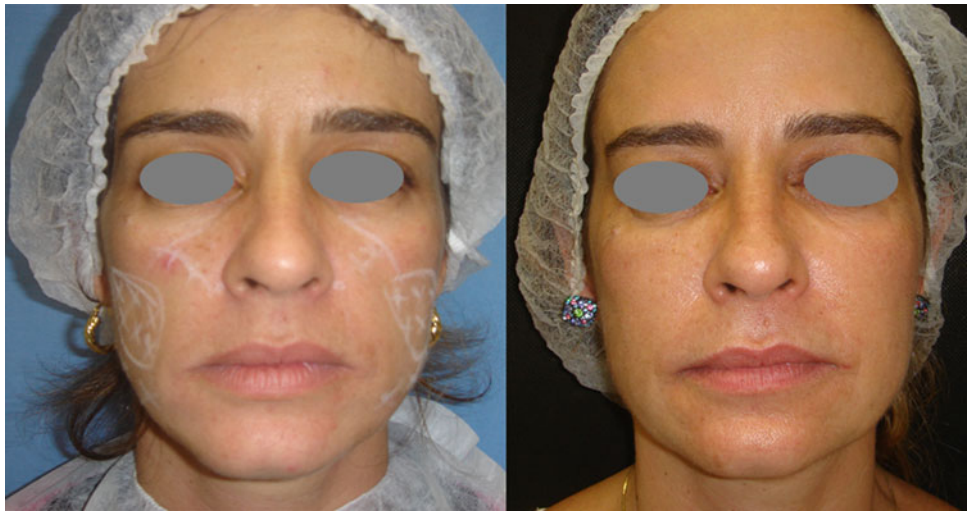

Fig. 1 (**a**) 42 years old, showing lipoatrophy, heavy smoker. (**b**) 50 years old, after seven sessions of PLLA and no additional soft tissue augmentation

The Product

PLLA is a biodegradable, reabsorbable polymer that chemically belongs to the alpha-hydroxy acid group. The product comes bottled in a powdered form and requires reconstitution prior to use. The microparticles (40,8%), measuring an average of 40–63 μm in diameter, are suspended in a CMC gel carrier (24,5%) and non-pyrogenic mannitol (34,7%) (Sculptra 2009). PLLA powder is available in 367,5 mg dose vials and must be reconstituted with sterile water for injection (SWFI) or bacteriostatic water at least 2 h prior to injection (Vleggaar et al. 2014a). The product should be hydrated at room temperature to ≥24 h.

The longer the dilution time, the easier it is to apply without needle obstruction due to the increased hydration of the product. The official recommendation is reconstitution with 5 ml of sterile water (Sculptra 2009). However, dilutions used by physicians in their clinical practices may vary. According to the new consensus recommendations, 7–8 ml of SWFI or bacteriostatic water should be added slowly to the powder. This dilution prevents many problems such as nodule formation or PLLA microclumps. The vial must not be shaken during hydration as this can result in the deposition of dry PLLA clumps on the vial wall. Reconstituted PLLA can be stored for up to 48 h at room temperature and for 3–4 weeks in the refrigerator when bacteriostatic water is used for reconstitution. The average temperature should be kept between 5 °C and 30 °C (4–85 °F). If desired, 1 or 2 ml of lidocaine 2% can be added to the solution at the time of application and immediately prior to use. The lidocaine can be with or without epinephrine. The volume of the final injection for facial treatment is 9 ml (Vleggaar et al. 2014a). PLLA is injected with a TERUMO 25–26 G needle × ½″ (0,45 × 12 mm) or 25G 1,5-in. (long) or 26 G 1′. However, experienced practitioners may also consider using a cannula (22 G, 50 mm), depending on the injection site.

Mechanism of Action

The PLLA mechanism of action appears to depend primarily on the host response and the slow degradation of the PLLA microspheres (Narins and Rotunda 2006). The microparticles in PLLA measure 40–63 μm in diameter. This product is not a filler but a stimulator of the patient's own collagen. The effects are not immediate. As the product is reabsorbed and

degraded, new collagen creates tissue volume. At the same time, and in response to the injected implant, local fibroblasts are stimulated to promote neocollagenesis leading to a long-term augmentation of soft tissue defects, with gradual volume enhancement (Moyle et al. 2004). Histologically, PLLA injections are accompanied by the proliferation of giant cells and histiocytes. These are highly controlled foreign body reactions. The macrophages play a central role in the reaction of foreign body types organizing the pro-inflammatory microenvironment around this biomaterial, secreting inflammation mediators, such as cytokines, chemokines and growth factors (Van Putten et al. 2013). The subclinical inflammatory tissue response and consequent fibroplasia produces the desired cosmetic result. After reabsorption, a significant increase of collagen fibers can be observed in the treated area. This effect is noticed clinically approximately 6 months after the injection (Vleggaar et al. 2014a).

Application Techniques

To obtain successful results with this product, there must be sufficient dermal thickness to achieve the correct depth of injection (Vleggaar et al. 2014a). PLLA is placed between the deep reticular dermis and subcutaneous tissue levels followed by a manual massage after injection to ensure proper PLLA distribution in the tissue (Bartus et al. 2013; Sadick 2008). Alternatively, it can be placed on the supraperiosteal area for more amount of volume. Superficial injections must be avoided as they may lead to visible nodules.

The author recommends frequent self-massage by the patients for 1–2 weeks after the procedure for better product distribution.

Retrograde Linear Threading

Pinch the skin to verify where the weakest area is and stretch it in the opposite direction at the moment of injection. Introduce the needle or cannula and lift it slightly and watch for the formation of a small roll beneath the skin. The correct place to inject the product is in the subcutaneous fat right under the dermis. A reflux maneuver must be performed slowly to ensure that no blood vessels have been hit. There are several techniques that can be considered: the cross-hatch pattern, fanning and cross-fanning. The technique selected will depend on the experience of each physician and depend on the anatomic area such as cheeks, submalar, and lateral face (Vleggaar et al. 2014a).

Depot Technique

Depot approaches can be used at the supraperiosteal level, in bolus. In all applications, and particularly with this technique, the injection, using needles, should be slow, and aspiration is absolutely essential to avoid any vessels. Other products can be added at the supraperiosteal regions to compensate the loss of volume. Depot technique using needles is indicated for zygoma, canine fossa, and mental area. This technique requires training and control by the professional. It is recommended for those with enough experience in the application of PLLA. After each depot approach, massage should be done immediately. Figure 2 shows some site recommendations for the injection of PLLA (Bartus et al. 2013; Vleggaar et al. 2014a; Fig. 2).

Site-Specific

Site-specific recommendations with PLLA for facial volumization are (Vleggaar et al. 2014a):

- *Upper face*: inject supraperiosteally using cannula in the temples and lateral brow
- *Medial cheek/mid-face*: inject supraperiosteally using depot technique with needles over the zygoma and canine fossa/pyriform aperture
- *Submalar/mid-cheek*: inject using cannula or needle into the deep subcutaneous layer
- *Lateral face, above the parotid gland and masseter muscle*: inject using cannula or needle in the superficial subcutaneous layer
- *Mental area*: depot technique, at the supraperiosteal level

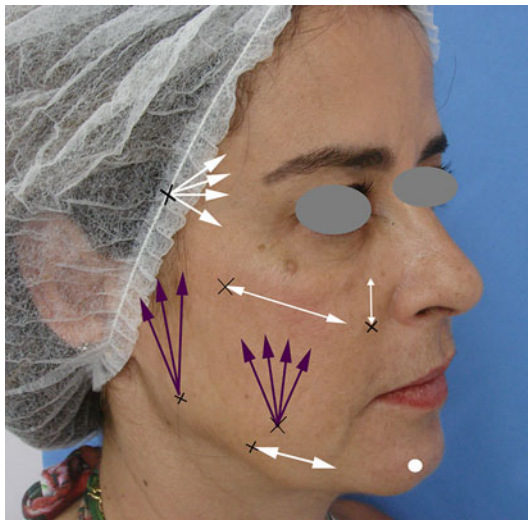

Fig. 2 Some examples of areas to correct with injection of PLLA. Recommended points to entry for each area, *Black* "X"; *white arrows* and *ball*, supraperiosteal area; *purple arrows*, subcutaneous fat

Proscribed Areas

- Forehead
- Glabella
- Orbicularis oculi muscle (lower eyelid)
- Lips (contour or volume)
- Modiolus
- Depressor anguli oris muscle

Suggestion for Application and Reapplication

The amount of product used per session should be determined according to the facial surface. The number of sessions needed is defined by the total amount of volume loss (severity of lipoatrophy). Other factors influencing the total volume and the number of sessions are age, gender, bone structure, facial asymmetry, cost, and the desired cosmetic result.

Based on the author's experience, the proposed schedule is as follows (consider number of sessions as one vial of PLLA):

First session: initial treatment
Second session: 4–6 weeks from the initial treatment
Third session: 6–8 weeks after the second treatment

Suggested number of sessions:

Moderate loss of facial volume: two to three sessions
Pronounced lipoatrophy: more than three sessions
Additional sessions may be required after and each 18 months, to maintain the results and to keep up with the aging process. Subsequent treatments may need less product (Vleggaar et al. 2014a).

Figure 3a, b shows the evolution of the treatment of a patient who was 42 years old at the time of her first PLLA injection. She continued treatment for 10 years with sessions approximately 18 months apart.

Side Effects

Hematomas – Use ice pads or cold dressings for the following few hours and avoid sun exposure for the next 15 days; concealer or camouflage makeup on the area is allowed.

Subcutaneous and non-visible papules (less than 5 mm) – The most common area for papules to emerge is in the oral commissure region. These will usually disappear spontaneously in around 3 months (Vleggaar et al. 2014c; Vleggaar 2006).

Visible nodules (greater than or equal to 5 mm) – It appears 1–2 months after injection and the cause usually is technical error. This side effect tends to resolve itself spontaneously within 2 months (Van Putten et al. 2013; Vleggaar et al. 2014a). Those which do not disappear this way may be removed using a 26 G needle and syringe and saline solution (SS), introducing it into the small nodule to break it (Fig. 4a–c). This procedure was used by the author, to deal with this side effect and for the additional purpose of redistributing the PLLA particles in a more uniform manner in the area.

Histologically confirmed granulomas – Granulomatous reaction has been reported with many different types of fillers. It can appear 6–24 months

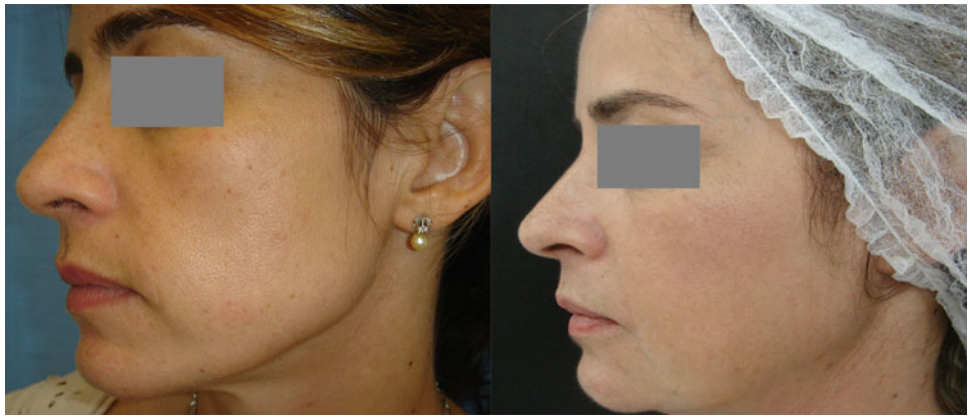

Fig. 3 (**a**) 2006: initial session. (**b**) 2016: seven sessions, 18 months apart

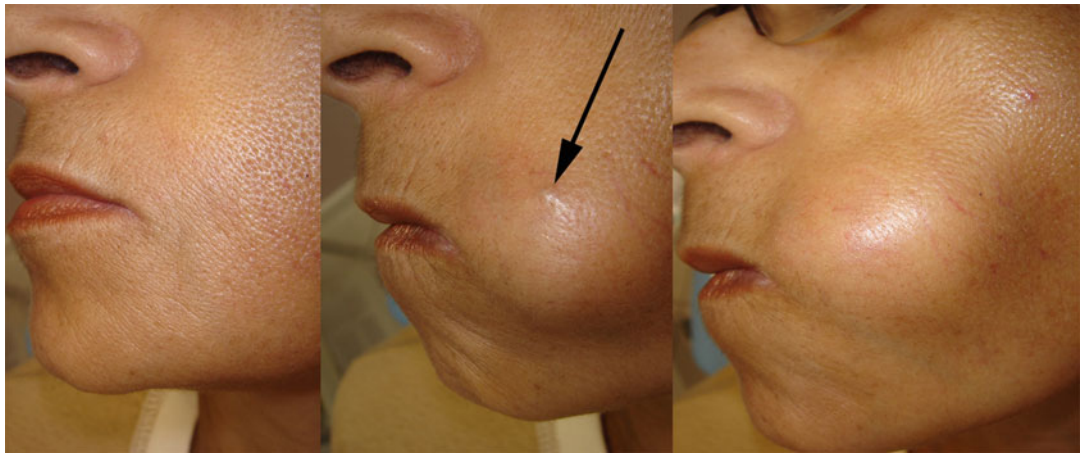

Fig. 4 (**a**) Existent nodule, not visible. (**b**) Nodule, made visible with tongue in cheek. (**c**) Nodule ruptured after subcision with SS (Reproduced with permission of Ed. Gen and AC Farmaceutica (book "Preenchedores"))

after injection. The treatment suggested is oral corticoids for 10 days and doxycycline 100 mg/day for at least 8 weeks (Vleggaar et al. 2014c). Some physicians use intralesional doses of steroids or antimitotics such as 5-fluorouracil (5FU), once a week to clear the lesion (Lemperle et al. 2009). However, others believe that steroid injection or 5FU have little clinical effect on these lesions, because most are product-dependent and not the host's reaction to the product (Vleggaar et al. 2014c).

Angioedema – This is a rare manifestation of a possible allergic reaction to PLLA injections (Guardiani and Davison 2012). There is a case report involving a patient who had a medical history of significant hypertension and was taking lisinopril at the time of injection. She had no prior history of medication allergies or sensitivities. She had received treatments of both PLLA and hyaluronic acid (HA) but had previous experience with HA without adverse reactions. This would imply that the reaction was caused by the PLLA itself. Angioedema caused by angiotensin-converting enzyme inhibitor can result in edema of the face, lips, upper airway, and gastrointestinal tract. It is thought to be caused by the accumulation of bradykinin in a patient with a predisposition who is using an angiotensin-converting enzyme inhibitor, which increases vascular permeability. This reaction can emerge anywhere

from hours to years after starting an angiotensin-converting enzyme inhibitor. A bradykinin response can also be induced by a local trauma. Despite the immediate hypersensitive reaction to dermal fillers being uncommon, doctors injecting dermal fillers in patients on angiotensin-converting enzyme inhibitor therapy should be aware of the fact that the local trauma from the injection could potentially induce angioedema (Guardiani and Davison 2012). This is a potentially fatal adverse reaction which requires immediate hospital treatment.

Contraindications

Contraindications are the same as for any facial filler: acne, infections or active herpes, collagen diseases, active autoimmune diseases, patients prone to keloids, pregnancy, breastfeeding, and previous definitive fillers of the same area.

Take Home Messages

- Injectable PLLA provides a flexible way to treat signs of aging such as volume loss by restoring the contour of the whole face and other areas without treating individual wrinkles.
- A physician must pay careful attention to get a thorough medical history from the patient and be clear about the results that can be achieved to avoid any unrealistic expectations.
- Developing the correct application skills will allow the doctor to restore the lost volume and give the patient back their natural youthful appearance. When injected correctly, there are relatively few adverse complications and all the benefits of a minimally invasive procedure.

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Poly-L-Lactic Acid for Body Treatment

Daniel Dal'Asta Coimbra, Betina Stefanello de Oliveira, and Natalia Caballero Uribe

Contents

Abstract

The poly-L-lactic acid (PLLA) injection technique stimulates neocollagenesis and provides a natural look. In recent years there has been a growing interest for using this in other body areas such as the neck, chest, back of the hands, lower breast region, thoraco-axillary fold, buttocks, arms, and medial thighs. There is no clear consensus regarding the best dilution or application techniques for the face and the body, and the description in this article is

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_29

based on the authors' experience. In this chapter I will approach a new technique for body areas and the dilution of the quantity of the product per application. The application of PLLA for rejuvenation of body areas is a minimally invasive procedure, with durable and low frequency of complications.

Keywords
Poly-L-lactic acid · Body area · Technique · Rejuvenation · Minimally invasive procedure

Introduction

Treatment of skin aging through nonsurgical rejuvenation is gaining more popularity over recent years. Important strategies to reverse signs of aging include restoring facial volume and improving skin laxity (Murad et al. 2008). The poly-L-lactic acid (PLLA) injection procedure is able to act in these two important points, stimulating neocollagenesis, providing a natural look (Distante et al. 2009).

The PLLA was approved in Europe in 1999 and approved in the United States in 2004 by FDA for the treatment of facial lipoatrophy associated with human immunodeficiency virus (HIV). In 2009 the FDA approved the cosmetic indication in immune-competent patient (Vleggaar and Bauer 2004; Vleggaar et al. 2014). In Brazil, the use of long-duration fillers, like PLLA, was approved for lipoatrophy in HIV-patient treatment. It is used as an off-label indication for cosmetic purposes in healthy patients.

Over the past 20 years of experience, PLLA has been used as safe and effective filler for cosmetic procedure. It has been used to restore volume in facial aging, treating the malar region, nasolabial fold, mentonian region, and lower face contour, as well as a biostimulator to induce neocollagenesis (Sherman 2006). In recent years, a new interest in PPLA use involves its indication for other areas, not the face. The use of PLLA in the body has been described in the neck, chest, back of the hands, lower breast region, thoraco-axillary fold, buttocks, arms, and medial thighs (Vleggaar et al. 2014; Lowe 2008; 2009; Palm et al. 2010; Peterson and Goldman 2011; Lam et al. 2006).

Poly-L-Lactic Acid Basic Concepts

The PLLA are aliphatic, biocompatible, biodegradable synthetic polymers. Actually, it is a biostimulator, inducing autologous collagen production, providing gradual tissue volume and progressive firmness. It cannot provide an immediate filling effect. The end result will depend on the quality of the neocollagenesis of the selected patient, on the PLLA reconstitution, on the PLLA plan of application, and on the depth level of application (Murad et al. 2008; Distante et al. 2009; Sculptra [prescribing information] 2006). It is mainly indicated to restore and/or correct facial fat loss caused by aging or in cases of lipoatrophy in people with HIV infection (Sculptra [prescribing information] 2006).

Histological studies about PPLA effects on tissue, in rats' skin, showed production of collagen (Bos et al. 1991; Gogolewski et al. 1993). Studies in human skin reported cellular response in cascade, orchestrated by macrophages and myofibroblasts, resulting in production of collagen type I and III (Vleggaar 2005; Lemperle et al. 2003; Stein et al. 2015). Studies in HIV patients with facial lipoatrophy showed that the treatment with PLLA promoted increase in dermal thickness, which was sustained for 2 years (Lowe et al. 2009; Valantin et al. 2003).

The cellular cascade response to PLLA injection occurs during a period after the application, promoting a progressive effect. Series of injections are necessary to reach natural volumetric correction. On the other hand, it is important to have an interval of 4–6 weeks between the sessions of treatment to allow restorative biological processes and to avoid overcorrection (Sherman 2006; Sculptra [prescribing information] 2006; Vleggaar 2005; Mandy 2007; Vleggaar and Fitzgerald 2008; Sadick 2008; Woerle et al. 2004; Mandy n.d.). There is a sentence to define this approach: "treat to repair, wait to restore and evaluate to refine" (Sherman 2006; Lowe 2008; Mandy n.d.; Mest and Humble 2006).

It is important to know that PPLA requires a reconstitution using sterile water. The amount of water usually used for the face is 5–8 cc. After that, the product should stay at room temperature for at least 2 h, varying from 2 to 48 h, for hydration (Sculptra [prescribing information] 2006). In clinical practice, many physicians include lidocaine after the hydration period, just before procedure (Vleggaar and Bauer 2004; Sherman 2006; Lam et al. 2006; Vleggaar 2005; Mandy 2007 n.d.; Fitzgerald and Vleggaar 2011; Teimourian and Malekzadeh 1998). When treating the body, non-facial areas, the product should be re-diluted with more sterile water. In the end of each session, for all areas (face or body), it is essential to massage the treated area thoroughly.

Poly-L-Lactic Acid for Non-facial Areas

Literature Review

Radaelli, in 2006, described a technique for PLLA dilution. He diluted PLLA with sterile water (6–8 cc) and 3% mepivacaine hydrochloride without epinephrine (0.5 cc), 24–48 h before the procedure to treat the cervical region or hands. After dilution, the preparation was maintained at room temperature, and the reconstituted product was stirred just before its application. The amount of 0.05 cc per point of injection using a 25–27 °C needle was used (Mazzuco and Sadick 2016).

Radaelli and Forte (2009) reported a study with 568 patients treated with PLLA for cosmetic purposes, where new areas (breast, axillary fold, arm, and medial thigh) were treated with promising results, including stratum corneum hydration, increasing in dermal thickness and improvement in skin elasticity (Sadick and Arruda 2016).

In most cases the retrograde linear technique is used, and many linear injections are spread in all over the area according to the plan of treatment. These lines of application can be crossed, mainly when volume is desired. Another possible technique is the "fan" technique, in which a long needle (25–42 mm, needle 26 G) enters the subcutaneous layer through the skin and an in-and-out movement is done (Mazzuco and Sadick 2016; Sadick and Arruda 2016). The product should be injected in the deep dermis and in the subcutaneous tissue layer. Superficial injection is not indicated (Mazzuco and Sadick 2016; Sadick and Arruda 2016).

The total volume injected varies according to the area to be treated, but in general, the average amount is 1.5–2.0 cc/area. For the face, 0.1 cc is injected in each point of application. In area where the skin is thinner, as the neck, the amount of product injected per point is 0.05 cc (Mazzuco and Sadick 2016; Sadick and Arruda 2016). When treating the hands, 0.05 cc is injected, avoiding the vessels, but other techniques are described with a needle (three points of injection – 0.3 cc/each point) or using a cannula to spread all the volume in different points (Mazzuco and Sadick 2016; Sadick and Arruda 2016).

Mazzuco and Hexsel (2009) reported a study with 36 patients with different degrees of cutaneous laxity, atrophy, and wrinkles in the neck and chest who were treated with PLLA. In the photographic analysis, 81–100% of improvement was reported ($p < 001$). In the questionnaire regarding the degree of satisfaction, 91.6% said they were pleased with the procedure results and that they would do it again. The results were maintained for 18 months of follow-up (Mazzuco and Hexsel 2009). Authors described the following technique: topical anesthesia (prilocaine and lidocaine) was applied 30 min before procedure, and ice was applied immediately before the injections. Some patients received sublingually analgesia with ketorolac trometamol (10 mg) 30 min before the procedure (Mazzuco and Hexsel 2009). PLLA vials were diluted in 10 cc of sterile water for injection 2–3 days before. After dilution, the vials were kept at room temperature before procedure. A 1 cc Luer-lock syringe was used with 27 G needle (0.4 × 4 mm), and 0.1 cc of 2% lidocaine was added in each 0.9 cc of diluted PLLA suspension (Mazzuco and Hexsel 2009). Injections were performed between the index finger and the thumb in points 1 cm equidistant from the previously marked area. The injection was done in the transition between the deep dermis and subcutaneous tissue, with the needle inserted at an angle of 60°.

The volume per point was 0.05 cc of the diluted solution. Immediately after the procedure, the area was vigorously massaged for 2 min. The patients were instructed to rub the entire area over 5 min, three times daily, for 7–14 days to prevent subcutaneous nodules. Depending on the sagging, one to four sessions were required. In the neck, the volume per session ranged from 4 to 7 cc with an average of 3.9 cc. In the chest, the amount of product injected was 1 cc per session, and only one or two sessions were necessary. In general, the results persisted for 18 months or more (Mazzuco and Hexsel 2009).

