Botulinum Toxin Treatment of Pain Disorders

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Preface

Very few pharmaceutical agents in medicine have shown efficacy for treatment of so many diverse categories of disorders as botulinum neurotoxins (BoNTs). BoNTs are useful in the treatment of involuntary movements (mostly dystonias), disorders of muscle tone (spasticity), autonomic derangements (sialorrhea and hyperhidrosis), and pain, to name a few. In the latter category, animal studies have provided clear evidence for the analgesic effect of BoNTs through a variety of mechanisms, most notable among them being inhibition of pain mediator release and anti-inflammatory effects.

With the emergence of controlled data on the efficacy of onabotulinum toxin A (and, more recently, other neurotoxins) in different kinds of human pain, it became clear that a textbook with updated clinical and research data in this field is needed, and such a book would be of value to both clinicians and researchers. The analgesic effect of BoNTs has been one of my areas of interest for the past 25 years, and I take credit for some of the earlier human studies in this field. At Yale, where I currently practice, several of our ongoing clinical trials are focused on this issue.

The first chapter of this book briefly discusses the molecular structure, toxin types, mode of action, immunology, and side effects of currently available BoNTs. The pathophysiology of human pain, data from animal studies, and studies on the analgesic effects of BoNTs are presented in the second chapter. The following 14 chapters review the literature (mostly from controlled and blinded studies) in different clinical pain disorders. Case reports and video clips are provided from my experience with various disorders to illustrate injection techniques, treatment results, and the relief experienced and described by the patients. The last chapter (Chap. 17) briefly addresses new developments and future potentials for BoNT use in the management of pain.

I need to acknowledge the help of several people who were instrumental in the development and completion of this book. Fattaneh Tavassoli, M.D., provided invaluable editorial assistance. Damoun Safarpour, M.D., and Tahereh Moussavi, M.D., provided the artwork and drawings. Douglas Forbush from Yale IT section spent many hours with me to prepare and finalize the videotapes. Manika Power from Springer, who first approached me about the writing of this book, has provided

most useful guidance and advice throughout the entire project. Foremost, I am much indebted to the patients who agreed to be videotaped not only for the technical section but also for interviews on the long-term effect of botulinum neurotoxin therapy on their pain.

I hope this book will be of help to the clinicians and researchers alike, ultimately providing better care to our patients suffering from pain.

New Haven, CT, USA
November 23rd, 2014

Bahman Jabbari, M.D. FAAN

Contents

Chapter 1
Molecular Structure, Mode of Action, and Immunology of Botulinum Neurotoxins

Abstract Botulinum neurotoxins (BoNTs) are now widely used in clinical medicine for treatment of a variety of hyperactive movement disorders, autonomic dysfunctions (sialorrhea and hyperhidrosis), spasticity, and chronic migraine. Further indications in other pain disorders are being actively explored based on animal studies and laboratory data indicating an analgesic effect for BoNTs through diverse mechanisms.

This chapter provides an overview of the molecular structure, pharmacological characteristics, mode of action, immunology, and side effects of botulinum neurotoxins.

Keywords Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA (onaA) • AbobotulinumtoxinA (aboA) • IncobotulinumtoxinA (incoA) • RimabotulinumtoxinB (rimaB)

Introduction

The first detailed description of clinical symptoms related to botulinum neurotoxins was published by Justinus Kerner M.D. after an outbreak of food poisoning in the years 1817–1822 resulting from the consumption of rotten sausage in southern Germany (Erbguth 2004). Kerner also predicted the future therapeutic potential of the "poison" based on its muscle weakening effect. In 1895, a Belgian bacteriologist Emile van Ermengem from the University of Ghent isolated the gram-positive rods of botulinum toxin bacilli from smoked ham. He called the responsible agent bacillus botulinum. American investigator Lamanna et al. (1946) at the US Army's Fort Detrick facility developed techniques for the concentration/crystallization of toxins which helped Edward Schantz from the University of Wisconsin to produce the first batch of the BoNT. Allan Scott, an ophthalmologist who had worked during the 1960s and 1970s on the paralyzing effects of BoNTs, published the weakening effect of BoNT-A on extraocular muscles of primates (Scott et al. 1973) and subsequently received permission from the FDA to conduct the first study on the potential of BoNT-A for strabismus in human subjects (1978). The FDA's approval of BoNT-A for the treatment of strabismus in 1989 opened the door for further human research and discoveries.