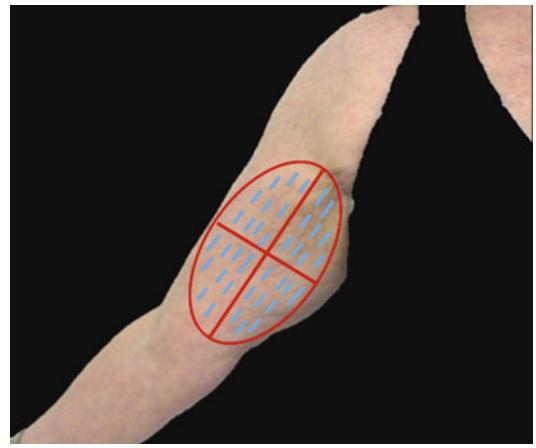

Fig. 1 Arms – Division of the area to be treated in four quadrants. Application was done in parallel sticks

Authors' Experience

Coimbra and Amorim described the use of PLLA technique for medial and anterior arms. The arm region to be treated was demarcated and divided into four areas. The PLLA was reconstituted 24–36 h before procedure with 8 cc of sterile water for injection and was maintained at room temperature. Immediately before use, the bottle was gently shacked until reaching the homogeneity of the product. Simultaneously, another solution was prepared with 8 cc of sterile water and 4 cc of 2% lidocaine without epinephrine (Coimbra and AGF n.d.). Using Luer-lock syringes of 1 cc, authors mixed 0.4 cc of the product (diluted PLLS) and 0.6 cc of solution (water + lidocaine) to have the final preparation.

The application technique was linear retrograde (Fig. 1), injecting parallel cylinders (sticks) of product using approximately 0.05 cc of the final solution in the deep dermis. In each quadrant, approximately 1,25 cc of the product was used. Each session required only 10 cc of the product for both arms. After application, 10 min of vigorous massage on the treated area was performed, and the patient was instructed to perform the same at home, twice daily for 10 days, according to the literature (Coimbra and AGF n.d.).

The number of sessions varied from 2 to 4, with 4–6 weeks of interval. Four weeks after the first application, it was possible to notice an improvement in the skin texture and sagging, as well as in cellulite. The results were more evident after the second application (Coimbra and AGF n.d.) (Fig. 2). In some cases the improvement was evident 4 months after the first injection. According to the authors' experience, patients who have greater sagging skin should be treated with 10 cc of solution in each arm, and the injection is done around all the circumference (Coimbra and AGF n.d.). The result can last more than 24 months.

Similar results are achieved in the buttocks, legs (thigh), and abdomen. The PLLA in the legs and buttocks are used to improve the quality of the skin, especially if there is cellulite, sagging, and loss of volume. In the legs and buttocks, the application is done through parallel horizontal sticks, according to Fig. 3. The same is performed in the buttocks, except on the cellulites depression in which the X (cross sticks) technique is performed according to Fig. 4. The needle is inserted, at a 60 angle, between the deep dermis and superficial fat tissue, using 0.1 cc per injection point placed approximately 1 cm apart from one another, until all marked area is treated. Patients are asked to massage the treated area for 5 min, three times a day, for 7 days. In some cases the improvement is evident 4 months after the first application. The result can last more than 24 months (Fig. 5).

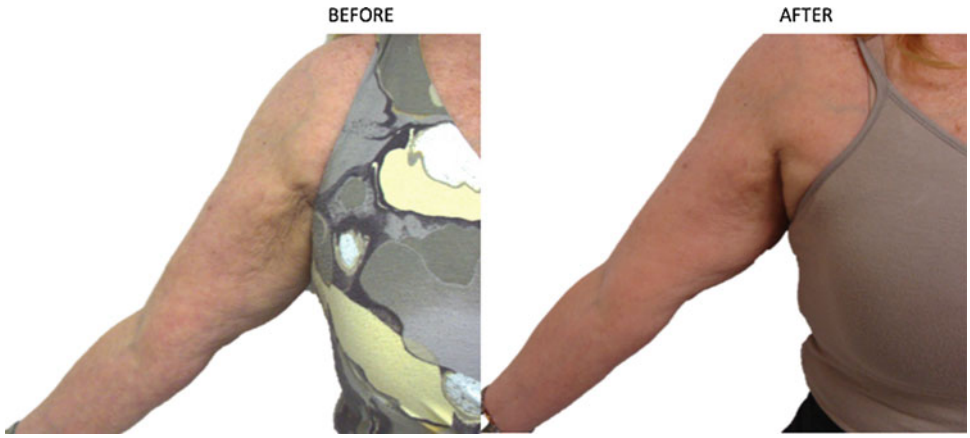

Fig. 2 Arms – Before and after four sessions, 6 weeks apart: improvement of the skin texture, with reduced sagging and cellulite appearance

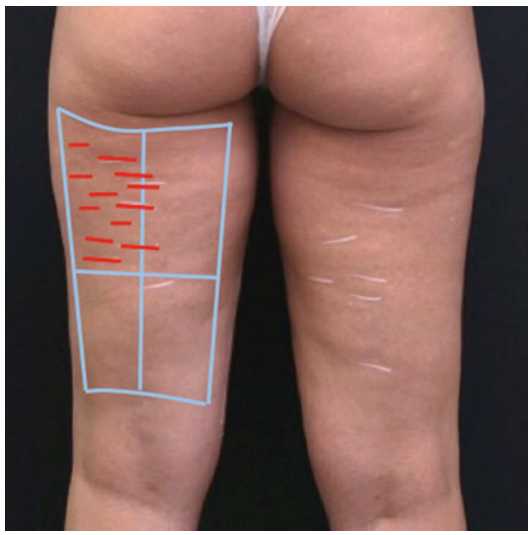

Fig. 3 Legs – Division of the area to be treated with application in parallel sticks

In the abdomen for laxity treatment, the application is similar. Abdominal exercise should be avoided for 6 weeks.

Contraindications

The PPLA procedure is not indicated for patients with a past history of permanent fillers in the area to be treated, autoimmune disease, granulomatous disease, connective tissue disease, and keloids (Vleggaar et al. 2014; Duffy 2005).

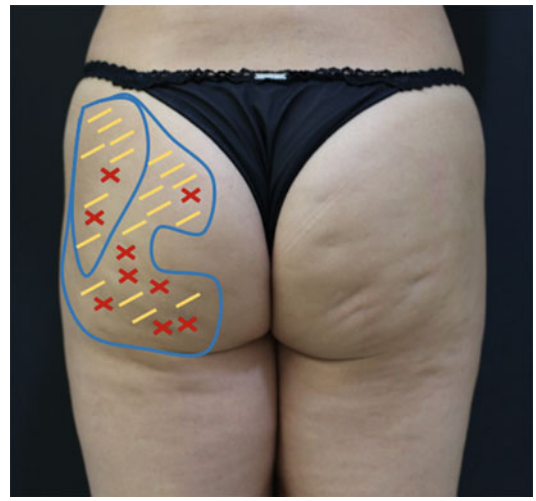

Fig. 4 Buttocks – Division of the area to be treated, application with cross stick technique

Side Effects

Side effects are generally self-limited and include pain during application, erythema, local edema, transient bruising, papules, or nodules. The incidence of nodules and papules is reduced by diluting the product, i.e. PLLA,

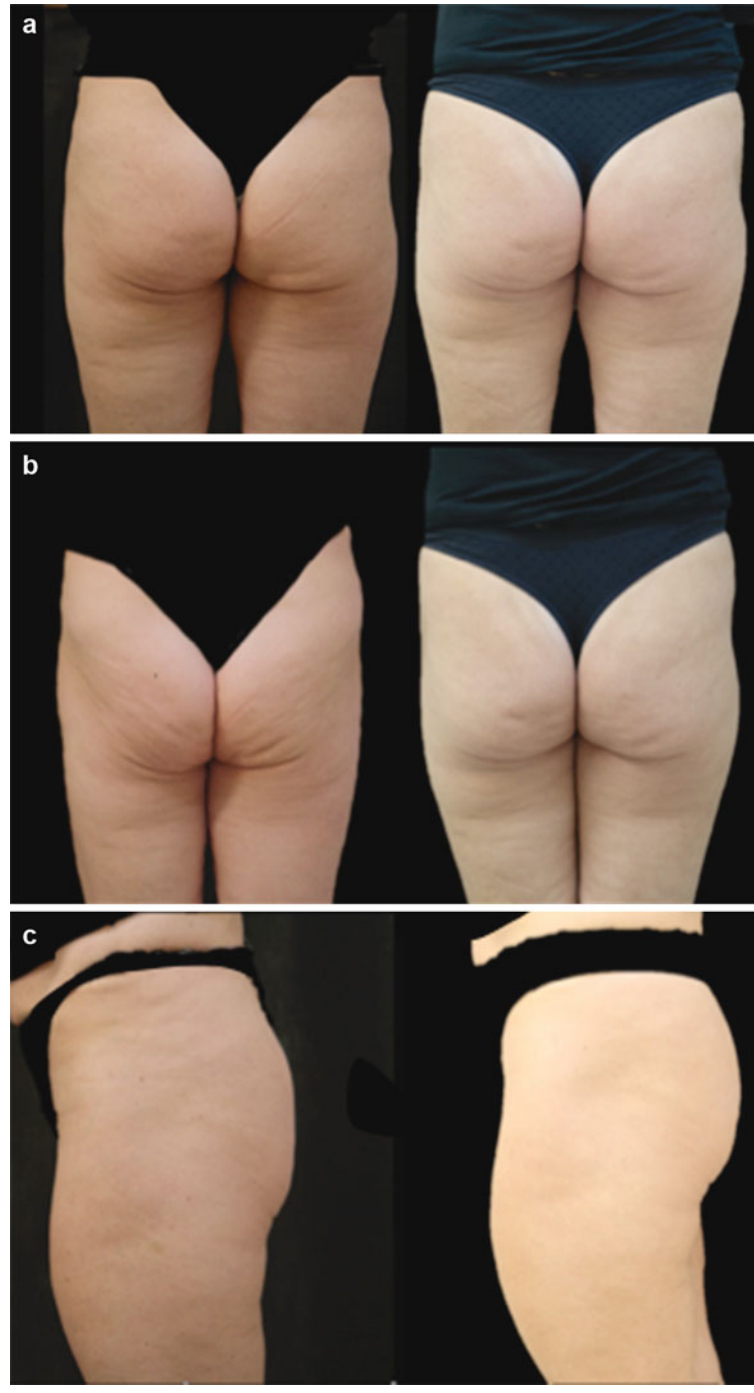

Fig. 5 Buttocks and thighs – Before and after four sessions, 6 weeks apart: improvement of the skin texture, sagging, and cellulite appearance in the treated area. (**a**) Relaxed muscles. (**b**) With muscular contraction. (**c**) Lateral view

using subcutaneous injections, avoiding both superficial injections and massaging the area of the injection the week following the procedure. Most of the nodules have spontaneous resolution in a few months or years (Murad et al. 2008; Duffy 2005; Lowe et al. 2005; Gladstone and Cohen 2007).

The occurrence of inflammatory granulomas is very rare and the pathophysiology is not known. There is no standard treatment for this granuloma,

but in general there is a good response with oral minocycline associated or not with oral and intralesional corticosteroid. There are reports of the use of intravenous 5-fluorouracil in the treatment of inflammatory nodules related to application of PLLA (Duffy 2005; Lowe et al. 2005; Gladstone and Cohen 2007).

Conclusion

When choosing the treatment with PLLA for skin rejuvenation, treating the face or the body, dermatologists should consider that the results vary from patient to patient and they are directly related to the PLLA dilution and the volume of product used and also to the depth of injections (Fitzgerald and Vleggaar 2011).

To avoid small late nodules (after 12 months), Coimbra suggests the dilution of 20 cc and recommends the application of a small amount (0.05) in the deep dermis.

There is no consensus in the literature about the quantity of product used per session. Usually one vial of PLLA is indicated for each session when treating the abdomen or arm or thigh or buttocks (Peterson and Goldman 2011; Teimourian and Malekzadeh 1998).

Good results can be achieved after three to five sessions and the results can be sustained for 2 years.

Take Home Messages

- PLLA stimulates neocollagenesis and provides a natural look.
- With a correct dilution, it can be used in body areas such as the neck, chest, back of the hands, lower breast region, thoraco-axillary fold, buttocks, arms, and medial thighs with good results.
- It is good to keep in mind that when using PLLA we have to consider the following sentence: treat to repair, wait to restore, and evaluate to refine.
- Treatment sessions should be spaced with 4–6 weeks of interval to avoid overcorrection.
- When treating the face, PPLA reconstitution is done with 5–8 cc of sterile water. After that, a period of 48 h (or at least 2 h) is necessary for hydration.
- For body treatment, PLLA should be re-diluted after the period of hydration to avoid nodule formation.
- At the final of the session, it's essential to massage the treated area thoroughly;
- In clinical practice, many physicians include lidocaine during the reconstitution step, after hydration and just before the procedure.
- The final result will depend on the patients' ability to induce neocollagenesis and on the correct way of dilution and technique of application.

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Fillers and Collagen Stimulator for Body Rejuvenation and Cellulitis

Gabriella Correa de Albuquerque

Contents

Abstract

More and more we have noticed the use of fillers in extra-facial regions with the aim of improving sagging and firmness. Dermal fillers, as a category of implantable medical devices, consist of a wide array of products that differ significantly in their chemical composition, mechanism of action, duration, safety, and interaction with host tissues. Their ability to synthesize new collagen and their rate of metabolism are the important rules that must be followed when it comes to body rejuvenation. It is the aim of this chapter to present a review in the literature and to estimate the safety and results of this new technique in order to improve the skin tones and irregularities (atrophies) of the skin surface in the body area, such as the neck, thighs, abdomen, brachial zones, as well as buttocks.

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_27

Keywords
Body rejuvenation · Collagen stimulator · Biostimulators · Fillers · Hyaluronic acid · Poly-L-lactic acid · Calcium hydroxylapatite

Introduction

It is widely known that body contour is deeply related to adipose tissue. Alongside with the skin aging process, there is a replacement of adipocytes by fibrotic structures. Some regions suffer from a process of fat loss (such as the buttocks) that promotes modification in the body shape. In addition, loss of collagen and elastin in the dermis may decrease elasticity, more noticeable in the thighs, arms, abdomen, and buttocks (Mahmoud and Ozog 2012; Pavicic 2013).

The use of fillers such as hyaluronic acid (HA) and also injectable collagen stimulators such as poly-L-lactic acid (PLLA) and calcium hydroxylapatite (CaHA) has been reported by the current literature and has already been effectively used on the face. These products can also be selected because of the safety as good fillers and the ability to produce collagen and they are biocompatible material, latex-free, nontoxic, non-mutagenic, and physiologically inert (Wasylkowski 2015; Chao et al. 2011; Redaelli and Forte 2009; Coimbra and Amorim 2012; Pavicic 2015). Hyaluronic acid has been used for a while in some body areas to correct atrophic areas so as to replace contour. Very recently, some studies have been reported about the ability of hyaluronic acid to cause neocollagenesis (Wanick et al. 2016). The mechanism of action of CaHA and PLLA is to induce synthesis of collagen, thus promoting a constant and gradual improvement of the skin surface for months after the last procedure, and CaHA and PLLA are considered as biostimulators. It is also known that CaHA can also produce a discrete and immediate volumization after application in the body, but this effect is not sustained as HA (Wasylkowski 2015; Chao et al. 2011). Given the specific anatomical features of these regions together with the fact that the results of HA, CaHA, and PLLA are both dependent on patient's response to collagen production and on the practice of the user, it is recommended that experienced physicians perform the body rejuvenation injections (Pavicic 2015).

Fillers and Collagen Stimulator for Body Rejuvenation and Cellulits

Calcium Hydroxyapatite

CaHA is identical to the major mineral component of human body structures and provokes little immune response. Extensive preclinical testing has shown that CaHA is inert and non-antigenic. No patient sensitivity testing is required prior to treatment with CaHA. Injectable CaHA (Radiesse®, Merz Pharmaceuticals GmbH, Frankfurt, Germany) is a biodegradable product composed of approximately 30% CaHA microspheres, 25–45 μm in diameter, combined with a 70% sodium carboxymethyl cellulose carrier gel, sterile water, and glycerin (Ridenour and Kontis 2009). Although these microspheres are made of calcium and phosphate, no osteogenesis has been reported. In literature overview, a scientific article (Marmur et al. 2004) states that clinical, histological and electron microscopic findings after injection of a CaHA cause an immediate correction made by the carboxymethyl cellulose carrier gel. After 4–12 weeks, all the gel is completely absorbed, with reduction of this initial clinical effect. In the next step, microspheres remain in place to act as a scaffold to migration of histiocytes and fibroblast stretch. As the matrix of new collagen is deposited, the implant becomes more integrated into the surrounding soft tissue, which provides for its longer-lasting effects.

Radiesse® received a Conformité Européenne (CE) certification mark (medical device class 3) for plastic and reconstructive surgery, including deep dermal and subdermal soft tissue augmentation of the facial area in 2003. It may be injected into the deep dermis, the subcutaneous tissue, or supraperiosteally depending on the area of the face and body to be treated.

Poly-L-Lactic Acid

PLLA has numerous applications in medicine and has been used for over 30 years. Injectable PLLA (Sculptra; Valeant, Bridgewater, NJ) is biocompatible, biodegradable, immunologically inert semipermanent synthetic soft-tissue stimulators that induce gradual new collagen synthesis by fibroblasts. It is generally injected into the reticular dermis and subcutaneous tissue planes; correction can last 2 years or longer (Vleggaar 2006). This product gained approval in 2009 for correction of shallow to deep nasolabial folds, contour deficiencies, and other facial rhytides. Since its introduction into cosmetic practice, PLLA has also been used in other locations including the hands, neck, chest, and atrophic scars (Redaelli and Forte 2009).

To our knowledge, the effect of body rejuvenation with these products has been reported in few articles in the literature, and further discussion of the phenomenon is awaited with great interest (Redaelli and Forte 2009; Coimbra and Amorim 2012).

Hyaluronic Acid

Stabilized hyaluronic acid (HA) of nonanimal origin manufactured using the patented NASHA(®) technology (Macrolane; Q-Med, a Galderma division, UK) has been developed for use in body shaping. The stabilized HA gel is a safe and effective treatment for temporary esthetic volume restauration and shaping of body surface, especially the buttocks and breast as reported in the literature (De Meyere et al. 2014; Camenisch et al. 2013). Although the substance degrades over time, a good proportion of the subjects still rated their buttocks as improved (40%) and expressed satisfaction (33%) 24 months after treatment. Larger quantities are recommended for volume restauration (mean of 163 mL of nonanimal stabilized hyaluronic acid gel per buttock in one article (Camenisch et al. 2013). It can also be used to correct depressions of cellulite. HA can be associated to CaHA or PLLA in the same region.

Procedures: Preparing Substances

CAHA

A more conservative approach to be used in the body was suggested by Wasylkowski (2015) with 3 mL syringe of CaHA diluted (in line with the US Food and Drug Administration approval) with 0.6 mL lidocaine (2% without epinephrine) to correct depressions on the buttocks. On the other hand, Chao et al. (2011)) mixed a 1:1 ratio CaHA with 2% lidocaine for horizontal necklines correction, and the total amount used for injection in each case of necklines was between 0.7 and 1.4 mL. In our experience, a 1:1 ratio is safer, promoting greater spreadability with fewer side effects.

After mixing, the diluted mixture can be injected horizontally beneath the skin at the dermal-subdermal junction using a 27-G cannula or a needle. Deposition of the dilution CaHA can be achieved through serial punctures in a linear threading pattern around the region to be treated.

Very recently, a new dilution of CaHa for body treatment has been reported. For each 1.5 ml of CaHa, it is now proposed to add 5.0 ml of physiologic solution 0.9% plus 1.0 ml of lidocaine (2% without epinephrine, completing a total amount of 7.5 ml to be injected with cannula 25G/22G or needle 27G (0.05 ml per injection point every 1–2 cm).

PLLA

In the Brazilian experience (Coimbra and Amorim 2012) with PLLA, another promising result is arm rejuvenation. The author uses one vial of PLLA with 8-mL dilution in sterile water for injection (SWFI) or bacteriostatic water (De Meyere et al. 2014) and stored for hydration at room temperature for $\geq$24 h. Do not shake the vial during hydration. Shaking can result in the deposition of dry PLLA clumps on the vial wall. In the time of the injection, the 8 mL previously diluted in SWFI is mixed with 4 mL of 2% lidocaine (without or with epinephrine 1:100,000). As noted, this differs from the reconstitution method outlined in the package insert, which recommends the use of 5 mL of sterile

water alone (Vleggaar et al. 2014). With increased dilution of the active principle, the dispersion consequently becomes less concentrated and is safer.

In our practice, we inject mostly with a linear retrograde technique with multiple parallel sticks with a distance of 2 cm per injection point using 0.05–0.1 mL per infusion (Coimbra and Amorim 2012) using a 25-G needle × 1.5 in. size. In some areas with marked lipoatrophy, a linear retrograde technique with cross sticks can be done in order to produce more volume. We can also use cannulas for product placement in in areas near known vascular landmarks to reduce the incidence of common, transitory adverse events such as hematomas (Vleggaar et al. 2014).

Hyaluronic Acid

HA fillers must be injected respecting the anatomical structures of the muscles and the volume needed. The syringe comes with HA ready to be applied. Needles or cannulas, preferably, are used (De Meyere et al. 2014; Camenisch et al. 2013).

Procedures: Area Approach and Injection Techniques

Vectoring approach is an effective method for restoring skin laxity. Busso (Shono et al. 2012) has already documented it to facial contouring. It seems that anchorage points and vectoring approach are the best options for body rejuvenation.

Recently, a clinical study (Wasylkowski 2015) demonstrated that the body vectoring technique, using Radiesse®, induced notable reductions in skin flaccidity, increased skin density, and increased skin thickness in three body zones.

Favored regions for CaHA and PLLA treatment include the abdomen, buttocks, thighs, and arms:

Abdomen – Two anchor points can be fixed under the ribs, and four lines are drawn from these points: two lines downward crossing above the navel and two lines downward at a 45° angled (Fig. 1). Several stick lines are drawn to cover the entire zone inside the triangle formed with the lines. This approach helps to correct navel shape and improves abdominal skin quality and sagging.

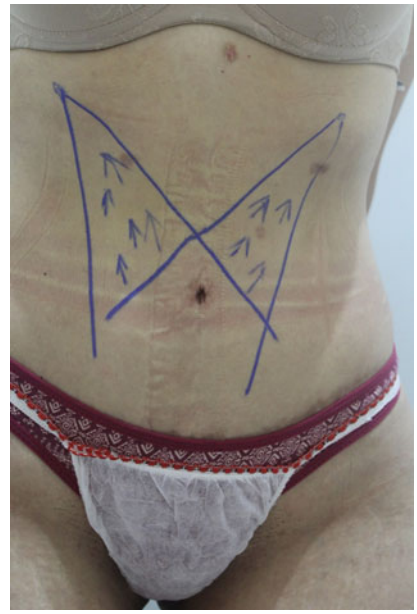

Fig. 1 Abdomen approach

Buttocks – At first, we should palpate the posterior iliac crest spine and draw two parallel lines from this point, on the superior area of the buttocks, with the aim to sustain the skin. Other areas are marked according to the depressions, and loss of volume. The X crossed stick technique, eventually with more volume, is preferred to fill larger depression. Parallel sticks on all the areas are used to improve the skin quality, improving sagging (Fig. 2).

Thighs and arms – These areas are marked according to the laxity of the region. Generally, we can notice the different quality of the skin in the inner part of the thighs/arms. All the areas should be marked, and usually parallel stick technique are used inside the area demarked. We should not use great volume for each point to avoid nodule formation, as the skin is very thin in these regions (Figs. 3 and 4).