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Over the past 30 years, a variety of indications for the use of BoNTs emerged based on the muscle weakening effect of the toxin following intramuscular injection. Currently, major clinical indications include treatment of focal and segmental dystonias (blepharospasm, cervical dystonia, focal limb, and task-specific dystonias) as well as spasticity and cosmetic indications (Jankovic et al. 2008), mainly based on the inhibitory effect of the toxin upon acetylcholine release from the presynaptic vesicles. The inhibition of acetylcholine release from cholinergic postganglionic nerve endings, which innervate sweat and salivary glands, provided an effective treatment for sialorrhea and hyperhidrosis (Lakraj et al. 2013a, b).

In the field of pain, early observations in cervical dystonia suggested an analgesic effect for onabotulinumtoxinA (onaA) since the associated neck pain often improved earlier and independent of the improvement of neck posture (Jankovic and Schwartz 1990). Over the past 15 years, animal observations and human studies have illustrated a variety of mechanisms through which BoNTs can influence pain mediators. By the turn of the century, the pain indications of BoNTs had begun to be explored actively in human subjects. These efforts led to the recent approval of onabotulinumtoxinA for the treatment of chronic migraine in Europe and the USA (2010).

Structure and Mode of Action

Clostridium botulinum is a gram-positive anaerobic bacillus that produces the botulinum neurotoxin (BoNT). There are seven serotypes of BoNTs designated as A, B, C, D, E, F, and G. Each serotype has a distinct molecular structure, but there is significant homology between different toxins and between the structure of BoNT and tetanus toxin (Atassi 2004). Only serotypes A and B are currently used in clinical practice. Serotype F has a shorter duration of action and faster recovery, hence presenting a potential for future use in certain clinical conditions.

The neurotoxin complex is composed of BoNT itself (core toxin) with a molecular weight of 150 KD and a nontoxic protein complex that protects the toxin when exposed to deactivating factors (stomach acid, high temperature, and proteases) (Fig. 1.1). The nontoxic protein complex (NAPS) consists of hemagglutinin proteins (HA proteins) and non-HA proteins. The non-hemagglutinin protein fraction includes specific antigenic proteins which are the source of antibody formation against the toxin after BoNT therapy. The core toxin is composed of a heavy chain (HC) of 100 KD and a light chain (LC) of 50 KD linked by a single disulfide bond. The HC provides the toxin's binding and translocation domain and LC its catalytic domain. Within minutes after intramuscular injection, the core toxin dissociates from the protein complex (Pickett 2009) and the molecule is activated (nicked). The type A toxin activation (nicking) takes place through its own protease (Simpson 2013), while for other toxin serotypes activation occurs through tissue proteases. The heavy chain has two distinct terminals

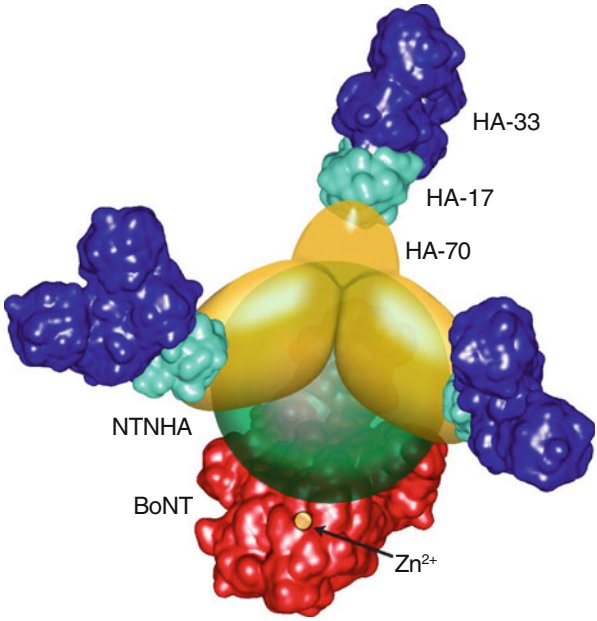

Fig. 1.1 Botulinum neurotoxin complex—core toxin and toxin-associated proteins (Reprinted with permission from *Journal of Biology and Chemistry*, Hasegawa et al. © 2007 The American Society for Biochemistry and Molecular Biology)

Hc and Hn. Through Hc, the heavy chain of the toxin binds the core toxin complex to the specific cell membrane receptor made of ganglioside and possibly other materials (Swaminathan 2011). The membrane receptor sites are different for type A and type B toxins. The receptor is "vesicle membrane protein 2" for type A and "synaptotagmins I and II" for type B toxin. At this stage, the core toxin (HC–LC) enters an endosome (membrane bound compartment) inside which the disulfide bond breaks and HC and LC separate from each other. The HC domain of the toxin opens a channel in the cell membrane and translocates the light chain (LC) into the cytosol (intracellular fluid matrix) (Fig. 1.2). The LC, a protease with a zinc motif, then lands and catalyzes one of the soluble NSF proteins (SNARE) present in the presynaptic space (Rothman 1996). Deactivation of the SNARE complex prevents vesicle fusion and release of neurotransmitters (acetylcholine and others) from the presynaptic vesicles. Different serotypes of the BoNT act upon different types of SNARE proteins. BoNT-A acts upon SNAP25 (synaptosomal-associated protein), which is attached to the cell membrane (Blasi et al. 1993), whereas BoNT-B inhibits the function of synaptobrevin, a SNARE protein that is within the vesicle membrane itself (Fig. 1.2).

Currently, four types of BoNTs are used widely in clinical practice with the following FDA designations and trade names:

OnabotulinumtoxinA (onaA—trade name, Botox—Allergan, Inc., Irvine, CA), abobotulinumtoxinA (aboA—trade name, Dysport—Ipsen Biopharm Ltd., Wrexham, UK), incobotulinumtoxinA (incoA—trade name, Xeomin—Merz Pharmaceuticals LLC, Greensboro, NC), and rimabotulinumtoxinB (rimaB—

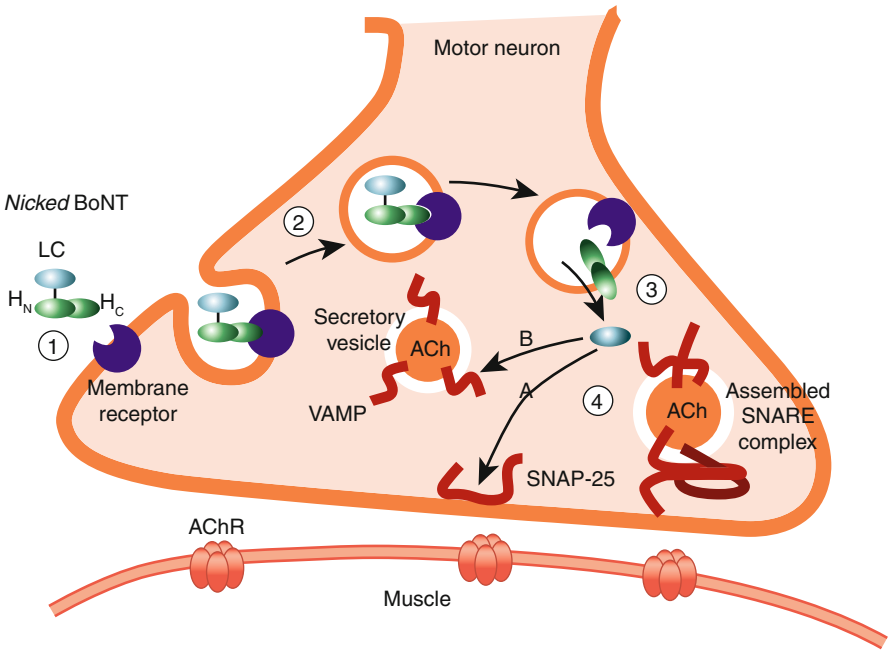

Fig. 1.2 Endocytosis of heavy and light chain (HC and LC) of botulinum neurotoxin types A and B with selective cleaving of LC to SNAP25 and synaptobrevin (From Chen and Dashtipour 2013, with permission from John Wiley and Sons © 2012 Pharmacotherapy Publications, Inc)

trade name, Myobloc in the USA and NeuroBloc in Europe—Solstice Neurosciences, Inc., San Francisco, CA). OnaA is provided in 100 and 200 unit vials, incoA in 50 and 100 unit vials, and aboA in 300 and 500 unit vials. RimaB comes in 2,500 and 5,000 and 10,000 units/vial. Although, as emphasized by the FDA, units of various BoNTs are not interchangeable, in randomized comparator clinical trials (RCTs), approximate equivalence of the toxins is sometimes used (1 onaA unit = 1 incoA = 2.5 aboA = 40–50 units of rimaB).