After Procedure

In order to avoid lumps, exhaustive massage must be done after the procedure. Some moisturizers can be applied to help with the massage (Pavicic 2013; Vleggaar et al. 2014). Adverse

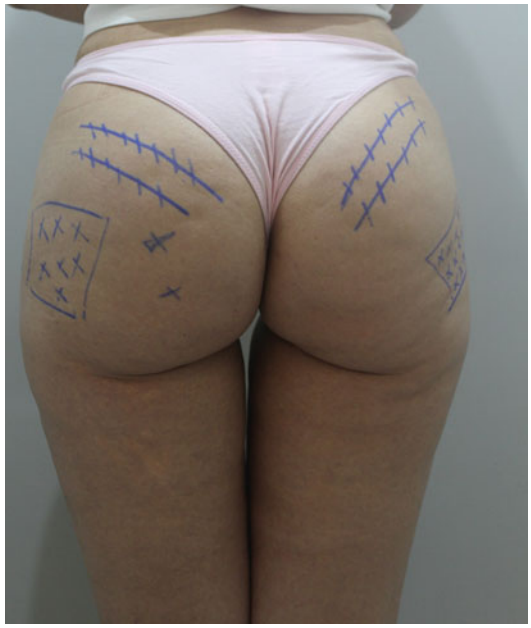

Fig. 2 Buttocks approach

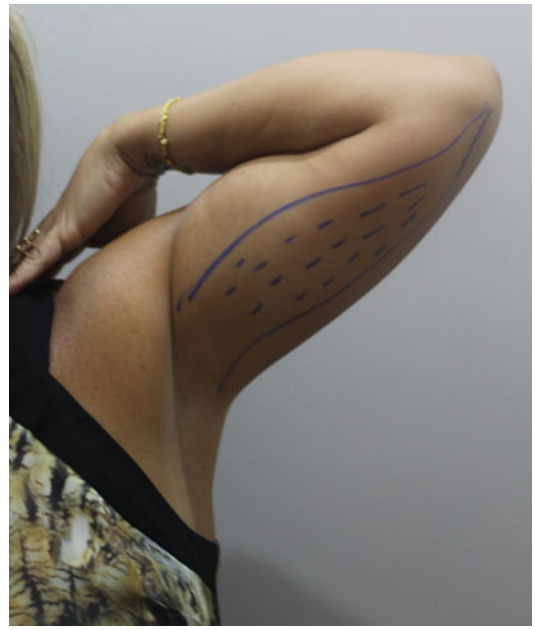

Fig. 4 Arm approach

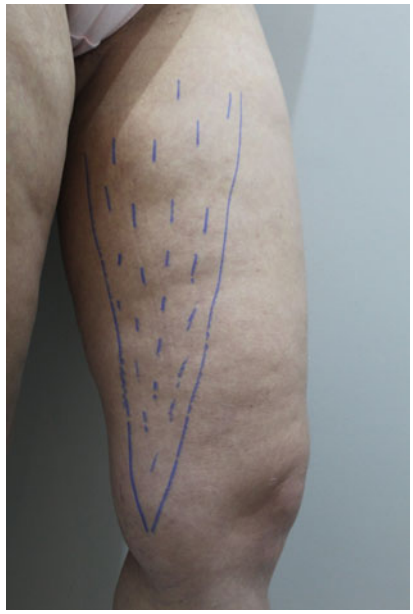

Fig. 3 Thighs approach

events, such as bruising and edema, can occur but are limited to the area injected and resolve spontaneously after a few days. Patients are advised to use some ice bags at home to reduce hematoma and to do massage (three to five times a day) at home for at least 5 days after procedure.

Avoiding Complications

Cannulas can be used to reduce bruising and edema, which occurs after multiple micropunctures with needles, and to avoid vessel obstruction (DeJoseph 2012).

Linear retrograde injection with parallel stick technique is performed using small volumes (0.05–0.1 mL) per injection, to avoid nodule formation (Busso 2009; Shono et al. 2012). A greater volume can be used in X crossed technique in cellulite depression on the buttocks.

Conclusion

The use of filler and collagen stimulator for body rejuvenation is a recent good option when well indicated. In general, better results are reached in younger patients, who are able to induce new collagen synthesis, but it can also be used for

older patients (Figs. 5 and 6). These procedures can be used in association with others to intensify the results of body contouring. Non-ablative radiofrequency (see chapter "Non-ablative Radiofrequency for Cellulite (Gynoid Lipodystrophy) and Laxity" in volume *Lasers, Lights and Other Technologies*) helps to improve laxity of the body skin, ultrasound for body contour (see chapter "Ultrasound for Lipolysis" in volume *Lasers, Lights and Other Technologies*), and cryolipolysis

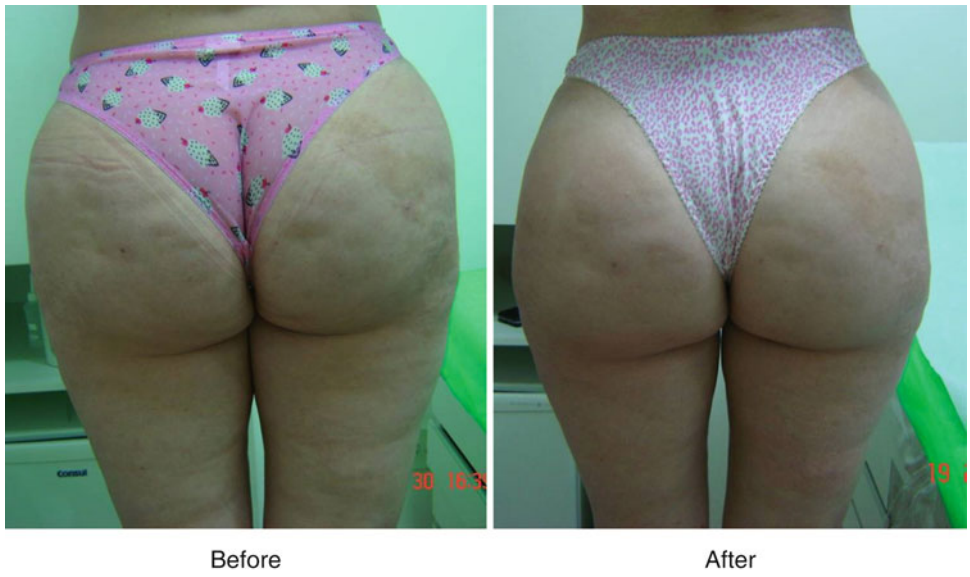

Fig. 5 Before and after 2 vials of PLLA on the buttocks

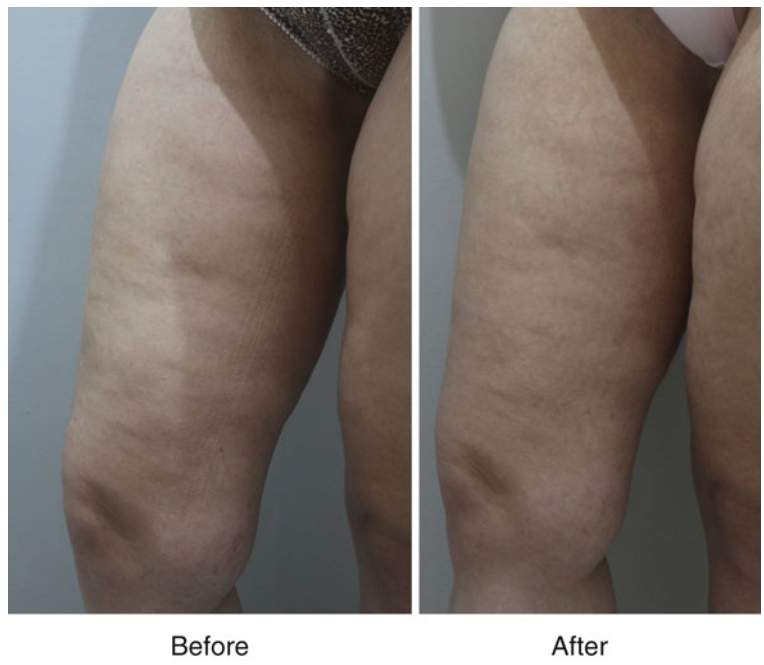

Fig. 6 Before and after 1 vial of PLLA on thigh

(see chapter "Cryolipolysis for Body Sculpting" in volume *Lasers, Lights and Other Technologies*) help to reduce localized fat.

Take Home Messages

- PLLA and CaHA have a different and specific dilution for body treatment. Greater dilution is required comparing to the face.
- Vectoring approach is important to reach lifting effect.
- Linear retrograde injection with parallel stick technique is the most used to skin laxity. Crossed sticks are better to correct depressions.
- HA is better indicated to replace volume and to treat cellulite depressions and can be associated to CaHA or PLLA in the same area.
- Applying exhaustive massage after treatment is mandatory to avoid nodules.
- Patients are advised to use cold packs and to do the massage at home for at least 5 days after the procedure.

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Thread Lifting

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_38

Abstract

The thread lifting technique is a method of antiaging treatment, minimally invasive, capable of correcting moderate skin laxity by improving the contours of soft tissues. It not only stays between surgical lifting and less invasive procedures but also complement them. This chapter is going to discuss about the main nonabsorbable and absorbable suture threads commercially available, its indications and contraindications, some insertion techniques, post-procedure care, and common adverse reactions. Dermatologists must be aware of this procedure as an additional tool for skin rejuvenation treatment.

Keywords

Thread Lift · Skin rejuvenation · Minimally invasive procedure · Absorbable threads · Nonabsorbable threads

Introduction

For the last few decades, the search for treatment of skin aging has been growing especially among younger patients. They go to dermatologists to look for less invasive procedures, before choosing a surgical lifting. In general, they are individuals between 40 and 60 years old, active professionals, who presents mild to moderate skin laxity and that can be dealt with in clinics. These procedures require little downtime, they seldom leave scars and they frequently show satisfactory results (The American Society for Aesthetic Plastic Surgery).

In the USA, noninvasive procedures have increased by more than 350% since 1997, compared to an increase by only 70% in traditional cosmetic surgical procedures (Prendergast 2013). After the boom of surgical lifting, endoscopic surgery came up right after, followed by lasers (see chapters "Erbium Laser for Photorejuvenation," "CO_2 Laser for Photorejuvenation," and "Non-ablative Lasers for Photorejuvenation" in volume *Lasers, Lights and Other Technologies*), dermal fillers (see chapters ▶ "Hyaluronic Acid Filler for the Malar Area" and ▶ "Hyaluronic Acid for Mental and Mandibular Contour" in this volume, and "Fillers" in volume *Daily Routine in Cosmetic Dermatology*), and thread lifts, aiming to reduce scars of plastic surgery and its side effects.

The thread lifting technique is a method of antiaging, minimally invasive, capable of correcting skin laxity by improving the contours of soft tissues. It not only stays between surgical lifting and less invasive procedures but also complement them (Lee and Isse 2005; Bisaccia et al. 2009).

Therefore, thread lifts retard skin aging, preserving the beauty with no need of invasive surgical intervention, in other words, no scars and fewer side effects.

History

In 1956, Alcamo patented the barbed suture, but they initially were not used on soft tissue elevation. Buncke, in his 1997 patent on surgical methods, presented the use of the barbed suture on lifting procedures to provide subdermal support on ptotic tissues (Kress 2008). In 1998, the Russian surgeon Sulamanidze patented the APTOS (antiptosis suture), a bidirectional barbed suture to perform minimally invasive lifting (Sulamanidze et al. 2002).

New suture threads with new materials and structures were developed in different countries. After the experience with unidirectional barbed thread (Isse Endo Progressive Facelift Suture), North American surgeons Isse and Kolster designed a suture with cones instead of barbs named Silhouette, approved in 2006 by the FDA (US Food and Drug Administration) (Isse 2008).

The Lifting by Suture

Doctors must warn their patients about the big difference between the final result of a surgical lifting and a thread lifting. This distinction is mainly due to the following aspects:

1. The technique: surgical lifting not only has soft tissue elevation sutures in the musculoaponeurotic system (SMAS), but it also fixes soft tissues into deeper structures. On the other hand, thread lifting does not make sutures in the SMAS, but it only places soft tissues near to fixed points.
2. Scar tissue due to surgical trauma in traditional lifting is much bigger than the one in thread lift.

In this way, the less invasive procedure done by thread lift does not correct tissue ptoses as much as surgical procedure, and its results last less long than surgery. On the other hand, thread lift is an ambulatory care procedure, fast, and it has little downtime (Flynn 2005). Surgical lifting, furthermore, involves bigger complications, such as risk of general anesthesia, bruising, and nerve injury.

Thread lifting can vary according to the type of thread used and technique. There are nonabsorbable, absorbable, or mixed threads, as well as threads with or without barbs or cones in their extension to suspend the tissue they pass through. The barbs and cones disposition can also vary: it can be unidirectional or bidirectional. The different techniques vary mainly according to implantation area and to the way the threads anchor or not through soft tissues. Thread lift can turn into invasive procedure if there is anchoring through the SMAS, for instance. In that case, general anesthesia is required.

The Suture Threads

The first suture threads weren't efficient and safe because their soft tissue support during facial movements was insufficient. In the beginning, the threads were made from nonabsorbable material, which caused discomfort along the time and higher complication rates, requiring challenging removal when necessary.

Over the last years, absorbable suture was introduced on the development of such threads due to better long-term safety and patient satisfaction.

In this chapter, we will describe and discuss the main nonabsorbable and absorbable suture threads commercially available.

Nonabsorbable Threads

Polypropylene

APTOS Thread Polypropylene threads with unilateral prominences attached to a long needle. The APTOS thread holds the tissue due to their prominences, which may be arranged, in a convergent or divergent fashion. Currently, there are several variations in diameter, length, and barb design.

They must be inserted into the hypodermis with single guide needle, and depending on the technique and barb distribution, they can be anchored on a fixed point or not. They can be used to rejuvenate any region of the body as long as it has enough subcutaneous tissue for the thread.

APTOS thread has a high complication rate. Intraoperative with thread breaks, since the barb insertion area is more fragile, and postoperatively they present higher rates of ecchymosis and edema as these threads have a more cutting effect on friable tissue. Later, due to lack of sufficient fixation on soft tissues, ptosis, extrusion, and migration are diagnosed. For all these reasons, they are being less frequently used (Sulamanidze and Sulamanidze 2009; Paul 2008; Kaminer et al. 2008; Abraham et al. 2009).

Silhouette Lift® Polypropylene 3.0 thread equipped in its distal segment of 10 knots that separates nine unidirectional, flexible, and absorbable cones (in 11 months, 75% of the material is absorbed); they are made of polylactic acid (82%) and glycolic acid (18%). The distal segment has a 20G blunt tip, and the proximal segment has a curved needle, which fixes the suture. This thread can be used in all of the face, neck, and body. The procedure must be done in a surgery room, under general anesthesia, since it is fixed to the deep

temporal fascia (DTF). The lifting made with Silhouette Lift suspends the tissues and produces immediate results. The 360° surface of its cones resists to suspension traction, and it fixes immediately to soft tissues. The cones act as a foreign body leading to an inflammatory reaction with collagen production. Therefore, the fibrosis reaction around the absorbable cones creates a solid support, which leads to a progressive improvement on the aged aspect noticed before the procedure. The maximum effect is reached around the fourth week, and the results last up to 3 years (Gamboa and Vasconez 2009; Benito et al.).

Absorbable Threads

Polycaproamide

Serdev Created by the Bulgarian surgeon Nikolay Serdev, it is a polycaproamide, semi-elastic, antibacterial, braided, synthetic, and absorbable suture (absorbed in 2–3 years). Unlike other sutures, it doesn't feature barbs or cones, but they retract a mobile tissue like the SMAS and fix it on a fascia or bone structure.

The technique doesn't require incision since they can be introduced with small perforations; however, they require better anatomical knowledge since it reaches deeper tissues. It can be used in various areas on the face and body (Padín 2013).

Caprolactone

Happy Lift Monofilament caprolactone threads (absorbable in 1 year) with barbs disposed in two directions (divergent and opposite). It is used for rejuvenation of face and body. The traction on its endings traps in the barb work as a hook, which prevents the sliding of the thread in opposite directions. For these reason, anchoring suture not always is necessary for its setting. In that way, superior and inferior regions of the face with less subcutaneous tissue can also be treated. Moreover, the process of reabsorption of the thread forms a fibrotic capsule, which promotes lasting results (Savoia et al. 2014).

Polydioxanone

Lead Fine Lift This is a V-shaped monofilament 5.0–7.0 thread, which is absorbed in 6 months. Several threads are placed inside the deep dermis without traction or fixation. The neocollagenesis generated where the thread is placed is responsible for the lifting effect (Shimizu and Terase 2013).

Polylactic Acid

Silhouette Soft® It is made of polylactic acid (PLA) and is absorbed in 2 years. It can be considered a result of an improvement on Silhouette Lift. The differences between them are described in Table 1. Silhouette Soft has 8, 12, or 16 cones over its extension composed of polylactic acid with polyglycolic acid separated by knots and placed bidirectional **(**Table 2**)**. Both extremities of the suture have a 23G needle to bidirectional traction. It is traditionally used on the face and neck (Russo and Pizzamiglio 2014) (Fig. 1).

Indications

Patients with potential benefit from thread lifting are those with mild to moderate ptosis. Middle-aged patients that want to avoid surgical scars associated with traditional surgical lifting don't want a long recovery period, but having a realistic expectation is better suited for these minimally

Table 1 Differences between Silhouette Lift and Silhouette Soft

	Silhouette Lift®	Silhouette Soft
Composition	Nonabsorbable polypropylene	Absorbable PLLA
Cones	Unidirectional	Bidirectional
Fixation	DTF (deep temporal fascia)	Hypodermis
Technique	Require incision	No incision

Table 2 Silhouette Soft: characteristics of different presentations

Silhouette Soft®	8 cones	12 cones	16 cones
Material	PLA	PLA	PLA
Cone direction	Bidirectional	Bidirectional	Bidirectional
Space between cones	5 mm	8 mm	8 mm
US P denomination	3.0	3.0	3.0
Length	30 cm	27,5 cm	26,8 cm
Needle	12 cm	12 cm	12 cm

Fig. 1 Silhouette Soft thread

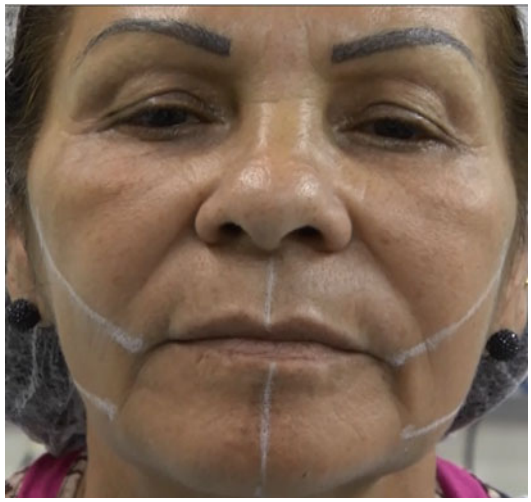

Fig. 2 Demarcation of the area before treatment of the face with Silhouette Soft thread

invasive procedures. But on the other hand, patients with excessive flaccidity, deep and numerous wrinkles, and excessively thin or heavy subcutaneous tissue must be alerted about the limits of the technique. Patients who are planning to lose a significant amount of weight after the procedure must not consider thread lifting as an option since its results will not be long lasting (Fig. 2).

Contraindications

The use of thread lifts are not recommended in the following cases:

- Chronic or acute dermatosis near to the thread insertion
- Clinical decompensated diseases
- Autoimmune diseases
- Hypersensitivity to the components
- Pregnancy or breastfeeding
- Patients under the age of 18
- Patients having permanent fillers in the area where the threads go through

Insertion Technique

Different techniques have been described about thread lifting, and they can vary according to the needs of each patient:

- Parallel vertical or horizontal line techniques
- The V technique
- The obtuse angle technique
- The U technique

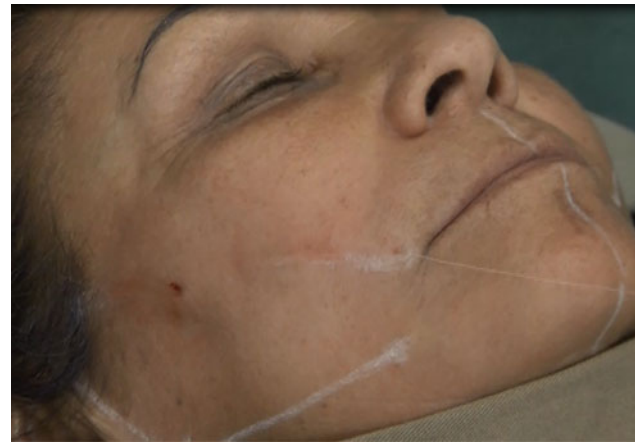

Fig. 3 During the procedure of the treatment of the face with Silhouette Soft thread

- The cross technique
- Others

There is no consensus among experts on which technique is best indicated. To choose one of them, each patient must be analyzed and given accordingly.

The authors of this chapter have more experience with Silhouette Soft, so the technique described here is mainly about it.

The most treated areas are the face and neck, although there are some studies, which report insertions in other parts of the body such as the abdomen, inner arms, and thighs (Figs. 3, 4, 5, 6, 7, and 8).