RimabotulinumtoxinA comes prepared in an already diluted form in the vial. All three type A toxins (ona, abo, and inco) need to be prepared and diluted with preservative-free saline. The commonly used dilutions are in 1–2 cc of 0.9 % saline. AboA is currently approved for 1 cc dilution, although a 2 cc dilution makes it easier to compare with the onaA units (an ongoing multicenter RCT is now assessing the efficacy of 2 cc dilution for aboA). IncoA does not need refrigeration, but all other toxins do. After mixing, gentle shaking is recommended for onaA. With incoA, the manufacturer recommends gentle shaking and multiple inversions of the vial. All manufactures recommend using the prepared solution of the toxin within 4–24 h before injection. In case of onabotulinumtoxinA, however, some studies have shown retained efficacy of prepared solution up to 6 weeks if kept refrigerated at 39.2 F (4 C) and even up to 6 months if frozen (Liu et al. 2012).

Diffusion and Spread of Neurotoxins

In a recent communication, Ramirez-Castaneda et al. (2013) reviewed the diffusion, spread, and migration of the neurotoxins. The information provided in this section is largely from this review article. Overall, the authors emphasize that in most clinical conditions, diffusion of the toxin is limited, a factor that accounts for its relative safety in clinical practice.

A variety of factors could potentially influence the diffusion of the BoNTs into the injected and adjacent muscles. The total dose, number of sites injected, volume of injected solution, type of toxin, state of muscle pathology, and amount of muscle activity after injection are potential contributors to more extensive toxin diffusion. Information implicating any of these factors is still scarce and evolving, however. Although various electrophysiological studies indicate that local injection of the BoNTs causes abnormal electrophysiological changes in distant and even contralateral muscles (Lange et al 1991; Garner et al. 1993), these changes do not seem to have meaningful clinical implications since significant weakness of distant muscles rarely occurs after local injection and contralateral weakness has not been convincingly documented in clinical settings (in therapeutic doses).

Data from animal studies suggest that the extent of diffusion is dose dependent. In one study (Brodic et al. 1994), injection of one unit of onaA into the longissimus dorsi muscle of the rabbit demonstrated marked reduction of diffusion gradient beyond 15–30 mm from the site of injection, whereas injection of five to ten units caused an effect within the entire muscle. The authors used acetylcholine esterase staining to define the extent of BoNT's spread.

The four readily available neurotoxins in the USA and Europe (ona, abo, inco, rima) have different molecular compositions (Table 1.1), and one would think that toxins with smaller molecular weight (for instance, incoA with 150 KD and practically no additional protein) would diffuse more readily and more extensively. A study in mice, however, has suggested that this may not be the case (Carli et al. 2009). Injection of ona-, abo-, and incoA toxins into the tibialis anterior muscle of mice showed very similar diffusion patterns for all three toxins regardless of their molecular weight. Most of the toxins remained close to the site of the injection and did not spread to the adjacent muscles. The investigators used neural cell adhesion molecule (N-CAM) as a measure of BoNT diffusion. N-CAM, which is present in embryonic muscle tissue and disappears in adult muscle, gets activated and reappears after the paralysis induced by intramuscular BoNT injection.

Limited evidence in human trials suggests that larger volumes of the toxin may increase the diffusion of toxin within the injected and adjacent muscles. In one experiment, the effect of toxin volume was studied in ten human volunteers by injecting two different volumes of onaA (2u/0.1 cc and 2units/0.02 cc into the forehead muscles (Hsu et al. 2004). In nine of ten patients, the side of the forehead which received the larger volume (and lower concentration) showed a more extensive diffusion effect. In a randomized, prospective study of 13 patients with spasticity (Fransisco et al. 2002), the investigators found no difference in efficacy between

Table 1.1 Properties of different therapeutic botulinum toxins

Nonproprietary name: BoNT type	OnabotulinumtoxinA	AbobotulinumtoxinA	IncobotulinumtoxinA	RimabotulinumtoxinB
Company	Allergan, Inc., Irvine, CA, USA	Ipsen Biopharm Ltd., Wrexham, UK	Merz Pharmaceuticals GmbH, Frankfurt, Germany	Europe/US WorldMeds, Louisville, KY, USA
Trade name	Botox	Dysport	Xeomin	NeuroBloc/Myobloc
Mechanism of action	Cleaves SNAP25	Cleaves SNAP25	Cleaves SNAP25	Cleaves VAMP
Molecular weight, kD	900	500–900	150	700
Dosage form	Spray-dried powder	Freeze-dried powder	Freeze-dried powder	Sterile solution
Shelf life, month	36	24	36	24
Storage temperature, °C	<8	<8	<25	<8
pH value after reconstitution	7.4	7.4	7.4	5.6
Excipients	500 mg HSA and 0.9 mg NaCl in 100 U vial	125 mg HSA and 2.5 mg lactose in 500 U vial	1,000 mg HSA and 4.7 mg sucrose in 100 U vial	0.5 mg/cm^3 HSA; 0.01 M sodium succinate; 0.1 M NaCl; and SWI in 2,500, 5,000, and 10,000 U vials
Units per vial	50, 100, 200	300, 500	50, 100	2,500; 5,000; 10,000
Recommended volume of reconstitution	Maximum, 10 mL	Maximum, 1 mM	Maximum, 8 mL	0.5 mL; 1 mL; 2 mL
Total protein, ng/vial	rv5	rv5	rv0.6	rv50
Antigenic protein load, ng/vial	rv0.8	Unknown	rv0.6	rv10.7
Biologic activity	100 MU-A/vial	500 MU-I/vial	100 MU-M/vial	1.0/2.5/10.0 kMU-E/vial
Specific activity, U/ng	20	40	167	75–125

From Ramirez-Castaneda et al. (2013) with permission from John Wiley and sons

BoNT botulinum toxin, *SNAP* soluble N-ethylmaleimide-sensitive fusion protein (NSF) attachment protein, *VAMP* vesicle-associated membrane protein, *HSA* human serum albumin, *NaCl* sodium chloride, *SWI* sterile water for injection, *MU-A* mouse units in the Allergan mouse lethality assay, *MU-I* mouse units in the Ipsen mouse lethality assay, *MU-M* mouse units in the Merz mouse lethality assay, *kMU-E* kilo-mouse unit equivalents

50 and 100 units/cc dilutions of onaA preparations. In another double-blind, placebo-controlled comparator study (Kranz et al. 2011), comparing the effect of onaA and rimaB volume in 18 patients with hyperhidrosis, the increased volume of the toxin preparation increased the anhidrotic field for both toxins. In equal volumes, the anhidrotic area was larger for rimaB, and comparable increases in volume also produced larger anhidrotic area for rimaB. The conversion ratio used in this study, however, was 1 onaA = 75 rimaB. Since the toxins are not truly interchangeable and different ratios have been used in the literature for onaA and rimaB (from 1:40 to 1:75), one could argue that the higher dose of B toxin used in this study might have influenced the results. Obviously, larger controlled data are needed in order to discern the impact of volume and toxin type on diffusion.

The effect of a single intramuscular injection versus multiple injections as a factor influencing BoNT's diffusion has not been thoroughly studied. Ramirez-Castaneda et al. (2013) state that multiple point injections along the length of the affected muscle contain the biological effect of the toxin within the targeted muscle better than a single injection.

Immunology of BoNTs

Several studies have shown that the nontoxic protein complex of the BoNT structure is its main source of antigenicity. Bryant et al. (2013) defined in detail the molecular structure and protein ratios within the nontoxic protein complex for BoNT: NBP (124 kDa), HC (90 kDa), LC (53 kDa), NAP-53 (50 kDa), NAP-33 (36 kDa), NAP-22 (24 kDa), and NAP-17 (17 kDa). Recently, indirect ELISA analysis of BoNT/A and its associated proteins have shown that the BoNT/A complex antigen has a 32-fold higher titer than BoNT/A antigen itself, and most of this antigenicity is related to the NAP-33 protein. In fact, activity of NAP-33 is equal to that of all the rest of the proteins in the NAP complex combined (Bryant et al. 2013). Atassi (2004) emphasized that the immune response to the botulinum neurotoxins is under genetic control, and probably major histocompatibility of the host controls the appearance of blocking antibodies and emergence of immunoresistance. Each epitope of the toxin seems to be under a separate genetic control.

Development of neutralizing antibodies in human subjects after treatment with BoNTs has been the focus of several recent investigations. Most of these studies have been conducted with onabotulinumtoxinA in patients with cervical dystonia (CD). Introduction of the new formulation of onaA which contains only 5 ng of complex proteins (rather than the 25 ng present in the old formulation) in 1997 has significantly reduced the development of neutralizing antibodies (nABs) and emergence of clinical unresponsiveness. This issue is particularly important when large doses of toxin may be needed such as for patients with severe spasticity or for some patients with advanced CD.