Besides, the minimum distance between the 2 exit points of the needles must be respected:

8 cones	10 cm
12 cones	16 cm
16 cones	20 cm

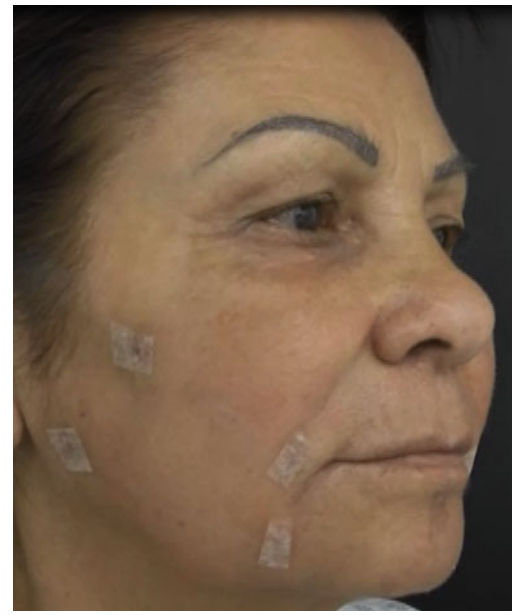

Fig. 4 Immediately after the procedure of the treatment of the face with Silhouette Soft thread

Post Procedure

Some post-procedure care should be taken by patients to improve results:

- Avoiding the manipulation of treated areas
- Sleeping in supine position for 1 week
- Avoiding physical activities for 1 week
- Avoiding excessive movements and the traction of treated areas
- Avoiding dental procedures for 3 weeks
- Avoiding saunas

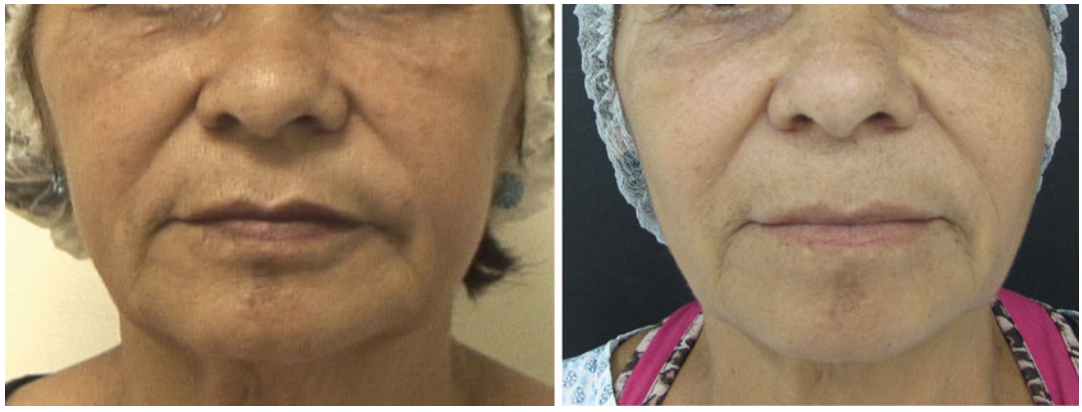

Fig. 5 Pre- and posttreatment of the face with Silhouette Soft thread

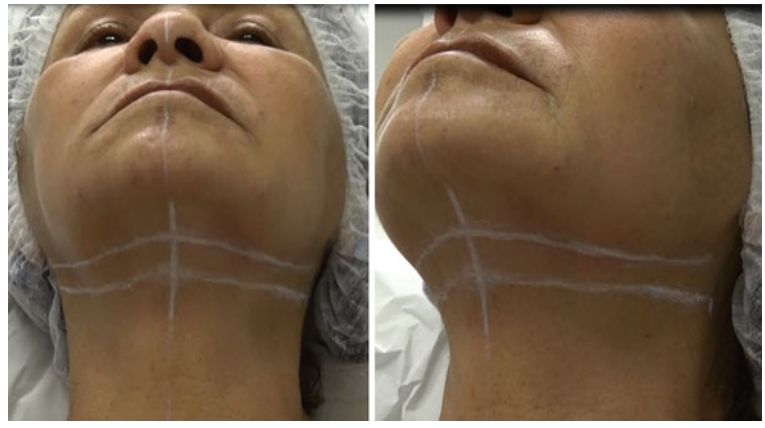

Fig. 6 Demarcation of the area before treatment of the neck with Silhouette Soft thread

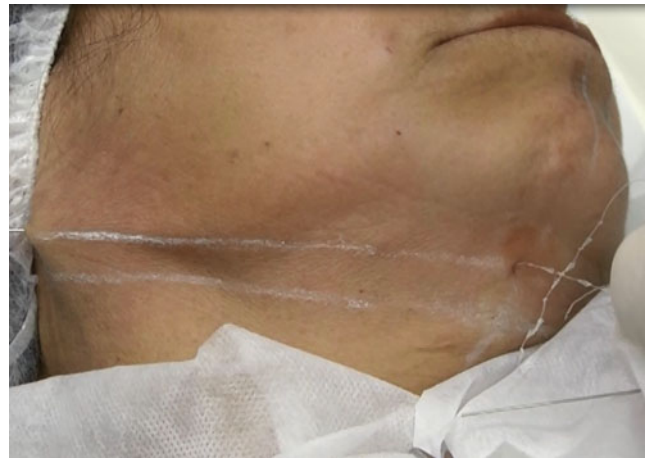

Fig. 7 During the procedure of the treatment of the neck with Silhouette Soft thread

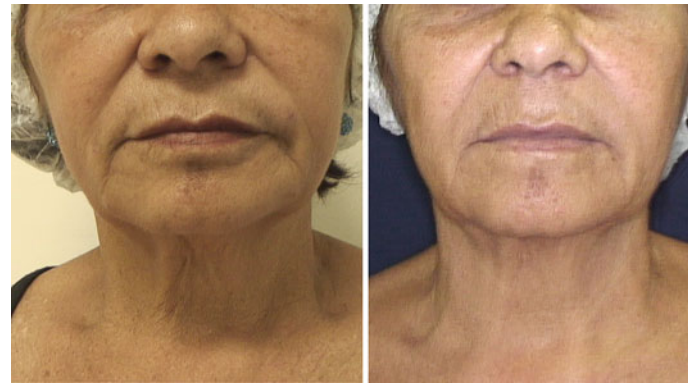

Fig. 8 Pre- and posttreatment of the face and neck with Silhouette Soft thread

Adverse Reactions

Although adverse reactions associated to thread lifting are unusual, the patient must be aware of possible side effects of the procedure (Table 3). Adverse reactions depend upon the interaction between patient and biomaterial and can also be technique dependents.

Small hematomas and edema are inherent to the procedure but heal spontaneously after some weeks. Large hematomas can be formed, especially among patients with coagulopathy or among those who take anticoagulants. In these cases, drainage is required to avoid hematoma encapsulation and infection.

The puckering of the skin and epidermal irregularities along the suture thread are relatively common, and they occur due to the superficialization of the thread. However, these adverse effects tend to vanish in 2–4 weeks. In order to speed up that process, the patient should gently massage the area. In worse cases, dermic subincision can be done. The puckering can occur in the entrance and exit points of the thread, which usually heals in 15 days (Fig. 9).

Immediate or delayed allergic reaction to the components of the thread with subsequent foreign body granuloma formation occur more frequently with nonabsorbable materials. Small nodules along the thread with inflammatory signs can be detected. The treatment of this complication is difficult. Systemic or intralesional corticoid can be used, as well as antibiotics with anti-inflammatory benefits. The resection of the granuloma must be considered in some cases.

Prophylactic antibiotic therapy and aseptic technique minimize the risk of infection.

It is fundamental that the barbs or knots are settled in the hypoderm in order to avoid dermal

Table 3 Adverse reactions

Hematoma
Puckering of the skin
Foreign body granuloma
Infection
Nerve injury
Chronic pain
Asymmetry
Palpable and/or visible thread

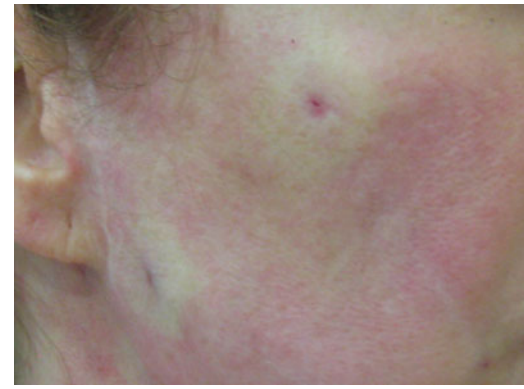

Fig. 9 Puckering of the skin immediately after the procedure with Silhouette Soft thread

irritation and late suture extrusion. This complication is more frequent in areas with thin subcutaneous tissue.

Sensory and motor damage due to nerve injury are rare, since the threads are placed superficially to the nerves, with the exception of the temporal branch of the facial nerve that if injured leads to frontal paralysis. Chronic pain caused by ramus trauma is more common and should be treated with analgesics, since it usually heals in 1 month.

Asymmetry and palpable thread are results of incorrect surgical technique, and they must be solved with the repositioning of the thread.

Other Indications

Even though thread lifts are used on rejuvenation with great outcome, recently, new studies are describing new applications of these threads on dermatology and plastic surgery:

- Facial reconstruction after trauma, tumor resection, or malformation
- Static correction of facial paralysis
- Complementary procedure to more invasive surgical procedures

Conclusion

Thread lifting is a minimally invasive alternative to surgical rejuvenation. Thus, the dermatologist must be aware of this procedure as an additional tool for patient care.

Physicians that want to use thread lifting must know the different types of threads available on the market, since the difference between each one determines its results.

Furthermore, the knowledge of anatomy and techniques of insertion are fundamental for prevention of side effects and good results.

More long-term studies after the thread lift must be done to establish its efficacy, duration, safety, and good quality of life, as a minimally invasive procedure.

Take Home Messages

- The thread lifting is a skin rejuvenation minimally invasive procedure.
- Patients with potential benefit from thread lifting are those with mild to moderate ptosis.
- Thread lifting can vary according to the type of thread used and technique.
- There are nonabsorbable, absorbable, or mixed threads, as well as threads with or without barbs or cones in their extension.
- Adverse reactions depend upon the interaction between patient and biomaterial and can also be technique dependents.

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Permanent Fillers

Márcio Soares Serra and Leonardo Zacharias Gonçalves

Contents

Abstract

Permanent fillers are mainly used in the correction of furrows and deep lines of the skin that are beyond the normal facial wrinkles that appear with aging. They can be an excellent option in facial rejuvenation, especially when there is need for facial and body volume restoration, such as in HIV lipodystrophy. Of the permanent fillers currently available, polymethyl methacrylate (PMMA) is the most commonly used, and has been shown to be safe, effective, and long lasting.

Keywords

Silicone · Polyacrylamide · Polyalkylimide · Polymethyl methacrylate · PMMA · Fillers · Lipoatrophy · HIV · Lipodystrophy

Introduction

Despite the recent advances in industrial medical research, there is no ideal filler available. The ideal material for filling would need to meet

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_30

certain criteria to be accepted by the medical community, such as being easy to apply, non-toxic, non-carcinogenic, non-immunogenic, and promoting a good cosmetic outcome. Currently, silicone-based products, polyalkylimide, polyacrylamide and polymethyl methacrylate (PMMA) are available on the world market. Of the permanent fillers available, only two are registered with ANVISA (Agência Nacional de Vigilância Sanitária, the Brazilian National Health Surveillance Agency) for use in Brazil: polyacrylamide and PMMA (Rorich et al. 2009; Casavantes 2004).

Types of Permanent Filler

Silicone

Liquid injectable silicone is a synthetic polymer composed of a common chain made of repetitive siloxane. Silicone has been used in the past as a filler because of its low cost and results; however, due to its capacity to migrate, its use as a filler has been banned in Brazil and several other countries. Recent research, mainly relating to the correction of facial lipoatrophy in patients with HIV, has demonstrated that if medical-grade silicone is used with the micro-droplet technique, silicone can be safe and have good filler aesthetics (Rorich et al. 2009; Jones et al. 2004).

Polyacrylamide and Polyalkylimide

Polyacrylamide (Aquamid®) and polyalkyimide (Bio-Alcamid®) are transparent biopolymers, hydrogels, biocompatible, non-toxic, physically and chemically stable, and non-reabsorb. They are indicated for the correction of cosmetic defects of the face caused by trauma or genetic damage, to increase soft tissue, to correct furrows, and to restore face contours as well as to increase the volume of the lips. According to their manufacturers, one of the advantages of these products is the ability to remove them; however, because of reports of infection of the hydrogel and other late complications they are no longer commonly used (Rorich et al. 2009; Casavantes 2004; Jones et al. 2007).

Polymethyl Methacrylate (PMMA)

Initially used as bone cement, PMMA is a vinyl polymer that is found in various products such as glasses, dental prostheses, and contact lenses. PMMA is the most commonly used permanent filler in Brazil, and five PMMA products have registration with ANVISA: one with import registration – Artecoll® – and four produced in Brazil – Metacrill®, LineaSafe®, Biossimetric®, and, more recently, Metaderm®. The main differentials among them is the vehicle, and the regularity and size of the particles. Artecoll® contains spherical PMMA particles with a smooth and polished surface, with 40 μ suspended in the ratio of 1:3 with 3.5% bovine collagen. Suitable for long-term correction of wrinkles and other skin defects, it is marketed in boxes with four syringes containing 0.5 ml of the product; according to the manufacturer, it should be implanted subdermally (Lemperle et al. 1998, 2000).

Although Artecoll® has recently been approved by the Food and Drug Administration (FDA) in the USA under the name of Artefill®, it has been widely used in Europe and Canada for some time. It has been used in more than 200,000 patients, and its worst complication, the formation of immune granuloma, has occurred in less than 0.01% of patients treated after more than 10 years of follow-up. It is not frequently used in Brazil, mainly because of its high cost and the need for testing prior to its use due to the possibility of bovine collagen allergic reaction (Rorich et al. 2009; Lemperle et al. 1998, 2000).

In Brazil, there are four formulations, produced here, based on PMMA registered with ANVISA: LeneaSafe®, which has hydroxyethyl cellulose as its carrier; and in Metacrill®, Biossimetric® and Metaderm®, the carrier of which is carboxymethyl cellulose, which makes it more fluid. These colloidal solutions include PMMA, with diameters between 30 and 80 μ, and are marketed at concentrations of 2%, 10% and 30% and sold in boxes containing 1 or 3 ml syringes. They are indicated

for the definitive correction of wrinkles, depressions, and other skin defects such as scar depressions caused by acne sequelae and definition of facial (back of nose, chin, lips) or body (hands, legs, buttocks) contours. These products are biocompatible and have no animal component, and being a permanent filler produce immediate and prolonged results. The injection should be made in the deep dermis or subcutaneous level. Although intramuscular use is indicated, there are no recent publications on intramuscular use or regarding the use of large volumes (Carvalho Costa et al. 2009; Serra 2000; Pereira and Poralla 2001; Serra 2001, 2002a, b).

Procedure

Referring to PMMA performed using retrograde injections such as "parallel sticks," "X crossed sticks," "network crossed sticks," or using the "fan" technique in the subcutaneous tissue (Fig. 1). When using needles, it is recommended that a luer-lock syringe be used and it should be aspirated before beginning the injection in order to prevent the material from being injected into the blood vessels. There are some important cautions to note prior to the procedure: suspend anticoagulants, when possible, 5 days prior; avoid analgesics and anti-inflammatories for 5 days before the procedure; and avoid natural substances such as *Ginkgo biloba*, which can also increase bleeding (Serra et al. 2004, 2013).

Prior to application, the implant site should be disinfected carefully with the help of a local antiseptic such as a chlorhexidine or alcohol 70% solution. Topical anesthesia, such as EMLA®, may be applied to the area to be treated. We currently prefer to use several small anesthetic buttons, using 0.05–0.1 ml of lidocaine with a vasoconstrictor, which makes the procedure less uncomfortable with reduced bleeding and less post-procedure edema (Figs. 2 and 3). Due to the high viscosity of PMMA, the area should be massaged after filling to ensure good molding of the product in the area.

Since PMMA is a permanent filler, care should be taken not to hypercorrect the area. If a complementary application is necessary, it should be performed after an interval of some weeks as otherwise initial tissue expansion and any excessive edema would make it difficult. In accordance with these consequences and the anatomy of the region, it is advised that any supplementary treatment be applied after a minimal interval of 30–45 days. During this period, the vehicle is absorbed and some histological changes can be observed. Cell migration and formation of collagen around the particles are reported. After the procedure, it is advisable to apply ice packs on the

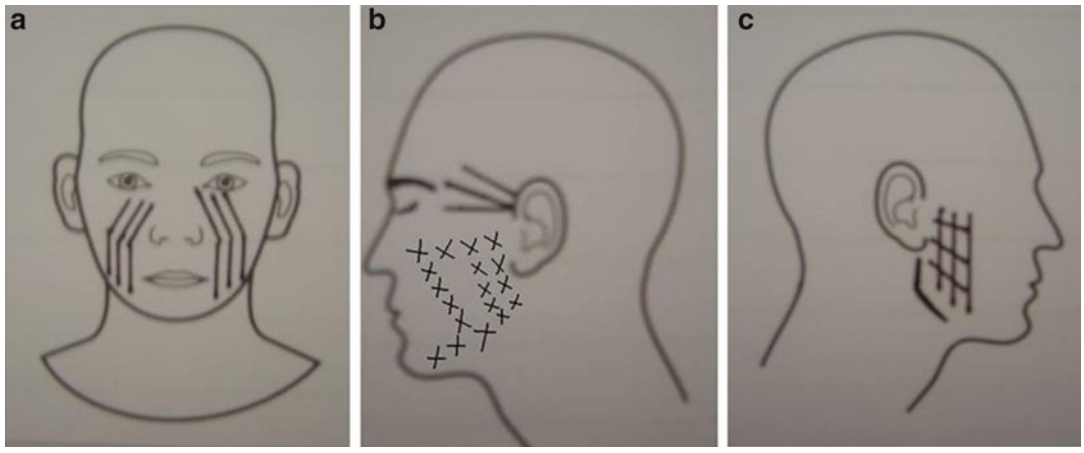

Fig. 1 (**a**) Paralell sticks technique on malar region and nasomental fold. (**b**) X crossed sticks technique on malar and mandibular regions and fan technique on temporal region. (**c**) Network crossed sticks on pre-auricular and mandibular regions

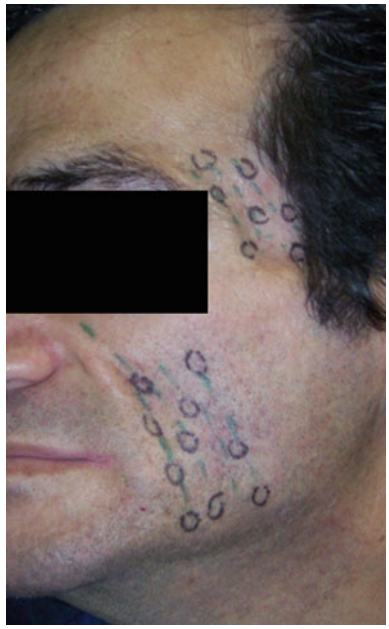

Fig. 2 Anesthetic buttons marked in *black* and the area to be filled marked in *blue* using paralell sticks technique

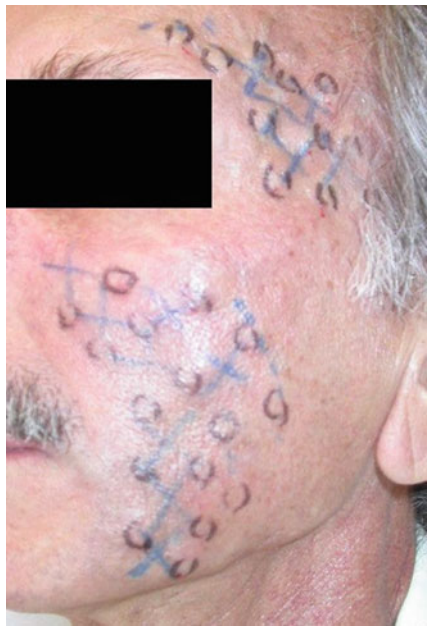

Fig. 3 Anesthetic buttons marked in *black* and the area to be filled marked in *blue* using crossed sticks technique

treated site for 15 min every 2 h or 10 min every hour on the day of filling. In case of persistent edema, we advise the use of cold compresses three times a day for another 3–5 days. Post-procedure, it is recommended that the following should be avoided for five days: heat, such as visiting a sauna or working close to an oven or stove; physical exercise; ingestion of alcohol; and excessive sun exposure for five days. There are no restrictions for the patient regarding sleeping position or eating before and after the facial filling procedure. Similar to other fillers, mild erythema and edema may occur. These reactions spontaneously improve (in more than 95% of cases) after 24–72 h (Serra et al. 2013).

Side Effects and Management

Every procedure that uses needles is capable of injuring small blood vessels, causing the appearance of ecchymosis, which may take 1–3 weeks to disappear. Other common symptoms after the procedure may be local pain, which usually resolves without medication, and edema in the treated area, which usually disappears after 3–7 days. In cases of more severe edema, anti-inflammatories or oral corticosteroids can be prescribed.

The injection may eventually cause the appearance of a discrete local erythema, which is a result of dilation of the blood vessel capillaries in the region, being part of the normal physiological response. These reactions are temporary and disappear spontaneously after 24–48 h.

However, as occurs with other fillers, PMMA may trigger additional local reactions such as visible and palpable nodules (Fig. 4a, b) and necrosis (Fig. 5). These nodules are mistakenly referred as "granulomas" but they are actually a consequence of incorrect technique, when the filler is injected very superficially in the skin. Necrosis occurs when the filler is injected inside the vessels, forming obstruction as "pistons." The glabella area is a risk zone due to the presence of superficial and large-caliber veins in the region; if the material is applied inside these veins, it may lead to emboli in the intraorbital veins, compromising the retina and, consequently, the patient's vision.

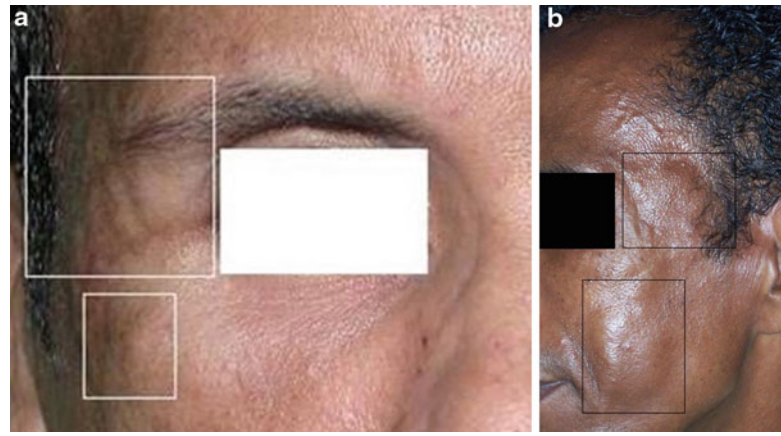

Fig. 4 (**a**, **b**) Visible and palpable nodules

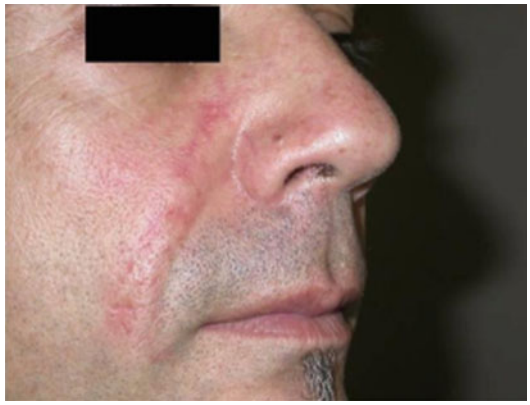

Fig. 5 Side effect: necrosis

It is recommended that this product should not be applied in glabellar wrinkles or the nasal area to avoid local necrosis and unaesthetic results (Fisher et al. 2007; Serra et al. 2008; Lemperle et al. 2009).

Some late side effects include modifications in the volume and hardening of the treated area during an episode of systemic or localized infection close to the area previously filled (Fig. 6a–c). Rhinitis, sinusitis, and infections of the oropharynx have been reported as triggers. The edema and hardening usually disappear after treating the infection. These signs may also occur during the use of interferon for hepatitis C treatment. Patients should be warned of the risk of these late side effects.

In Brazil, a colloidal solution with PMMA microspheres has been widely used for the correction of facial lipoatrophy with good results in patients with HIV/AIDS (Fig. 7) and is currently offered to patients in government referral centers for treatment of facial lipodystrophy. A case series report of 504 patients with 5 years of follow-up demonstrated that PMMA was safe and effective and there were no occurrences of long-term side effects such as infection or formation of immune granulomas.

Theoretically, any region of the body can be treated with this filler, as long as the tissue is distensible, and the treatment technique is basically retrograde injections into the subcutaneous tissue. The amount to be injected per area, the number of injections, and the interval between each session vary according to the patient, and the area to be corrected and the indication to correct or not must be determined by the physician (Carvalho Costa et al. 2009; Serra 2000, 2001, 2002a, b; Pereira and Poralla 2001; Serra et al. 2004, 2013; Soares and Costa 2011; Orsi et al. 2011). At the moment, there are no studies that have determined the maximum amount of PMMA that can be used in each session, the number of sessions, or the maximum quantity that can be used by one person. Extensive experience is fundamental to gaining the best results.