Jankovic et al. (2003) found no neutralizing antibodies (nABs) in any of the 119 patients who had received new onaA compared to 9.5 % in 130 patients who had used

the old formulation of toxin for the treatment of cervical dystonia. In another study (Charles et al. 2012), neutralizing antibodies to onaA were found in 32 of 191 patients (17 %) with CD who had received at least one to two injections of the old formulation (containing 25 ng of NAPs). These patients were enrolled first in an open-label and then in a double-blind, placebo-controlled study using the new toxin over a period of 2 years. Of this cohort, a total of 114 patients had antibody assessment both at the entry and at the exit time, and 2 of 114 (1.5 %) developed new neutralizing antibodies. These two patients, however, remained responsive to BoNT treatment during the course of the study. Brin et al. (2008) prospectively studied (open label) the development of nABs in 326 toxin-naïve patients who had an average of 9 injection sessions over a mean period of 2.5 years. Using the new formulation of onaA, the dose per session ranged from 148 to 213 mouse assay units. Four of the 326 subjects (1.2 %) developed neutralizing antibodies against the toxin, and 3 of these 4 (approximately 1 % of 326) became eventually unresponsive to treatment. Unresponsiveness was documented also by frontalis antibody test (FTAT). These data indicate that with the new formulation of onaA (used after 1997), only a small number of treated patients develop neutralizing antibodies and a very small number manifest clinical unresponsiveness. The relation of unresponsiveness to nAB titer and evolution of unresponsiveness over time is complex and deserves further investigation.

Regarding rimaB, an earlier communication based on data from a small number of patients with cervical dystonia (CD) had claimed that the high rates of nAB titers (in mouse assay) correspond to unresponsiveness after nine rimaB injection cycles in 44 % of the studied patients (Dressler and Elopara 2006). This data has been contested by the makers of type B toxin based on the small number ($n=9$) of patients in that report (Chinnapongse et al. 2012). These authors, in a review paper, scrutinized the data of four large-scale RCTs conducted on rimaB efficacy in CD (1,134 patients) in which nAB levels were provided. They found neutralizing antibodies in a large number of patients, but there was no difference between nAB+ and nBA– patients with regard to efficacy and continued responsiveness. The review concluded that the presence of neutralizing antibodies has no meaningful clinical significance in patients treated with rimaB. A close look at the data of this review discloses several interesting points. First, 30–42 % of the patients treated with rimaB eventually developed neutralizing antibodies at the completion of the study, a figure which is significantly higher than the 1.2 % reported for the current formulation of onaA (Brin et al. 2008). Second, contrary to most of the literature on onaA which emphasizes absence or low rate of unresponsiveness in patients who are nAB-, this review (Chinnapongse et al. 2012) found that >20 % of the rimaB-treated nAB- patients lost responsiveness. These issues suggest the existence of major immunological differences between the two toxins, the importance of which deserves further exploration.

Chen and Dashtipour (2013) summarized the relative immunogenicity of different commonly used BoNTs based on the total NAPs of each toxin:

> The total protein content (150 kD toxin including NABs)/100 units for ABO, INCO, ONA, and RIMA are 0.87, 0.44, 5, and 2.2 ng, respectively. Assuming that the dose equivalency ratio of INCO:ONA is 1:1, the total protein load with INCO (0.44 ng/100 units) would be at least 10-fold less than that of ONA (5 ng/100 units). If the dose equivalency ratio of

ABO: ONA were 2:1–3:1, then the total protein load with ABO would be 2–3-folds less than that of ONA for each clinical dose. Thus, theoretically, INCO would carry a lower risk of immunogenicity, followed by ABO, ONA, and RIMA.

There is evidence that some cross-reactivity exists between type A and type B toxins. The first toxin could prime the immune response to stimulate the production of neutralizing antibodies to the second serotype faster than in a naïve individual devoid of antitoxin antibodies (Aoki 2001).