In addition to the face, other areas of the body such as the back of the hands, buttocks, and chest have been treated with PMMA. Although some

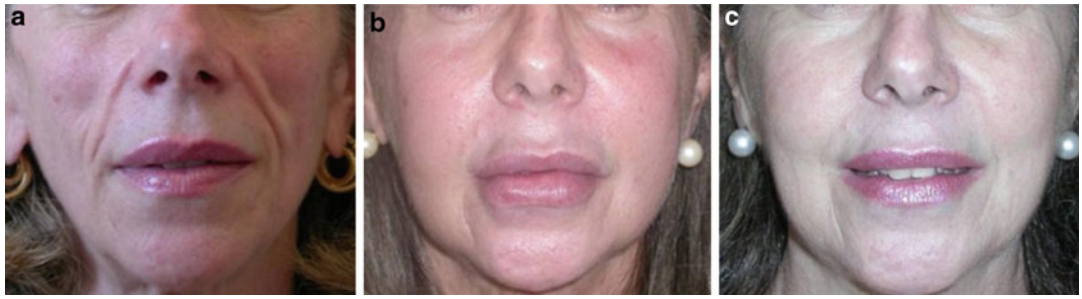

Fig. 6 (**a**) Pre procedure (malar region filling with PMMA). (**b**) Edema of the malar regions and lips in the presence of dental infection. (**c**) Complete recovery after treating the dental infection

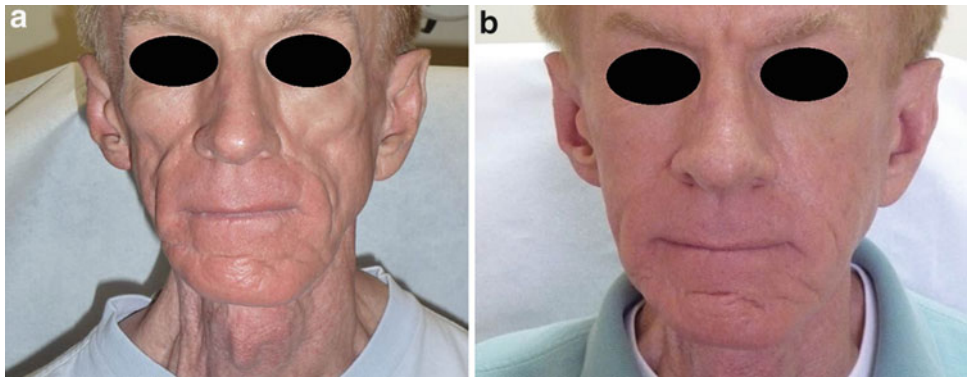

Fig. 7 (**a**, **b**) Before and after with PMMA for facial lypoatrophy in HIV patient

professionals apply PMMA intramuscularly to add volume to the calves and buttocks, there are no studies regarding this technique. We consider that the best use of PMMA for large areas such as buttocks is to improve the shape and contour rather than to give volume. Generally, we use 40–60 ml per session, but a maximum amount of 120 ml has been used. Subcutaneous retro-injections, using the "in network" technique, should be performed in all areas, with a 3-month interval between sessions (Serra et al. 2015).

A study on the use of PMMA in 616 HIV (Serra et al. 2008) patients over 10 years has been reported. The amount of PMMA used per patient for treatment ranged from 6 to 38 ml. For the buttocks, the amount used ranged from 40 to 250 ml per patient. For both regions, most patients required two to three sessions to achieve good results. This is in contrast with our experience, in which the largest amount we used to treat buttock lipoatrophy in a HIV-patient was 938 ml in total, divided into 11 sessions (Fig. 8) (Serra et al. 2015).

Conclusions

Permanent fillers are used to correct furrows and deep depressions in the skin and for volume replacement. Of all of the permanent fillers available on the market, PMMA is the only one that is regularly used. PMMA has been demonstrated to be safe, effective, and long lasting, with few adverse reactions when utilized correctly correctly.

Take Home Messages

- Permanent fillers are used for deep depression corrections and volume replacement.

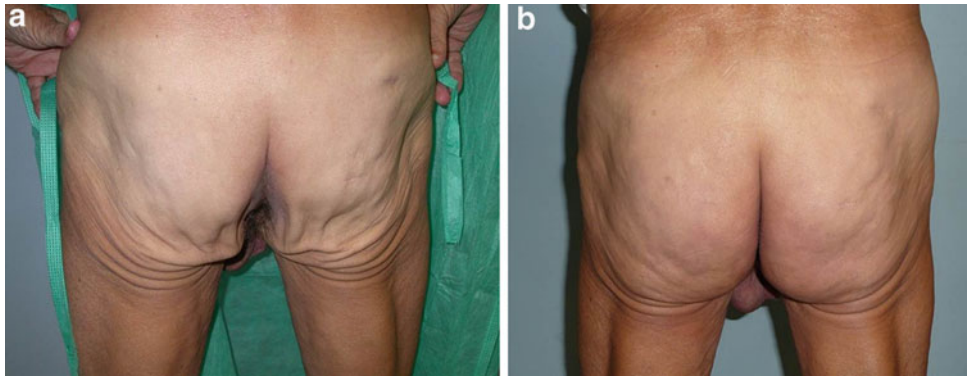

Fig. 8 (**a**, **b**) Before and after with PMMA for buttock lypoatrophy in HIV patient

- Silicone, polyacrylamide, polyalkylimide, and PMMA are the most common permanent fillers on the market.
- PMMA is the main permanent filler used currently.
- In Brazil, PMMA is widely used for correction of HIV lipoatrophy.
- PMMA can also be used for body volume restoration.

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Injectable Soft Tissues with Fibroblasts and Mesenchymal Cells

Neide Kalil Gaspar and Patricia Shu Kurizky

Contents

Abstract

The use of autologous cells expanded from dermis or mesenchymal cells of adipose tissue has been studied, and it seems to be a promising technique in cosmetic dermatology. This process consists in the implant of expanded cells obtained either by excision of skin graft from occipital area or taken by liposuction from adipose abdominal tissue. Even skin flaps from plastic surgery can be used. These materials are sent to laboratory in appropriate growth medium and expanded after submitted to microbiological control. After about 45 days, it is possible to provide ten syringes containing about 1 million cells each for implants. The patient's material is cryopreserved for further expansion and other injections. These cells are introduced in dermis by retro-injections. Improvement can be seen after the third week of implantation. This procedure is not approved in Brazil, and authors' experience is based on their investigative studies. In this chapter, the concept, mechanism of action, and clinical applications are going to be discussed.

Keywords

Injectable soft tissues · Fibroblasts and mesenchymal cells · Autologous cells · Adipose tissue · Skin graft · Dermis · Implantation · Soft tissue augmentation

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_31

Introduction

The longer longevity of the population demands greater investment in maintaining a youthful appearance, and it is the goal of numerous investigations. Soft tissue augmentation is a process of implanting tissues or materials where needed to restore a youthful or more esthetic look to the face. Correction of rhytides is performed frequently, but fillers, whether organic or nonorganic, can pose adverse reactions or unsatisfactory results. Ideally, injectable implants should offer long-term correction and compatibility with the natural aspect of the individual, not be allergenic, and not offer other risks.

Collagen and elastic fibers in the skin begin to break down as we age, and wrinkles emerge. In addition, some subcutaneous fat is lost on our bodies. In particular, the soft tissue atrophy on the face leads to a skeletal look (Rhee et al. 2014). The chronological aging is triggered by the shortening of telomeres, which are nucleoproteins complex located at the ends of each chromosome (Davis et al. 2003). They have the function of protecting the chromosome, being shortened at each cell division, to a critically short state, after which the cell can no longer divide in response to stimulation. Young people's fibroblasts have a greater division capacity.

The DNA damage induced by oxidative stress or by ultraviolet irradiation is also responsible for the shortening of telomeres. In senescent tissue, dermal matrix is disorganized and less vascularized, with flattening of the dermal papillae, loss of skin elasticity, and decreased dermal-epidermal interdigitation (Montagna and Carlisle 1979). Fibroblasts, also, express higher activity of proteases, digesting the matrix (Montagna and Carlisle 1979). This process is accompanied by the loss of collagen, which may reach 1% per year (Shuster et al. 1975).

In addition to these changes, environmental triggers, in particular UV rays, contribute to the damage of the connective tissue of the skin. The intrinsic and extrinsic aging processes have an overlap of biological, biochemical, and molecular mechanisms (Shuster et al. 1975; Greco et al. 2003). Oxidative stress of skin cells is caused by ultraviolet rays, via chromophores and photosensitizer's interaction. This results in the activation of cytoplasmic signal transduction pathways related to growth, differentiation, replicative capacity, and connective tissue degradation, finally leading to transient and/or permanent genetic damage (Ma et al. 2001).

The photodamaged skin is characterized by extensive degradation of type 1 and 3 collagen fibrils and by the increased expression of metalloproteinases (MMP), resulting in wrinkles and sagging (Nishimura et al. 2000). Although the destruction of the extracellular matrix undoubtedly is the center of the problem, the failure of new synthesis is a contributing factor (Varani et al. 2004).

Autologous Cultured Skin Fibroblast and Multipotent Mesenchymal Stem Cell Transplantation

The need for tissue replacement in a medical view is old, and replacement of bone's tissue was already established 300 years ago. In the present, specific implants include direct injection of autologous cells, such as autologous implants in adipose tissue and hair units. They can also be combined with biomaterials which act as templates for encapsulation or seeding of cells of bones or teeth, cartilage, and cornea (Mambelli et al. 2009; da Silva Meirelles et al. 2009; Stamm et al. 2003; Zucconi et al. 2010; Choi et al. 2011; Rodríguez et al. 2012; Dierickx et al. 2012). Of special interest, we emphasize the simple implantation of autologous cell suspension, expanded in the laboratory. The incorporation of fibroblasts (Eça et al. 2012; Smith et al. 2012; Munavalli et al. 2013a; Watson et al. 1999; Boss et al. 2000; Weiss et al. 2007a; Zhao et al. 2008) and mesenchymal cells from adipose tissue in tissue engineering has produced promising results in the recovery of skin aging scars. The therapy, developed by Watson et al. (1999), involves the restoration of the structure or function of the tissue through the use of living autologous cells. Autologous fibroblast are obtained by 3 mm biopsy and expanded in the laboratory for 8 weeks, after what they are applied locally in three sessions. These processes, called by Boss et al. as Isolagen, have been used effectively not only in the treatment of wrinkles but

also in depressed scars and skin irregularities (Boss et al. 2000) and were confirmed, in 2007, by Weiss et al. (2007a; Munavalli et al. 2013b).

In a subjective satisfaction survey conducted at the University of Medicine of Hackensack (New Jersey, USA), with a follow-up of 36–48 months, 92% of 94 patients treated between 1995 and 1999 declared themselves satisfied with the achieved results. Continuous improvement, beyond the original result, was reported in 70% of patients.

Kim et al. have used the optical topometry by stereo image as an effective method to evaluate the good results obtained with fibroblast injections on acne scars (Kim et al. 2011).

Since the first work of Montalcini et al. (1951), tissue stimulation by growth factors, which can be administered in vivo, has been subject of numerous investigations. The use of insulin-like growth factor in the recovery of tissues, as we published in 1984, has been conducted with the objective of stimulating the implants (Gaspar et al. 1984). In recent years, the indication and the use of insulin-like growth factor has been validated by different authors (Ish-Shalon et al. 1997; Fram et al. 2010; Goalstone et al. 1997; Denley et al. 2004; Masur et al. 2011; Lv et al. 2007; Tuvdendorj et al. 2011; Lee et al. 2013; Taylor et al. 2000).

Fibroblasts are a dynamic and versatile population of mesenchymal cells, which play a key role in the production of extracellular matrix. They produce glycosaminoglycans (GAGs), which form proteoglycans by covalent junctions to protein. Those proteoglycans bind to cytokines; to collagenous structural proteins, elastin, adhesion molecules, and fibronectin; and to laminin constituting the matrix that supports the epithelium (Nishimura et al. 2000; Gospodarowicz and Cheng 1987; Wong et al. 2007).

These cells are responsible not only for tissue architecture but also for the production of cytokines (IL1-alpha and beta, IL-6, IL-11), chemokines (IL-8, GRO-alpha, IP-10, MIP-alpha and beta, RANTES), and growth factors (GM-CSF, M-CSF, TNF-alpha and beta, SCF, MIP-alpha and beta, hepatic growth factor), essential for cellular microenvironment. Fibroblasts have a productive and multiplicative capacity defined and evaluated between 50 and 60 replications, after which there is a decrease of their ability to produce growth factors, cytokines, and matrix (Davis et al. 2003; Greco et al. 2003; Gospodarowicz and Cheng 1987; Zuk et al. 2001). When cultured, they tend to migrate slower and to respond less strongly to the addition of growth factors, compared to those obtained from younger individuals (Varani et al. 2004).

The growth parameters and characteristics of fibroblasts grown in cultures are influenced by the age of the donor, their lifestyle (smoking, sun exposition, alcohol, etc.), the number of culture passages, the topographic origin, and fibroblast subtype. With this in mind, the ideal would be the cryopreservation of cells collected at a young age, to be expanded and applied in the required age or situation.

Adipose tissue contains preadipocytes, mature adipocytes, fibroblasts, pericytes, endothelial cells, mast cells, immune cells, and a lot of multipotent stem cells (mesenchymal stromal stem cells, MSCs). These stromal mesenchymal cells are present in all adult tissues (stromal vascular fraction) and are capable of given rise to mesodermal and non-mesodermal tissues, constituting an excellent source for cultivation and implants (Zuk et al. 2001; Pittenger et al. 1999; Minguell et al. 2001).

At the same time, as stem cells from other sources, they have anti-inflammatory and immunosuppressive properties, which increase their therapeutic capacity (Minguell et al. 2000; Yang et al. 2009; Selleri et al. 2013). The activity of the implanted MSCs extends to the stimulation of local resident mesenchymal cells and production of cytokines and growth factors necessary for tissue reconstitution (Park et al. 2008). Their differentiation is driven by microenvironmental factors, as intercellular information molecules and neural stimuli.

Clinical Application of Injectable Implants of Fibroblasts: Authors' Experience

Elderly patients may be subjected to removal of small cutaneous fragment for in vitro evaluation of the reproductive capacity of their fibroblasts.

Thicker donor skin with plenty of hair follicles is likely to have well-preserved fibroblasts.

Although described in the literature the use of retro-auricular skin as a donor source of fibroblasts, we rather use hairy occipital skin, because of its protection from solar irradiation. Additionally, the high rate of the hair follicles, sebaceous glands, and stem cells increases the odds of fibroblasts with great reproductive potential (Taylor et al. 2000). The hairy pubic area might also be a donor site for cultivation. When skin flaps are available from plastic surgery, they can also be used, if in perfect vital and aseptic conditions.

For the sample collection, it is recommended to have a previous suspension of acetylsalicylic acid, *ginkgo biloba*, ginseng, or any substance that could interfere with platelet activity or coagulation. The patient must also have been examined for the presence of HIV 1 and 2, hepatitis B and C, HTLV1/HTLV2, cytomegalovirus, and Chagas' disease.

The donor area (consisting of a fragment of 0.5–0.6/1.5–2.0 cm) should be demarcated, shaved, and cleaned with acetone, chlorhexidine, and alcohol. Tumescent anesthesia is preferred, and the solution contains 7.5 ml of saline with 2.5 ml of 2% lidocaine and 0.1 ml of epinephrine. Incisions are made with a 15 blade and must be obliquus to the implantation of hair shafts, preserving them and resulting in a better healing aspect.

Clamping of the fragment and contact with antiseptic should be avoided. The sample must be washed with saline and immediately immersed in the preservation medium and cooled transport (DMEM culture medium 10%, supplemented with ciprofloxacin 1 mg/ml, and amphotericin B 0.5 mg/ml).

Simultaneously, a 20 ml sample of blood is obtained from the donor to be used as an autologous source of protein and growth factors in the final step of cultivation and on fibroblast implant solution.

Abdominal adipose tissues can also be taken from a patient by liposuction to obtain adipose-derived MSCs. The liposuction is performed under the umbilical area after anesthesia with 50 ml of Klein solution. The collected material must be decanted in the syringe for 10 min and then be immediately transferred to the preservation medium. A 20 ml sample of blood must also be obtained as previously described.

At specific laboratory, the samples are recorded in order to ensure the confidentiality of information and traceability of acquired data. All inputs that come into contact with the culture must undergo to microbiological control. Each syringe has about 1.0 million cells in suspension in physiological and autologous serum, with or without hyaluronic acid.

On average, after 45 days of in vitro expansion, the first injection can be scheduled. The material is cryopreserved for future expansions and applications. Cultured cells are injected by syringes with 30 gauges needles, under topical anesthesia or blockage. The implants are applied in the dermis by retro-injections (Fig. 1). Although these can be injected just under the rhytides, we prefer to cover all the surrounding skin area as the rhytides are caused both by flabbiness of the skin as by injury produced through personal mimic. When the purpose of the application is the correction of atrophic scars, we apply the cell immediately under the same, also by retro-injections.

In order to stimulate the implanted cells, we use 5UI of long-acting insulin mono-component diluted in 1 ml of physiological saline or lidocaine, applied in multiple intradermal

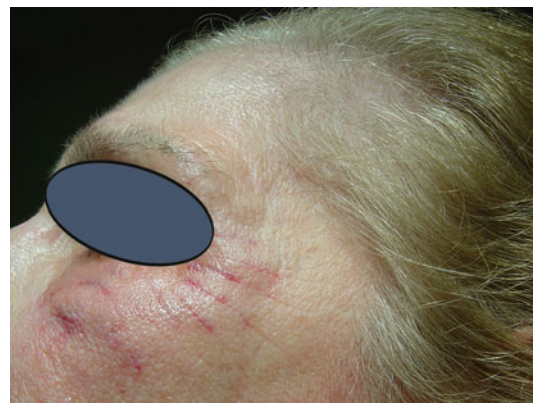

Fig. 1 Dermic implants are applied by retro-injections

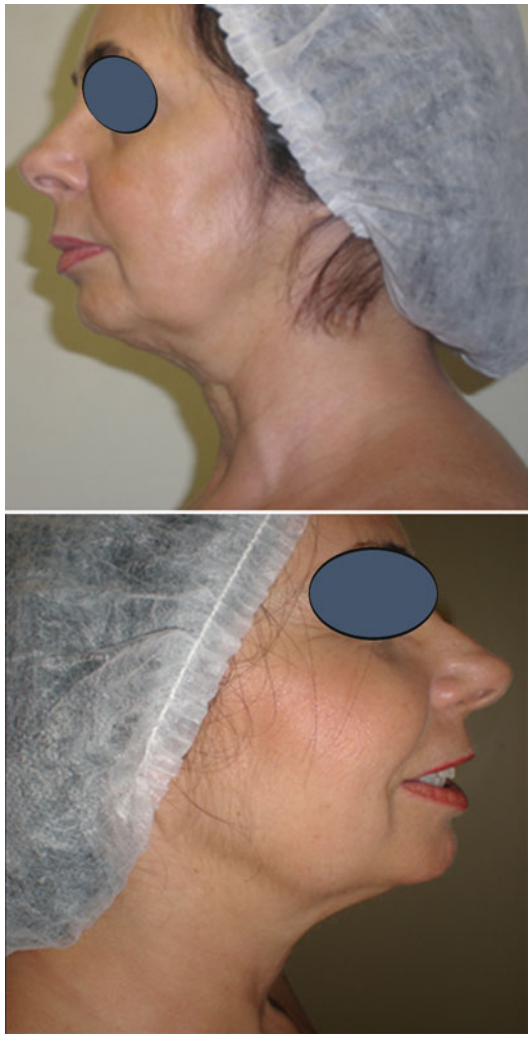

Fig. 2 Improvement of cervical area after 30 injections – before and after 1 year of follow-up

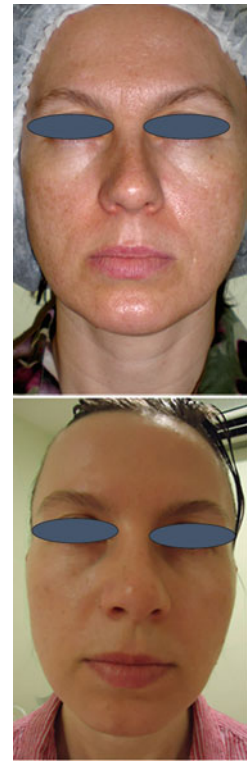

Fig. 3 Improvement of malar and perioral area – before and after 4 years of follow-up

fractional punctures, making numerous points throughout the implanted area, and repeated after 24 h.

After the injections, patients should save the treated area, avoiding, as much as possible, chewing and mimic. Cold compresses can be useful within the first hours, and vitamin C is recommended by its antioxidant and stimulatory activity on fibroblasts. Corticosteroid should be avoided.

No significant side effects are found. Erythema and edema can occur, generally lasting for 24–48 h. Patients with very thin skin or severe photodamage may have bruises, which can last for several days.

Improvement can be seen after the third week of implantation, and evaluations of the first implanted patients have revealed long-term results for over 2 years (Figs. 2, 3).

Take Home Messages

This is a living, dynamic, and autologous filler, capable to lead to long-term rhytide correction, without major adverse effect (Gospodarowicz and Cheng 1987; Weiss et al. 2007b).

Authors' results are similar to those described in the literature with a long clinical follow-up.

Dermatologists should have experience and a good clinical practice to start working with this very special treatment.

This procedure is not approved in Brazil for commercial use; it is only possible to do as part of investigative studies.

- The use of autologous cells expanded from dermis or mesenchymal cells of adipose tissue is a promising treatment in cosmetic dermatology (photodamaged and atrophic scars).
- The cells are obtained either by excision of skin graft from occipital area or taken by liposuction from adipose abdominal tissue. Even skin flaps from plastic surgery can be used.
- These materials are sent to a specific laboratory in appropriate growth medium and expanded after submitted to microbiological control.
- The patient's material is cryopreserved for further expansion and other applications.
- These cells are introduced in dermis by retroinjections.
- Improvement can be seen after the third week of implantation.

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Fillers: Complications and Their Management

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_34

Abstract

The fillers are emerging minimal invasive technique for rejuvenation. As the use and application of fillers grow, it is also important to know how to manage possible complications of the procedures. This chapter describes fillers' immediate, early, and late complications and also suggestions of management based on evidences and author's experience.

Keywords

Complications · Fillers · Granuloma · Hyaluronic acid · Infection · Management · Nodules · Treatment · Vascular occlusion

Introduction

Currently the search for aging delay has been constant and growing, leading to the emergence of a new marketing niche for healthcare industries, as well as for physicians, who have developed products and techniques to meet part of the aesthetic concerns of patients. Among these, is the filler, with the objective of restoring a groove or wrinkle, doing a volumizing treatment or collagen stimulation. These procedures are liable to complications and side effects which can be classified into early (often expected) and late (often unexpected). Today, there are several types of fillers that can be classified into temporary, semipermanent, and permanent. Each filler has physicochemical characteristics, properties, better indications, and contraindications; however, none of them is totally free of risk for complications and adverse effects. Although it is controversial, these authors consider the permanent fillers as more susceptible to late complications, once they definitely remain in the tissue. These complications are difficult to handle because with temporary fillers when there are complications, time itself can resolve them as the product undergoes degradation, but this does not occur with permanent fillers (Amin et al. 2004; Goldan et al. 2007; Jones et al. 2007). Hyaluronic acid is the temporary filler most commonly used in clinical practice. Although it has a lower incidence of complications compared to other fillers, its widespread use produces a significant number of complications that we must be prepared to prevent and treat (Cohen et al. 2013; Duffy 2005).

Classification

The adverse effects of fillers can be classified in several ways:

A. Related application time:
   1. Immediate (<14 days after application)
   2. Late (> 14 days after application)
B. Related to the procedure: potentially expected events ("side effects")
C. Related to the product ("adverse effects")
D. Related to application technique ("complications")

Immediate adverse effects: they are inherent to the procedure, which are generally expected and are limited to acute or immediate period.

Adverse effects and late complications should be analyzed from the following aspects (Sclafani and Fagien 2009):

1. Clinical impact
2. Aesthetic relevance

As we shall see, the management of these events involves only expectant management to surgical management, and these aspects should be, therefore, considered very well in order to choose the best conduct for each specific case (therapeutic individualization) (Alam and Dover 2007; Bailey et al. 2011; Lowe et al. 2005).

Clinical Presentation of the Immediate or Early Side Effects

The immediate and expected changes (side effects) after or during a filler procedure usually are:

1. Erythema
2. Swelling
3. Pain or tenderness

4. Bruise
5. Itching

The onset of these effects varies according to the patient and the applicator. It is estimated to occur in about 80% of applications.

These side effects depend upon some aspects as the reactivity of the patient, if the patient is taking medications (e.g., anticoagulants), the number of punctures and application site, the product used, and the applicator technique. An important issue in this type of events is to clarify the patient previously of the possibility of such changes, as well as its transient and manageable characteristics. Spontaneous resolution of these symptoms may take 5–10 days (Winslow 2009).

Clinical Presentation of Complications and Early Adverse Effects

Infection

After fillers injections, in the first days, there is the possibility of secondary infections due to the procedure. They can be elicited by viruses (herpes infection) or bacteria. Bacterial infections are presented as skin indurations with redness, pain, or itching that can evolve with fluctuation and even systemic symptoms such as fever, malaise, asthenia, leukocytosis, vomiting, and weight loss.

Hypersenstivity (Allergy)

Hypersensitivity to the fillers is unpredictable, except when using fillers of animal origin, such as the collagen, which is possible to allergic diagnostic pretesting. Although there is no well-established pretesting for the nonanimal origin products, allergic conditions may occur as idiosyncrasies. These are characterized by clinical conditions ranging from simple signs as inflammation with erythema, edema, heat, local pain, and itching, without any signs of infection, until signs as pus or lumps with fluctuation, angioedema and anaphylactic reactions.

Irregularities Caused by Poor Distribution of the Product

Both in acute and chronic periods, we can check visible or palpable irregularities, due to uneven distribution of filler. In the acute period, however, this problem may be related to improper technique or lack of patient compliance to post-procedure care such as guidance to do not massage the site of application or do vigorous exercise on the day of application.

Dyschromias

Most dyschromias occurs due to improper placement of the filler, when applied very superficially in the epidermis or superficial dermis, thus allowing visualization. They also may be due to persistent redness and ecchymosis (hemosiderosis) and can progress to post-inflammatory hyperchromies.

Tissue Necrosis Caused by Vascular Occlusion

This is one of the most serious and troubling complications that can occur in the acute phase after or during the application of fillers.

There have been reports of irreversible blindness secondary to vascular occlusion by fillers.

The application site of greatest risk is the region of glabella that, in our opinion, should not be filled except at a very superficial layer of the skin and in small quantities.

Other danger zones are the region of angular artery (near the piriform aperture) and the region of the temporal artery.

The use of fillers in areas close to medium-caliber vessels of the face leads to the risk of peri (external compression) or intravascular injection that can cause sub or total occlusion of the vasculature.

In case of arterial occlusion, it can be noticed immediately after application a blanching pattern drawing the area of the affected vessel irrigation, whether or not accompanied by severe pain depending on the filler composition (if it contains or not lidocaine), followed by purplish skin tone. In the case of venous occlusion, the symptom onset is slower and will evolve into the violet tone and less intense pain. If not noticed, vascular occlusion evolves with a reticular erythema,

sometimes purpuric, followed by necrosis of the affected area in about 3–5 days.

Predicting signs of necrosis:

- Skin blanching
- Dusky (i.e., grayish blue) skin
- Ecchymosis
- Reticulated erythema
- Intense pain in the treated area

Some cases of vision loss were reported among the last years and are often associated with injection on "danger zones." Some symptoms are linked with vision loss risk:

- Ocular pain in the affected eye immediately after injection
- Diminished vision
- Ptosis
- Headache
- Dizziness
- Nausea
- Ophthalmoplegia (i.e., extraocular muscle palsy) (Lemperle et al. 2006; Lowe et al. 2005; Requena et al. 2011)

Clinical Presentation of Complications and Adverse Late Effects

Hypertrophic Scar

Patients who already tend to hypertrophic scarring may eventually develop this type of healing process after fillers injections. Most reported cases are related to inadequate injection technique, but hypertrophic scar has been also reported following the use of filler at the right level.

Intermittent Edema

Intermittent swelling can occur months to years after fillers injections and is usually related to the consumption of alcohol, sun exposure, vigorous exercise, and episodes of vasodilation.

Dyschromia

Skin color changes may occur when the filler is applied superficially in the skin. Different wavelengths of light waves are reflected and scattered differently by substances present in the tissues: the Tyndall effect. As an example we know that the skin red wavelengths penetrate more deeply than the blue. Thus, the presence of a filler at very superficial skin layers can lead to a dyschromia due to the change of the reflectance of that tissue (bluish color in the implant area).

Migration

It can occur with any filler, but more often with permanent fillers. Migration of a filler may present clinically as nodules simulating granulomatous or neoplastic diseases. Silicone is the most susceptible product to this complication, and although banned in many countries, we can often encounter patients with complications arising from their illegal use or patients who have used this product many years ago. Migration to distant sites is not uncommon, for example, from the buttocks to the entire length of the lower limbs.

Nodules

The nodules may be caused by several factors such as those immediate after injection, due to overcorrection or poor distribution of the product, or those due to allergic reactions to the filler, which may be early or late. There are still nodules arising from infections, which may be single or multiple (Funt 2015).

The nodules may be dermal or subcutaneous and may be or not clinically apparent or palpable. The evaluation of clinical and aesthetic significance of these cases is the parameter of the treatment required or not (Fig. 1).

Recent advances in magnetic resonance imaging (MRI) studies for filler complications diagnosis described how this exam could help to differentiate between inflammatory and noninflammatory nodules which is not always possible with high-frequency US (Di Girolamo et al. 2015).

Foreign Body Granulomas

The granulomas can be clinically classified as nodules if no histopathological study is performed. The histopathological study will be necessary to clarify the diagnosis and help the treatment planning. In many cases the result is

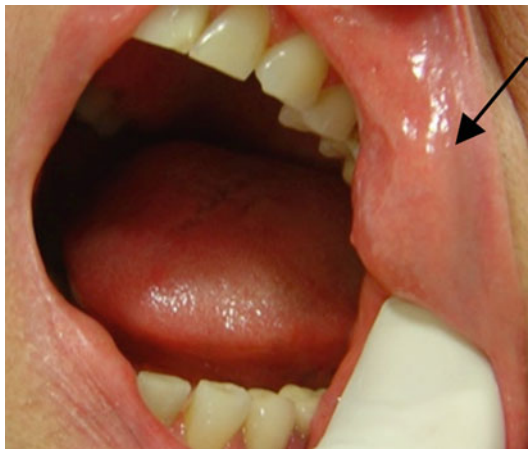

Fig. 1 PMMA post-application nodule (polymethylmethacrylate)

compatible with foreign body granuloma, without any evidence of infection or hypersensitivity.

The risk of foreign body granuloma formation cannot be predicted and may occur months to years after the use of a filler. Possible triggers can be systemic or localized infections.

Infection

The infection may emerge clinically as nodules, which are different in this case because they are accompanied by pain, warmth, redness, swelling, and fluctuation. Irregularity, inflammatory fibrous cords, and multiple nodules are some possibilities.

As the filling procedure involves punctures in the skin and introducing material into the tissue, the risk of infection will be high, if careful antiseptic measures are not taken.

We must remember that, due to the lack of regulation and supervision in some countries, this procedure is being performed by doctors without proper training or even by nonmedical professionals. Inevitably the chances that we encounter this kind of complication are growing.

The bacteria most commonly involved are *Streptococcus pyogenes* and *Staphylococcus aureus*, but infections that begin more than 2 weeks after the procedure are highly suggestive of atypical infectious agent such as mycobacteriosis.

Saprobe bacteria can find a favorable microenvironment for multiplying in the gel formed by the filler, as this limits the access to the inflammatory defense cells (neutrophils, macrophages, lymphocytes) and simultaneously allows passage of nutrients for bacterial metabolism.

The possibility of the so-called bacterial biofilms formation should be considered. These are complex bacterial biosystems formed by aggregated and adhered bacteria to the surface. This provision in colonies allows greater bacterial resistance and much more difficulty in treatment.

More severe symptoms can occur, including systemic symptoms such as hyperthermia, malaise, asthenia, leukocytosis, vomiting, and weight loss.

Lipoatrophy After Fillers

A rare reaction (idiosyncratic) was described after the use of fillers, in which the patient had lipoatrophy similar to that of patients on antiretroviral therapy for HIV.

Hypersensitivity Reactions

These reactions are characterized by redness, swelling, warmth, and pain, however without any evidence of infection. They are more frequent in early stage after filler injection but eventually may arise later. Currently they are less frequent due to increased biocompatibility of most used fillers but have been a much more common reaction during the predominance of the use of bovine and human collagen, as well as the hyaluronic acid of animal origin (rooster crest).

As the current hyaluronic acids are derived from industrial technology that employs a streptococcal bacterial fermentation, local hypersensitivity reactions may still occur due to the possible high protein level in fillers.

There are two main types of hypersensitivity reactions:

- Angioedema (antibody-mediated edema) that is due to IgE-mediated immune response that can be treated with antihistamines

- Nonantibody-mediated (delayed) edema that cannot be treated with antihistamines but possibly treated with steroids and the removal of the filler ((Hirsch and Stier 2009), Cox and Adigum 2011, (DeLorenzi 2013; Gilbert et al. 2012; Requena et al. 2011))

Complications in Specific Sites

A-Back of Hands

The rejuvenation of the dorsum of the hand with fillers has been widely used today. Like any other procedure, there can be some complications.

Recent review published about this specific site has compiled the most frequent late complications in this region: permanent swelling not relieved by classical therapies, tingling and numbness, and foreign body granuloma formation (Figs. 2 and 3) (Park et al. 2012).

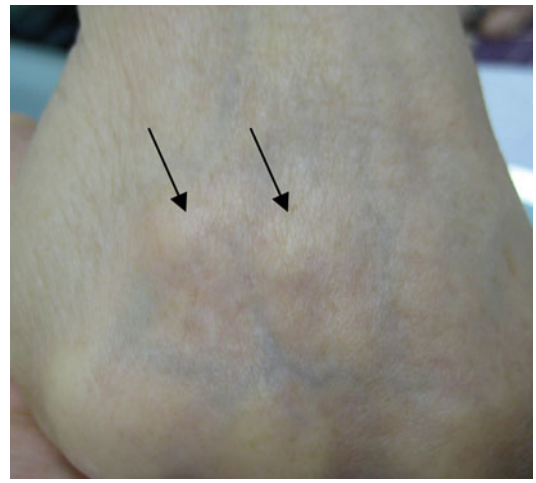

Fig. 2 Foreign body granuloma after calcium hydroxyapatite filler

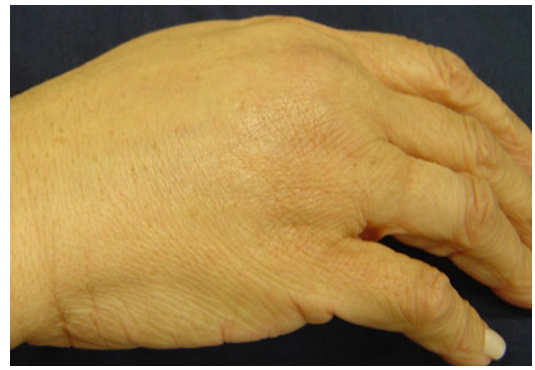

Fig. 3 Hand back filled with PMMA resulting in "cushion" aspect

B-Malar Edema

Malar edema may occur after superficial or deep injection in this region, but it is far more common when the filler is injected more superficially. The superficial lymphatic cheek drainage is naturally compromised, and even small amounts of filler can worsen it causing persistent edema. The deep drainage also can be impaired by bigger amounts of filler. Then special care must be taken when injecting fillers at this site.

Treatment

Prevention

Physicians should prevent complications with fillers by correct selection of eligible patients for this treatment

If a patient wishes to treat grooves for the first time but is unsure of the procedure, one should opt for temporary fillers. If the patient has already made temporary fillers with good results and no longer wishes to repeat the treatment periodically, only then physicians should think about the possibility of more permanent fillers such as calcium hydroxyapatite and PMMA.

About the selection of patients, the physician must actively investigate if the patient has a tendency to unaesthetic scars such as hypertrophic and keloid. Investigate autoimmune and granulomatous diseases, especially collagen diseases and sarcoidosis, which, if present, can lead to contraindication of the procedure, although this contraindication is not absolute.

Investigate the history of procedures already performed by the patient is very important because, although still controversial, some authors suggest that injections of different fillers on same areas already treated with permanent fillers can trigger immune reactions and adverse events, besides infections on permanent fillers. Besides that, previous surgeries on application site could induce anatomical variations, and, therefore, the "danger sites" could be different from the usual ones.

Gather information about daily use medications and sporadic use medications, because the use of

medications that have anticoagulant effects can influence the formation of bruises during application. The suspension or none of these drugs before the procedure should be evaluated considering the indication and necessity of the medication in use.

Even before the procedure, it is important to clearly explain to the patient about the procedure, the expected effects, side effects and adverse effects, and duration, assess the patient's expectations, and, after these steps, get the written informed and free consent (Engelman et al. 2005).

Using the correct technique (tips to avoid complications):

1. Visualization of the grayish color of the needle under the skin is warning that the positioning of the needle is too shallow and must be repositioned deeply. Exception is made when treating acne scars.
2. Intramuscular injection is also contraindicated for being a layer at high risk for formation of lumps and irregularities triggered by the migration of the filler when there is contraction of the injected muscle.
3. Submucosal injections in lips can also trigger irregularities and unaesthetic or uncomfortable lumps for the patient when injected very superficially.
4. Special care must be taken when applying fillers in areas with very thin skin such as eyelids, for example. The use of fillers to try to correct fine lines in this region can mistakenly lead to very superficial injection with visible irregularities of the skin surface by the filler's presence in inadequate dermal layer. In this section we would like to point out that specific products for fine lines have been developed. These products aim to make a "boost" in the dermis, may not possess crosslinking, or have it in a lesser degree, being less viscous and more rapidly absorbed. They are not therefore called fillers themselves, but "skin moisturizers," collagen enhancers, or skinboosters.
5. Groove correction may require more than one session in order to achieve the desired final effect. Do not overdo the correction in the first session. The patient should come back to show you the initial result, and a new procedure can be done to complement the initial one, if necessary. It should also be remembered that the patient does not have technical or anatomical knowledge to decide which procedure is the best for him. The decisions related to the anatomic facial area to be treated and the amount of product for this area should be determined by the doctor. Do not let patients interfere in your decision, because sometimes they can have body dysmorphic disorder and can desire much more than they deserve to have a good clinical result.
6. Post-injection guidance is important. Although not proven, the use of cold or frozen compress is often indicated to prevent edema, erythema, and post-procedure bruising. Recent evidence may contraindicate cold dressings and should be replaced by hot packs in the case of signs of ischemia/vascular occlusion. Massaging is also generally contraindicated but may be necessary in the case of ischemia/vascular occlusion and poor distribution of the product. Strenuous exercise and exaggeration in muscle contraction near filler application site in the first 3 days after application can lead to migration and product distribution irregularities.
7. Skin pretests must be made beforehand for the animal collagen-based fillers. These tests consist of the intradermal injection of 0.1 ml of the product in the volar forearm and reading after 48–72 hours. Some authors recommend a second test after 2 weeks based on the possibility of immune response development after first exposure (similar induction phase of allergic contact dermatitis). These tests are dispensed when dealing with human origin collagen products. Collagen products are not available anymore in Brazil.
8. PLLA when diluted in greater volume and time between reconstitution and application (36–48 h instead of 12–24 h) and applied

subcutaneously instead of reticular dermis followed by massage after application shows lower incidence of non-visible but palpable nodules.

9. Avoiding infections: washing hands before starting any procedure, remove all makeup and other topical products before the procedure, clean the application sites with antiseptic before the application, take the appropriate antiseptic care, and select the needle or appropriate cannula to perform the procedure. This will prevent infections and biofilm formation in the applied product.
10. Biofilms are commonly present in dental bacterial plaques. Consequently, intraoral injections of fillers are at increased risk of infectious complications and should be avoided. Furthermore, the massage for a better distribution of the filler with fingers inside the mouth should be avoided. This procedure contaminates the gloves and, therefore, should only be made after treatment, and the gloves should not come in contact again with the needle entry holes, where applications have been made. If needed one should proceed the exchange of gloves after this move.
11. Never inject the filler on areas with active infection, such as acne, cold sores, or impetigo, avoid using on patients with recent dental surgery, Inject on previous implants of other materials, as well as intraoral application as mentioned in the previous topic.
12. For prevention of vascular occlusions, some steps can be taken:
    - Take care with risk factors such as dangerous zones, large volumes of injection, small sharp needles or blunt cannulae (smaller than 27 gauge), previous scarring sites, and type of filler (permanent ones worst than temporary ones).
    - Aspirate with the syringe before injecting.
    - Inject small amounts in high-risk areas or do not apply in these areas.
    - Inject more in superficial planes using products listed for each plan.
    - Manually occlude the origin of important vessels with the nondominant finger.
    - Pinch the skin to provide more spaces between superficial branches of main arteries and to move away from underlying vasculature.
    - Take special care with high-risk areas such as glabella where anastomosing arteries and veins have great anatomical variability (Lemperle et al. 2006; Lee 2014; Sánchez-Carpintero et al. 2010; Sherman 2009).

Post-Procedure Care

The commonly used cold compress or ice has not presented any evidence of prevention of early or late complications such as swelling, redness, or bruising. However, it offers comfort to the patient, which is the reason for their acceptability as post-procedure care.

The hot compresses are formally indicated when there is evidence of vascular occlusion in an attempt to obtain thermal vasodilation and reestablishment of blood flow.

Immediate Side Effects

Often only local observation and care will be more than sufficient for the resolution of erythema, edema, bruising, local pain, and tenderness after the procedure. If necessary, as described above, one may employ the cold compresses (at first) or hot compresses (as second step).

Persistent erythema can be treated with corticosteroids or intense pulsed light devices.

The cold packs may be useful for patient comfort in the case of pain. The use of Arnica and Bromelain before and after the procedure has been reported as helpful, although there are no studies on this use.

In the case of bruises, early compression can be useful.

The recent introduction of fine gauge cannula also shows promise in preventing the events described above.

Treatment of Immediate Adverse Effects

Infection Treatment

In the case of herpes infection, oral antiviral should be immediately initiated (acyclovir, valacyclovir, penciclovir), with full cycle and full dose.

In the case of acute bacterial infections, empirical treatment could be used with antibiotics whose spectrum covers skin biota bacteria. In case of no improvement, further investigation like the one in late infectious complications should be made.

Hypersensitivity Treatment

According to hypersensitivity of severity, antihistamines and corticosteroids can be employed.

Treatment of Irregularities Caused by Poor Distribution of the Product

In the case of immediate irregularities, the applicator can try a more vigorous massage modeling and better distributing of the product, which will only work in the early hours after application. Another option is the removal of localized quantities of product through needle punctures on the affected site.

In the case of hyaluronic acid, the use of hyaluronidase may be tried.

Treatment of Vascular Occlusion/ Necrosis

As soon as one notices an early sign of vascular occlusion, one should immediately suspend the procedure. If cold compresses are being used, this should be immediately suspended and replaced with hot compresses to promote vasodilation.

A quick light massage in circular movements, not compressive, must be made on site.

The use of topical nitroglycerin derivatives is indicated and can be of great help (Kleydman et al. 2012). Patients should be advised that this medication can trigger headaches and even hypotension in susceptible patients.

When the product used is hyaluronic acid, the use of hyaluronidase is indicated to attempt to remove the cause of vascular occlusion.

The low molecular weight heparin can be used as a treatment modality for vascular embolic occlusions, as well as acetylsalicylic acid.

Hyperbaric oxygen therapy can be used when available.

A follow-up within a very short period should be made to detect early signs caused by necrosis and, if this is so, treat properly with daily care, debridement, and dressing to try to prevent scarring.

If a scar is formed, it should be treated at the correct time for its minimization, which will be on average after three months, when new adequate collateral circulation can be formed.

Brennan in 2014 summarized this procedure in topics:

- No ice.
- Warm immediate compresses.
- Massage or tap the area to facilitate vasodilation and dispersion of material.
- Aspirin (80 mg).
- Topical nitroglycerin derivatives.
- Hyaluronidase (only if using HA).
- Corticosteroids.
- If ischemia is not reversed, and necrosis is unresponsive, contact a plastic or reconstructive surgeon.
- Subcutaneous injections of low molecular weight heparin may be helpful.
- Antibiotics.
- Antivirals (if impending necrosis is around the mouth).
- Hyperbaric oxygen for 1 month may be required.
- Multiple laser treatment after 3-month postinjection.

There are five existing phases that might occur after vascular occlusion:

1. Pallor or blanching (mediated by arterial contraction)
2. Livedo (indicates that oxygen supply is being consumed)
3. Blue or gray-blue (oxygen was consumed and deoxygenated blood predominates)

4. Demarcation (ischemia progresses to necrosis and a margin of hyperemia surrounds a zone of necrosis)
5. Repair and remodeling (inflammation subsides and tissue repair and remodeling occurs)

Treatment of Late Complications

Treatment of Hypertrophic Scar

The treatment of hypertrophic scars should be done in the same way as that of postsurgical or traumatic hypertrophic scars, i.e., the use of intralesional corticosteroid injections to generate atrophy with the aim of improving aesthetic results.

Treatment of Intermittent Edema

Intermittent swelling will occur only in "crisis," and corticosteroids or tacrolimus topical creams can be used.

Treatment of Dyschromia

Tyndall effects will be treated according to the filler used. In the case of hyaluronic acid, it can be solved with intense massage, as you may need the use of hyaluronidase (an enzyme that degrades hyaluronic acid). Visible white spots after using calcium hydroxyapatite can be solved with small incisions and removal of the product because it is visible. Permanent fillers have more complicated management and may require surgical removal of the applied product.

Post-inflammatory hypochromia can be managed with topical hydroquinone, and other hypochromias are more difficult to treat. One can try the whitening of the skin around to decrease the contrast using laser and chemical peels, most often however, with poor results.

Migrated or Poorly Positioned Filler Removal or Overcorrection

Nodules can be treated with vigorous massage to better repositioning when forming in the recent period after application of the filler. Late nodules respond less to this technique because it is already integrated in the tissue.

In much fewer cases, the fillers may eventually be removed when causing unsightly effects by displacement, malposition, or overcorrection. This can occur even later when, for reasons not well clarified, integration or encapsulation of the entire filler to the biological tissue does not occur. The extraction of the substance after an incision with a scalpel blade and light expression with two swabs or digital pressure can be resolute (Fig. 4) (Sclafani and Fagien 2009).

Another option is the use of hyaluronidase if the product used is hyaluronic acid. Although the correct doses have not been well established, this enzyme has been shown to correct unsightly effects. Besides being very useful in acute vaso-occlusive events, it can also be applied at later times for the complications in question (Fig. 5)

Use of Hyaluronidase

Hyaluronidase, hyalozima, or hialuronoglucosaminidase is an enzyme that facilitates the diffusion of injected fluids, extracted from bovine testicles. The hyaluronidase term is also used to describe two different enzymes, which

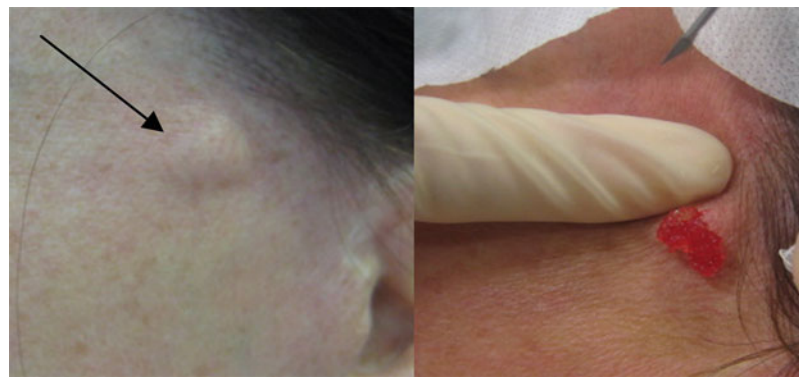

Fig. 4 Nodule caused by HA migration that has been removed through an incision and the contents removed. Palpation observed that the product had not been "encapsulated"

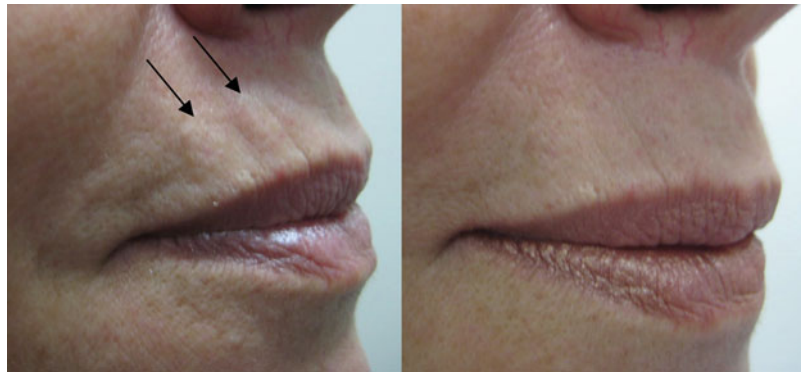

Fig. 5 Hyaluronidase application for overcorrection in supralabial wrinkles with AH

act in various parts of the hyaluronic acid molecule, which are hialuronoglicuronosidase and hialuronatoliase.

Hyaluronidase acts reversibly depolymerizing hyaluronic acid in the existing cement around the connective tissue cells, thereby temporarily reducing the viscosity of this tissue and making it more permeable to the diffusion of liquids. Based on this mechanism of action, hyaluronidase has been used for promoting the degradation of HA injected in cases of complications and/or adverse reactions, such as treatment with improvement.

Repeat the application, if necessary, 10–15 days later. After dilution, remainder must be totally discarded and should not be saved and applied under any circumstances. The need and usefulness of skin testing for its allergenic power is questionable.

Before using hyaluronidase, the patient should be interviewed about the use of drugs like furosemide, benzodiazepines, phenytoin, dopamine, and α-adrenergic agonists, anti-inflammatory agents (e.g., indomethacin, dexamethasone, and salicylates), numerous plant-based drugs (e.g., flavonoids and antioxidants), antihistamines, mast cell stabilizers, heparin, vitamin C, and dicumarene. The interaction with these drugs must mimic tissue resistance to hyaluronidase.Some reactions can be caused by hyaluronidase injection, but urticaria and angioedema are reported in less than 0.1% of cases (Brody 2005; Cavallini et al. 2013).

Treatment of Foreign Body Granulomas

The foreign body granulomas that have clinical or aesthetical impact can be treated successfully with the use of intralesional or systemic corticosteroids that are the first choice in these cases. These medications can have side effects such as atrophy and telangiectasia.

Other therapeutic options already reported in the literature are minocycline, 5-fluorouracil, hydroxychloroquine, bleomycin, isotretinoin, allopurinol, azathioprine, tacrolimus, and imiquimod. For single circumscribed granulomas, surgical excision can also be an option.

Application of the laser with wavelengths of 532 and 1064 nm has been described for small and large noninflammatory granulomas and inflammatory granulomas, respectively. The effects of these lasers are decreasing telangiectasias and neovascularization and reducing volume and stiffness of the nodes.

It has been reported the use of etanercept to control granulomatous reaction to silicone.

Treatment of Infection

Generally short cycles of antibiotics with coverage for bacteria associated with skin and subcutaneous tissue infections are sufficient to solve these complications (e.g., cephalosporins such as cephalexin). However, if the suspicion is of an atypical agent, one must try, if possible, to identify it with cultures to better guide the choice of antibiotics. In such cases it will often be necessary for a broader spectrum coverage, with antibiotic associations (e.g., macrolides such as clarithromycin, fluoroquinolones such as ciprofloxacin, and tetracyclines such as minocycline).

Contraindications Post-Permanent Fillers Application

There are reports of patients with severe inflammatory adverse reactions years after application of fillers when these patients were exposed to therapies with interferon use. It has been suggested so that patients with these types of fillers have contraindication to the use of interferon. Yet it is good sense to ponder that, often, the use of interferon may be important to treat major diseases. So this contraindication should be relative, analyzing the risk X benefit of interferon use ((Fischer et al. 2007)).

Another recommendation is that patients with permanent fillers should always receive systemic antibiotics when they are affected by any infection for a period of 10 years after application in order to prevent late cross-immune responses.

Treatment of Hypersensitivity Reactions

Hypersensitivity reactions can be dealt either with close observation, if they are mild and little impact as with the use of drugs such as topical, intralesional, or even with systemic corticosteroids besides topical tacrolimus. Hyaluronidase rarely needs to be used in these cases, also because it is of a heterologous origin and there is relative risk of triggering allergic reactions. There is already a recombinant human hyaluronidase whose potential for allergic reactions is much lower.

Treatment of Fillers of Complications in the Back of the Hands

Park TH et cols. suggested an algorithm for treating such complications:

First of all, put ice on the back of the hands, do massage, and keep hands high.

After this, if necessary, use two types of antibiotics. If the reaction persists, the next step depends on the type of filler used:

- Hyaluronic acid – treat with hyaluronidase
- Calcium hydroxyapatite – surgical removal
- Others fillers – infiltration with corticosteroids

If the treatment with hyaluronidase and corticosteroids infiltration failed, it's necessary to have surgical removal.

The most important point is the follow-up of the patient in a short period of time. The complications not mentioned hereby can be treated as described above.

Histological Aspects of Fillers Adverse Reactions

The histopathological findings allow us to specifically identify the agent used in the dermal filler. This is necessary because only the histopathological examination can identify precisely which filler is involved and determine what kind of inflammatory reaction can optimize the treatment.

Whenever two different products were injected on different occasions, the histopathological evaluation can be used as a proof to identify what product caused the reaction (Christensen 2007).

Hyaluronic Acid (HA)

Two types of adverse reaction to HA can be observed: hypersensitivity reaction and foreign body reaction.

The cases of hypersensitivity reactions are much less frequent than the foreign body and are characterized by diffuse inflammatory infiltration throughout the dermis represented by lymphocytes and plasma cells intermingled with a large number of eosinophil leukocytes (Fig. 6). In this case the HA gel is not observed even with the aid of special stains as alcian blue or colloidal iron. The diagnosis of this reaction can only be carried out with the clinical information of filler application in the biopsied area provided.

In cases of granulomatous foreign body reaction, which is more frequent in the dermis, are observed a large number of multinucleated giant cells surrounding large amount of amorphous extracellular material and basophilic corresponds to HA gel injected (Fig. 7). A small amount of this material can be seen in the cytoplasm of giant cells. In some cases large number of eosinophil leukocytes can be observed among the giant cells.

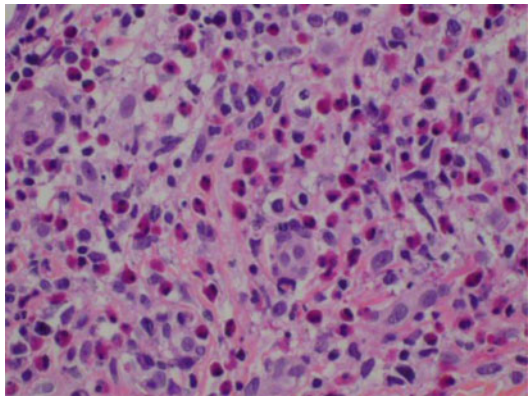

Fig. 6 Hypersensitivity reaction to Restylane that is not visualized in this case with mixed inflammatory infiltrate throughout the dermis represented by lymphocytes and plasma cells intermingled with a large number of eosinophil leukocytes. (hematoxylin-eosin, original magnification x400)

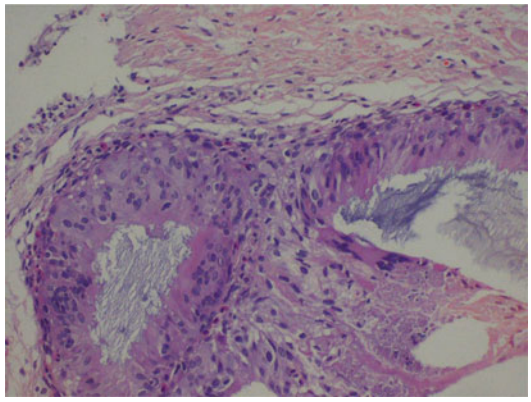

Fig. 7 Restylane (hematoxylin-eosin, original magnification x200). Foreign body type giant cells surrounding basophilic amorphous material; eosinophils are seen beside the giant cells

The HA gel is heavily stained by alcian blue and also by colloidal iron.

(Dadzie et al. 2008; El-Khalawany et al. 2015; Parada et al. 2005; Requena et al. 2011; Zimmermann and Clerici 2004).

Hyaluronic Acid + Dextranomer

Dense inflammatory infiltrate of granulomatous foreign body type, sometimes nodular and

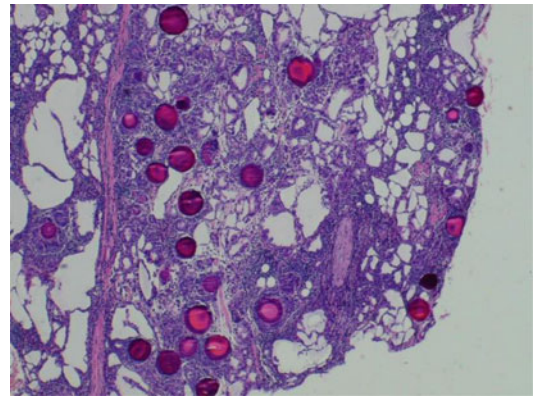

Fig. 8 Dense inflammatory infiltrate of granulomatous foreign body type is observed in the dermis with giant cells of foreign body involving or containing cytoplasm spherical particles of a blue-magenta color, corresponding to the microparticles dextranomer amid. (hematoxylin-eosin, original magnification x200)

sometimes diffuse, is observed in the dermis with large numbers of giant cells of foreign body involving or containing cytoplasm spherical particles of a blue-magenta color, corresponding to the microparticles dextranomer amid numerous eosinophil leukocytes, macrophages, and few neutrophils leukocytes (Fig. 8).

Hydroxyapatite Calcium

The lump is made up of large numbers of giant cells of foreign body phagocytizing or involving microspheres blue-brown and refractive material with the characters of calcium hydroxyapatite surrounded macrophages and fibroblast proliferation and especially thin collagen fibers (Fig. 9).

Polymethylmethacrylate (Metacril®)

Dense sometimes nodular and diffuse inflammatory infiltrate is now observed in the dermis and hypodermis and consists of foreign body granuloma represented by multinucleated giant cells containing the cytoplasm regular cystic spaces of various sizes, some containing non-birefringent and translucent spherical microspheres, and

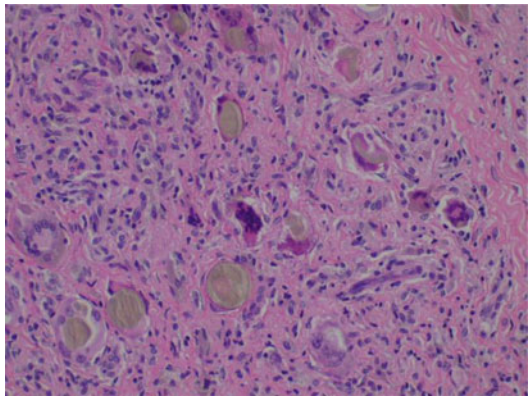

Fig. 9 Granulomatous Foreign body type reaction with giant cells phagocytizing or involving microspheres blue-brown and refractive material with the characters of calcium hydroxyapatite (hematoxylin-eosin, original magnification x200)

epithelioid granuloma represented by epithelioid histiocytes and giant Langhans type giant cells forming granulomas sometimes nodular and diffuse and sometimes being permeated by numerous lymphocytes (Fig. 10).

Polymethylmethacrylate + Collagen (Artecol®)

The histological picture is similar to that observed in the case of Metacril®, the only difference lies in the fact that with this filler cystic spaces are larger and of the same size while with Metacril variable sizes are seen (Fig. 11).

L-Polylactic Acid (Sculptra® or Newfill®)

The node is represented by inflammatory infiltrate composed almost exclusively by giant foreign body type giant cells containing in the cytoplasm translucent particles of variable sizes with most fusiform or oblong shapes (Fig. 12) being birefringent when subjected to polarized light (Fig. 13). Often, asteroid bodies in the cytoplasm of giant cells are also observed. There are small numbers of macrophages and lymphocytes permeating.

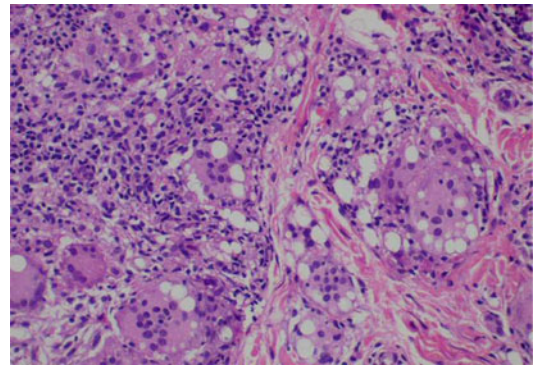

Fig. 10 Metacril (hematoxylin-eosin, original magnification x200). Foreign body-type giant cells with multiple round and irregular size vacuoles, beside nodular tuberculoid granuloma

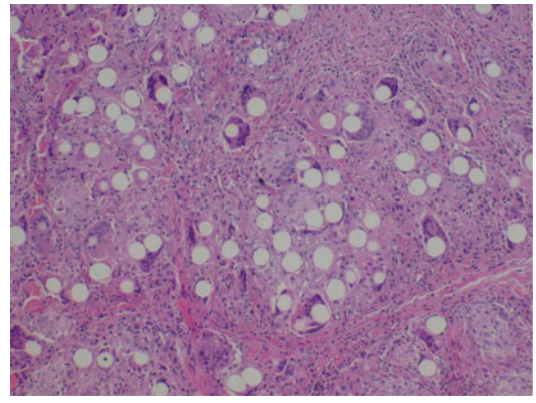

Fig. 11 Artecoll (hematoxylin-eosin, original magnification x100). Foreign body-type giant cells with round and regular vacuoles, beside nodular tuberculoid granuloma

Silicon

The adverse reaction caused by silicon varies according to the type of silicon injected. The silicon which is used by most dermatological and plastic surgeons is dimethyl-siloxan whose adverse reaction is characterized by diffuse or focal macrophage infiltration with multiple cytoplasmic vacuoles of different sizes and irregular and basophilic nuclei and large clear spaces delimited by macrophages (Fig. 14). The infiltrate is distributed among the collagen fibers often replacing the entire dermis and often also present in the hypodermis.

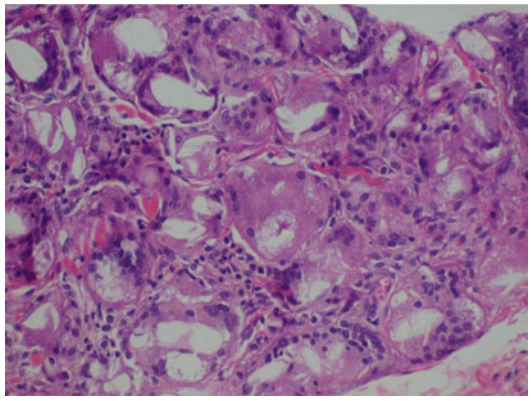

Fig. 12 New-FiII (hematoxylin-eosin, original magnification x400). Foreign body type giant cells containing cytoplasm with long, spiky, and translucent particles; asteroid bodies are seen in two giant cells

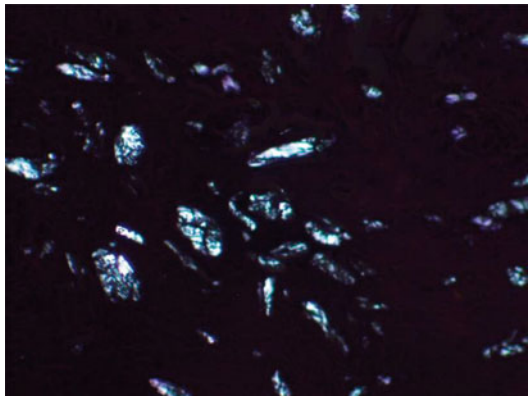

Fig. 13 Poly-L-Lactic acid crystals being birefringent when subjected to polarized light (400x)

Take Home Messages

- There are three main complications with fillers: immediate, early, and late complications.
- The immediate complications are common and expected. Their treatment is simple and the resolution in hours or days.
- The early complications are potentially serious, and the most feared is vascular occlusion.
- The late complications are insidious and unexpected. Their management can be difficult, and the resolution slows such as some kind of infections, nodules, and granulomas.

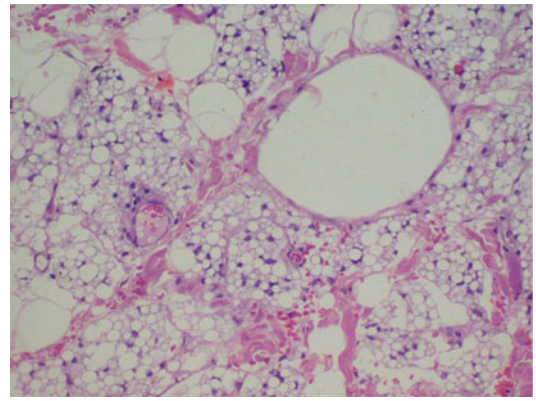

Fig. 14 Liquid silicone (hematoxylin-eosin, original magnification x200). Macrophages with multiple cytoplasmic vacuoles with "Swiss cheese" pattern

- The use of temporary fillers is recommended based on the complications described above.

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My Personal Experience with Fillers

Maria Claudia Almeida Issa

Contents

Abstract

Facial aging is the major indication for minimal invasive aesthetic procedures, including peelings, neuromodulators (botulinum toxin), fillers, and lasers. Combined treatments are usually indicated for a better result, and dermatologists should know from where to start. Fillers and botulinum toxin bring fast results, and if they are indicated, we usually start with these procedures. Patient's assessment is an essential step. In our routine, topical and oral treatments are prescribed at the first visit, when the number and the order of procedures are planned according to patient's clinical approach and complaints. In this chapter, we are going to show our experience with fillers in aesthetic dermatology.

Keywords

Fillers · Hyaluronic acid · Poly-L-Lactic Acid · Calcium hydroxiapatite · Skinbooster · Aging · Aesthetic dermatology · Asymmetry · Photodamaged · Rejuvenation · Skeletal remodeling · Subcutaneous fat loss

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M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9_33

Introduction

It is accepted that facial aging is the result of deterioration of cutaneous structures due to downward gravitational pulling, hormonal changes, photodamage, and smoking, among other factors. However, skeletal remodeling and subcutaneous fat loss and redistribution are key elements for the age appearance (Muhn et al. 2012).

Nowadays, it is possible to minimize the signs of aging and tiredness using fillers after a correct patient assessment. Dermatologists should have a thorough knowledge of all soft tissue and skeletal structures, from superficial to deep layers. An understanding of the volume deficiencies and the lifting or volumizing capacity of the different filler substances are essential (Sykes et al. 2015).

A three-dimensional clinical approach, which addresses volume loss in soft and bone tissues, enables the physicians to treat both cause and effect of facial aging (Muhn et al. 2012). To achieve more natural results, it is useful to evaluate patient's facial shape and volume during youth. This can be used as a parameter to plan the treatment.

Fillers and botulinum toxin bring fast results; therefore we usually start with these procedures, whenever possible. Sessions of peelings and lasers are programed according to the clinical indications. Injectable fillers promote facial sculpting and also correct asymmetries. In our clinical practice, hyaluronic acid (HA) is the most common filler used to treat the face.

The use of facial fillers has been rapidly increased as the range of injectable products and indications are continuously expanding. It is important to keep on mind that injectable fillers are prone to complications even in the hands of experience injectors. Injectors should know the anatomy, dominate the technique, and understand the biochemical properties and flow characteristics of the selected HA gel. Complications arise from improper placement or inadequate techniques (Sykes et al. 2015).

The best results are achieved when injectable fillers correct different layers of the facial envelope. This includes: (a) creating a foundation for deep structural support in the supraperiosteal or submuscular plane; (b) volume restoration of subcutaneous fat compartments; and (c) reestablishment of dermal/ subdermal support to minimize cutaneous rhytids, grooves, and furrows (Muhn et al. 2012). Because volume loss in the midface and upper face causes ptosis of skin below, it is important to support these regions before treating the lower face (Cotofana et al. 2015).

Procedures

Nowadays, HA fillers are associated with anesthetic. Therefore, topical and local anesthetic are not essential. It is indicated mainly when multiple punctures are planned, especially for nonhyaluronic products injections and for HA skinboosters. The procedures can be performed in an office setting on an outpatient basis. Patients must provide specific informed consent for the treatment.

Patients must be warned to avoid agents that can cause bleeding, for example, aspirin and some anti-inflammatory drugs, for 7 days prior to injection, which can help reduce hematoma formation. Patients with any history of herpes virus infection are given valacyclovir (2x/day) 2 days before treatment completing 5 days.

Treatments are usually performed with the patient in a sitting or semisitting position, which allows the physician to inject dermal filler while effects of gravity influence the skin.

It is fundamental to clean the skin properly. Before antisepsis, make-up remover is applied with cotton. After that, exhaustive antisepsis is done with 2% chlorhexidine sterile watery solution followed or not by 70% alcohol and sterile gauze. Sterile gloves are necessary (Fig. 1a, b).

The anatomical area to be treated and the strategic points of fillers injections can be drawn on a sheet of paper. It facilitates patient's follow up and can be used as a model for programed future sessions.

Either cannula or needle can be used for the procedure according to the area to be treated and the physician's experience (Fig. 2). Usually cannula is used for most procedures, but needles are necessary to treat some specific regions, mainly the fine lines around the lips and in the

Fig. 1 (**a**) Make-up remover. (**b**) 2% chlorhexidine sterile water solution, sterile gauze, and sterile gloves

Fig. 2 Cannula or needle can be used for the procedure depending on the area to be treated and the physician's experience

cutaneous–semimucosa lips junction (white roll). We also use needles to supraperiosteal injections, collagen stimulators, and skinboosters. Proper aspiration is mandatory when using needles.

Fillers and Collagen Stimulators

Hyaluronic Acid Filler

Hyaluronic acid (HA) injectable filler, a viscoelastic gel, is the most widely used filler, as it provides a natural-look and is a nonpermanent filler. HA fillers are manufactured by different industries and have different biochemical properties and flow characteristics, mainly elasticity, viscosity, and cohesiveness. For instances: Juvederm® (Allergan, USA); Emervel® and Restylane® (Galderma SA, Switzerland); Belotero® (Merz Aesthetic, Germany) (Fig. 3). Dermatologist should know these properties before choosing the product according to the area to be filled.

Among rheological parameters used to describe the viscoelastic properties of HA fillers are: G* – measures overall viscoelastic properties or "hardness"; G′ – measures elastic properties; G″ – measures viscous properties; Tan δ – measures the ratio between viscous and elastic properties. Elasticity represents the ability of the HA gel to resist to deformations, maintaining the original form. It depends on the degree of crosslinking. The greater the crosslinking the greater gel elasticity and firmness. Viscosity represents the fluidity of the gel, allowing its permeation through the needle. The size and molecular weight (MW) of HA gel particles determine the viscosity. Cohesiveness represents the internal adhesion and the strength of attractiveness between the particles. It depends on the HA concentration and on the type of crosslinking and its technology. It is related to the lifting and the volumizing ability of the gel. The higher the cohesiveness the higher the lifting and volumizing ability (Stocks et al. 2011; Edsman et al. 2012).

Fig. 3 HA fillers are manufactured by different industries and present different properties, mainly elasticity, viscosity, and cohesiveness

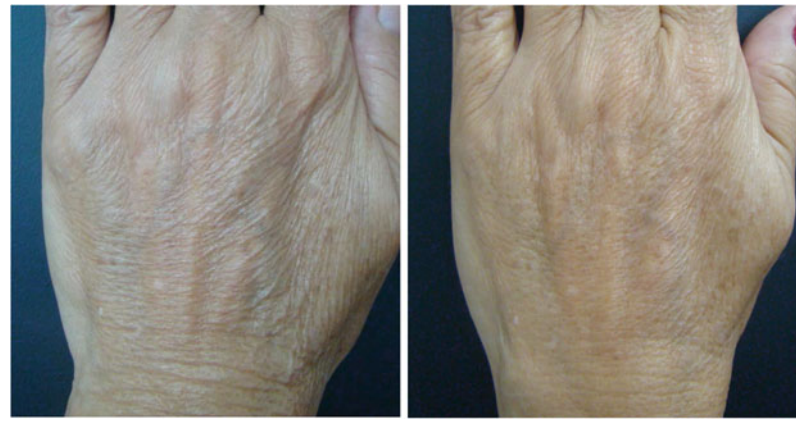


Fig. 4 Before and 3 months after skinbooster application (restylane vital) – one session

Skinbooster

Boosters can be understood as "intensifiers," which are used with the aim of replenishing HA and collagen fibers lost with aging, promoting hydration, and improving skin texture (Fig. 4). Skinboosters are well indicated to complement HA fillers mainly around the eyes, around the lips, neck, "V" shape area, and hands. It improves fine lines, texture, and hydration (Bertucci and Lynde 2015).

The uncrosslinked HA skinbooster does not promote volume or fill sulcus; therefore they are indicated to restore skin's smoothness and hydration. Usually 2–3 sessions are necessary with 2–4 weeks interval. In general, we use needles to inject into superficial dermis through micropuncture's technique, forming micropapules (Fig. 5), which should be submitted to massage just after procedure (see chapter ▶ "Hyaluronic Acid for Skin Booster on the Face" this volume).

The crosslinked HA skinbooster has the same purpose, and it can also promotes some filling in fine lines but the injection should be deeper to avoid lumps formation (Fig. 6).

Calcium Hydroxiapatite (CaHa)

CaHA (Radiesse®) may be considered synthetic and long-lasting/semipermanent dermal filler. The product is supplied in 1.3 ml disposable syringes with Luer-lock fittings – Radiesse® (Bioform Inc, USA). Before injection we add 0.3 ml of

anesthetic solution (lidocaine), mixing with back and forth movements until reaching a homogenous preparation (Fig. 7a, b). The suggested needles for injections are 27-gauge and 25-gauge. The product must be injected in the deep dermis or subdermally, placing the needle with an angle of 30–45°, mainly to treat the hands. When treating the face, cannula (25G) is a better option (Fathi and Cohen 2016).

We preferably indicate CaHa to fill the hands. In this region, the procedure brings a good and natural volume using just one syringe, in only one session (Fig. 8). Less commonly we use CaHa to give support and to volumize the face, as well as to stimulate collagen production on the malar, mandibular, and mentual regions (see chapter ▶ "Calcium Hydroxylapatite to Treat the Face," this volume). Usually two-three sessions are necessary to treat the face. The average lasting result is from 12 to 18 months.

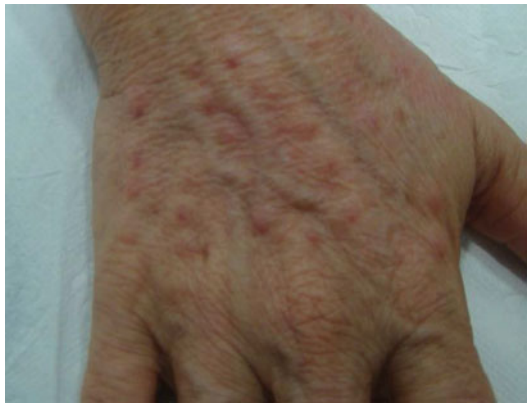


Fig. 5 Superficial dermis application of noncross-linked HA skinbooster through micropuncture technique, forming micropapules

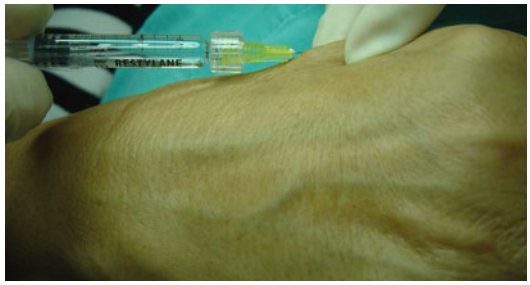


Fig. 6 Deep dermis application of cross-linked HA skinbooster

Poly-L-Lactic Acid (PLLA)

PLLA (Sculptra; Valeant, Bridgewater, N.J.) is a soft-tissue biostimulator, which gradually induces neocollagenesis. It can be injected into subcutaneous tissue and periosteal plane to restructure the volume of the face and to promote skin firmness (Fig. 9). Clinical results are observed 2–3 months after 1–3 sessions and last for 18–24 months (see chapter ▶ "Poly-L-Lactic Acid for Facial Treatment," this volume).

We frequently use HA filler and PLLA on the face, in different sessions, or at the same session in different areas, with the aim of having the immediate lifting and volumizing effect of HA gel filler and to induce neocollagenesis for future laxity and texture improvement through PLLA injection,

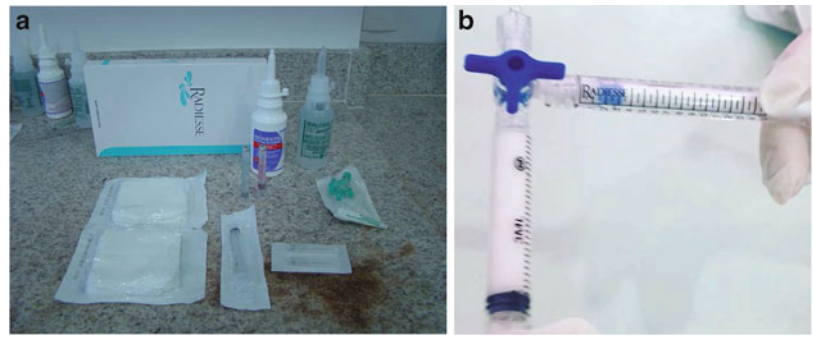


Fig. 7 (**a**) Material to prepare CaHa – Radiesse. (**b**) Homogeneous preparation – CaHa with liodocaine

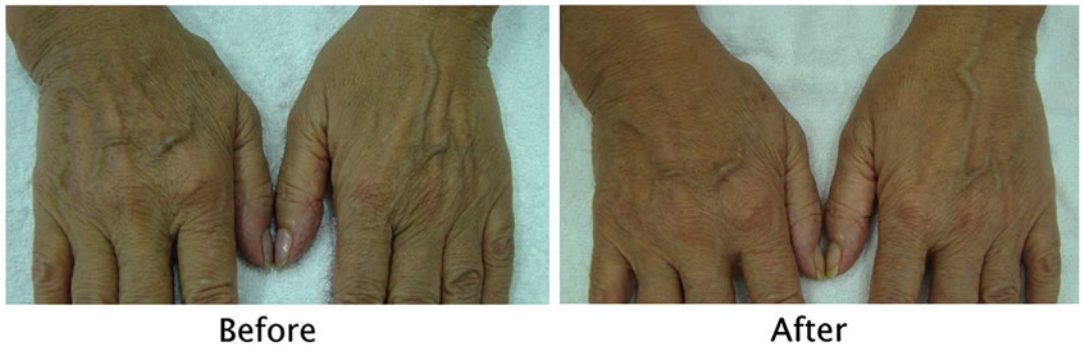


Fig. 8 Before and after 1 session of CaHa application

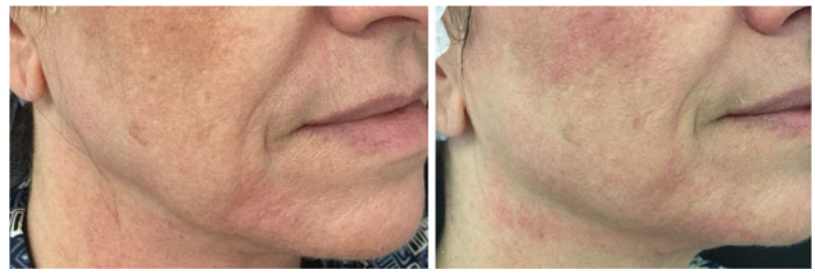


Fig. 9 Before and after PLLA application (2 months after one session): improvement of skin laxity, mandibular contour, and prejowl

Fig. 10 Material to prepare PLLA – Sculptra

respectively. We also have good results when treating body laxity and gynoid lipodystrophy.

Special preparation is required. PLLA has to be hydrated in 8 ml of sterile water for 48 h before procedure. At the moment to be injected, anesthetic solution (lidocaine) can be added to diminish the pain of the procedure (Fig. 10). The volume to be injected is variable according to the area. For subdermis/subcutaneous planes, we use needle 26 Gx ½ or cannula 22G. For supraperiosteal injection, we prefer neddle 24 Gx ¾ (DC and Goldman 2016).

Facial Anatomical Areas

Midface

Volumetric facial rejuvenation has great beneficial effects on nontreated neighboring aesthetic units (Wollina 2015). Midface approach is one of the most important interventions when treating age-related changes of the face (see chapter ▶ "Hyaluronic Acid Filler for the Malar Area," this volume).

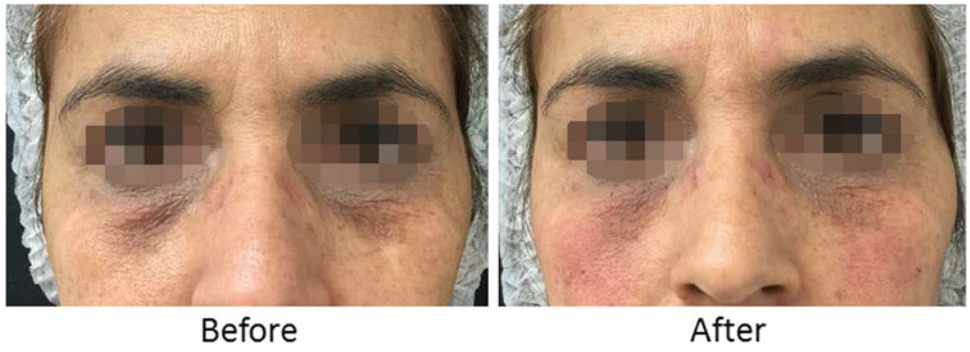
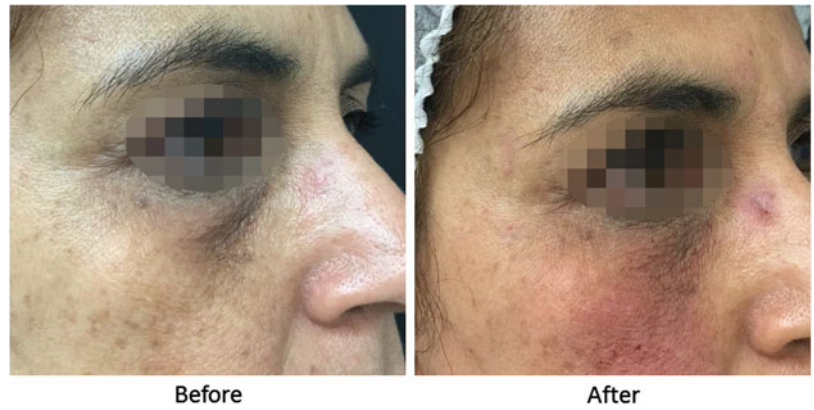


Fig. 11 Before and after – HA filler on the midface (*frontal view*)

Fig. 12 Before and after – HA filler on the midface (*lateral view*)



In our practice, we start with the points of anchorage on the zigomatic area (supraperiosteal injection) using high G* HA products, associating or not HA to refill or volumize malar fat pad. These procedures reduce the sagging aspect, improve prejow, and diminish nasolabial fold and tear trough (Figs. 11, 12).

Cannulas (25G) are better indicated to avoid vascular complications when treating anterior malar region. Cannula is also indicated to inject HA gel to refill or reshape lateral midface.

The amount of product should be evaluated during procedure. Usually 3 points of 0.1 ml of high G prime gel is injected periosteal on the zigomatic area (anchorage points), improving laxity. Different amount of HA gel can be used to refill or reshape the malar area, but large volume are not indicated to avoid excessive volumization.

Temporal Area

To treat the temporal fossa we delimit this region, which is bounded by the curved superior temporal line (anteriorly and superiorly), the frontal process of the zigomatic bone (anterior-inferiorly), and the zygomatic arch (inferiorly) (see chapter ▶ "Hyaluronic Acid Filler for Forehead, Temporal, and Periorbicular Regions," this volume). The HA filler in this region promotes great rejuvenation when patient has a visual depression in this area. It also helps to lift the face and to elevate the eyebrow.

We use needle through a deep injection supraperiosteal using a high G prime HA gel. We do a single puncture, vertically oriented down to bone 1 cm up the temporal fusion line and 1 cm lateral, parallel to the supraorbital rim (one up, one over). Aspiration prior to injection is

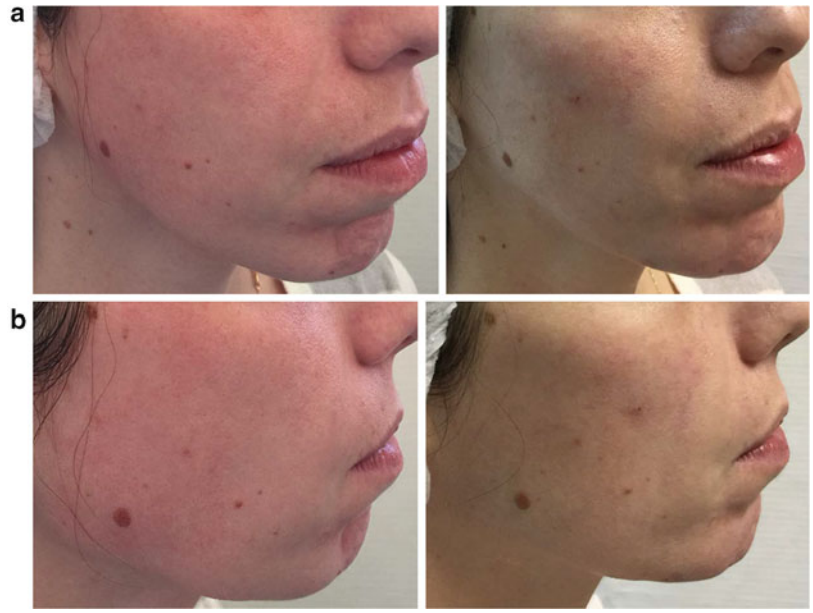


Fig. 13 (**a**) (*Diagonal view*): Before and after HA filler on mental area to project the region forward (**b**) (*Lateral view*): Before and after HA filler on mental area to project the region forward

fundamental, although the absence of blood reflux is not a guarantee of extravascular location of the needle tip (Sykes et al. 2015).

Lower Face

Aging face has sagging aspect with prejowl, loss of mandibular angle, loss of volume in the mentual area, and appearance of labiomental folds (Braz et al. 2015). After correcting the midface, we usually fill the lower face using a high G* HA gel to treat the mandibular line and prejowl with cannula (25G). If necessary, HA gel with less viscoelasticity is used to treat the folds using cannula or needle. Mentual area can also be filled with cannula or needle with high G prime HA gel to improve volume, project mentual region forward (Fig. 13a, b), or sustain the lips (see chapter ► "Hyaluronic Acid for Mental and Mandibular Contour," this volume).

Lips/Perilabial Area

In our experience the reconstruction of the lips and perilabial area can really rejuvenate, but it is extremely important not to exaggerate and to maintain the proportion and harmony of the patient's face. It is quite common to fill the lips to correct some degree of asymmetry, both for young (Fig. 14) and aging patients (Fig. 15a, b). Sometimes, it is only necessary to correct the perilabial area, to sustain the lips, and the commissures, to fill the cutaneous area around the lips (Fig. 16) (see chapter ► "Hyaluronic Acid Filler for the Lips and Perioral Area," this volume).

Cannula (22G, 25G) is better indicated to fill the lips, avoiding vascular complications, but needles (30G) can be used to do the contour, the commissure, the philtrum, and the cupid bow. In this region, it is important to inject HA gel slowly and precisely into the lips to avoid lumps and asymmetry. Fast injections lead to more irregularities, less precise placement, and more immediate swelling. Minimal massage is indicated to dissolve any lump just after injection (Vent et al. 2014; Sarnoff and Gotkin 2012).

Periocular

Filling the tear trough and palpebromalar fold is an important step to complement the rejuvenation (Fig. 17) or to treat dark circles around eyes in young patients (Fig. 18). It is important to

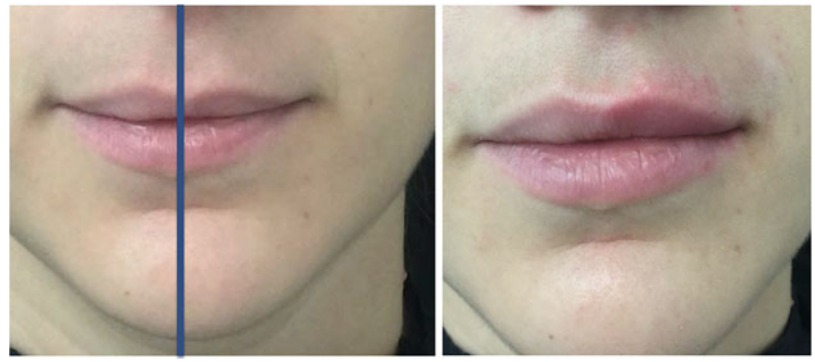


Fig. 14 HA filling in the left side of lips to treat the asymmetry

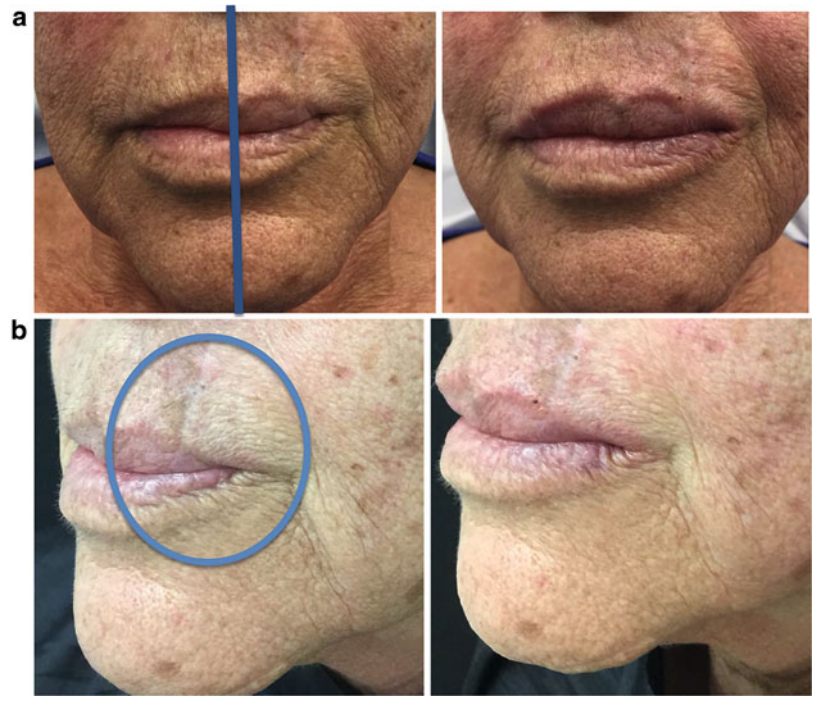


Fig. 15 (**a**) (*Frontal view*): HA filling in the left side of lips and in the scar. (**b**) (*Lateral view*): HA filling in the left side of lips and in the scar

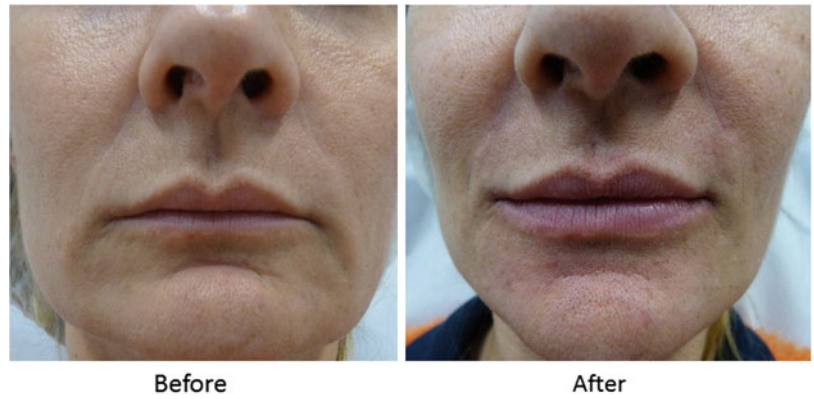


Fig. 16 Before and after HA filler on the lips to improve the proportion between the superior and inferior lips associated with HA on mental area

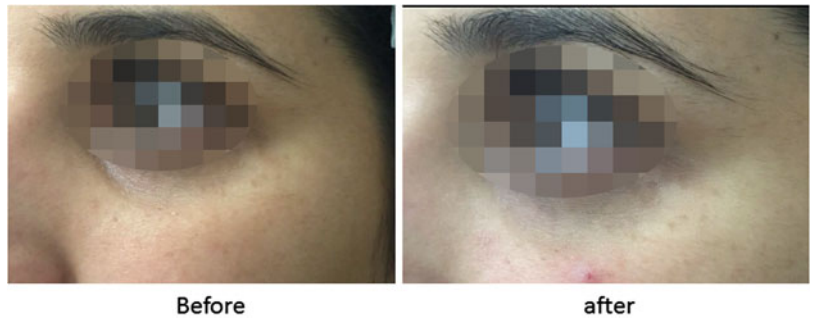


Fig. 17 Before and after: Tear trough filling with low G* HA

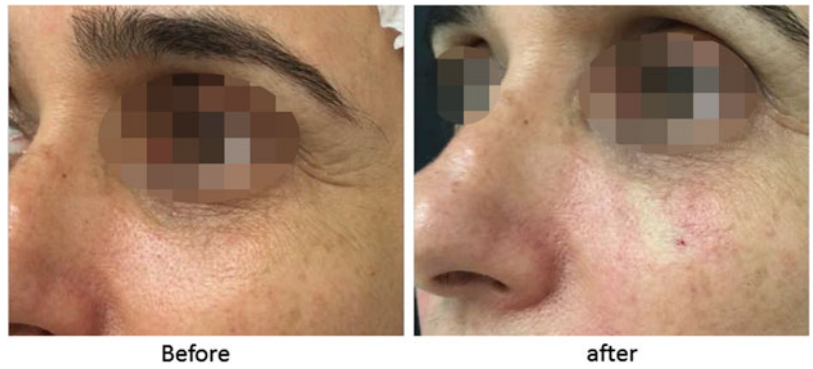


Fig. 18 Before and after: Tear trough filling with low G* HA

reconstruct the midface to sustain the orbital-malar junction before treating the tear trough in aging patients (see chapter ▶ "Hyaluronic Acid Filler for Forehead, Temporal, and Periorbicular Regions," this volume).

For this region, HA gel should be less viscous, with low G*, and should be applied in the submuscular plane (suborbicularis oculi fat – SOOF). Cannula is indicated to avoid vascular complications. We prefer to inject slowly and small amount in drops not to promote a "sausage" aspect (Lee and Yen 2017).

Take Home Messages

- In our clinical practice, hyaluronic acid is the most common filler used to treat the face.
- Dermatologists should know the HA properties before choosing the right product for each area.
- Filler should match the characteristics of the anatomic region.
- Filler procedures should obey an order.
- The amount of filler should be evaluated during procedure and usually it is better to use less than more, especially for periocular and perioral areas.
- Collagen biostimulator can be associated with HA fillers to improve skin laxity and countour.

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Index

M. C. A. Issa, B. Tamura (eds.), *Botulinum Toxins, Fillers and Related Substances*, Clinical Approaches and Procedures in Cosmetic Dermatology 4, https://doi.org/10.1007/978-3-319-16802-9