Overall, the aforementioned data indicate the low impact of immunogenicity in the current practice with all four FDA-approved BoNTs. For the three type A toxins, development of neutralizing antibodies is low as is conversion from responder to nonresponder (1 % for onaA, Brin et al. 2008). This figure is most likely lower for incoA that practically has no immunogenic proteins. Regarding type B toxin, a sizeable number of patients develop neutralizing antibodies. The true level of nonresponsiveness for this toxin still needs to be established. Development of nonresponsiveness in three of nAB+ patients after conversion to the nAB- state (Brin et al. 2008) demonstrates the complexity of immunogenicity in relation to clinical response. As emphasized by Atassi (2004), many factors influence the development of neutralizing antibodies and the clinical immune response; among these factors are genetic makeup of the individual and prior exposures to toxins with similar homology. Since immunogenicity increases with the dose of the toxin and frequency of administration, it is prudent to avoid excessive dosing and short intervals of application (especially with larger doses).

Most botulinum toxin clinics in the USA use a brief clinical test for defining unresponsiveness rather than measuring neutralizing antibodies through the cumbersome mouse immune-assay test. The most widely used clinical test is the frontalis antibody test (FTAT) in which the BoNT is injected at two points into the frontalis muscle on one side (two 10 units for onaA). The injected frontalis muscle is then compared with the uninjected frontalis muscle on the other side in 10–14 days. If the BoNT is still effective, the frontalis muscle on the injected side flattens and contracts less compared to the contralateral uninjected side. Alternatively, one could use the response of the abductor digiti minimi (ADM) for this purpose. Injection of 20 units of onaA or other toxins in a comparable dose often weakens the muscle sufficiently for comparison with the other side. The ADM injections should be performed under EMG guidance. Finally, the response to toxin can be also measured electrophysiologically by recording the change in amplitude of compound muscle action potential (CMAP) on EMG; a substantial reduction would be noted if the toxin is active. In complex patients, I often use both FTAT and ADM tests in the same session.

Side Effects of BoNTs

Most side effects of BoNTs are mild and transient. Pain at the site of injection, small local bleeding, and local infection may occur. The latter is rare and, in my experience, is seen mainly in immunocompromised patients. It has been suggested that

Table 1.2 Adverse events occurring in at least 5 % of subjects in either group

	Open period	Double-blind period adverse event	
Adverse event	OnabotA ($n=214$)	OnabotA ($n=88$)	Placebo ($n=82$)
Upper respiratory tract infection	18 (8.4 %)	11 (12.5 %)	6 (7.3 %)
Neck pain	20 (9.3 %)	7 (8.0 %)	6 (7.3 %)
Back pain	9 (4.2 %)	6 (6.8 %)	3 (3.7 %)
Dysphagia	18 (8.4 %)	6 (6.8 %)	3 (3.7 %)
Rhinitis	8 (3.7 %)	6 (6.8 %)	0*
Headache	20 (9.3 %)	5 (5.7 %)	6 (7.3 %)
Hypertonia	6 (2.8 %)	5 (5.7 %)	0
Increased cough	11 (5.1 %)	5 (5.7 %)	3 (3.7 %)
Pain	14 (6.5 %)	3 (3.4 %)	7 (8.5 %)
Flu syndrome	10 (4.7 %)	3 (3.4 %)	6 (7.3 %)
Muscle weakness	18 (8.4 %)	1 (1.1 %)	0
Sinus infection	1 (0.5 %)	1 (1.1 %)	6 (7.3 %)

*P **G** 0.05, comparison of onabotulinumtoxinA (OnabotA) and placebo groups in period 2 for the overall population
Data presented as n (%)
From (Charles et al. 2012) printed with permission from Wolters Kluwer Health

local injection of rimaB may cause more pain (compared to A toxins) due to the acidity of the solution, but convincing studies are lacking. The pH of rimaB solution is 5.6 compared to 7.4 for the BoNT-A types. Mild transient dysphagia after injection of the neck muscles occurs in 15–20 % of patients with cervical dystonia but is often ignored by the patient and is not expressed until asked. More severe dysphagia may develop especially in patients with small neck when larger doses are used and especially with bilateral injections into anterior neck muscles. The incidence of such dysphagias varies widely among injectors and is uncommon with experienced injectors. Careful identification of sternocleidomastoid muscles (if needed with EMG) is very helpful to avoid this issue. If the SCM muscle cannot be clearly identified in sitting up position, supine position with head rotation and elevation is often helpful. Chronic cough and upper respiratory tract infection are among patients' complaints after BoNT treatment.

In a recent prospective study using the new formulation of onaA in 170 CD patients (Charles et al. 2012), the incidence of none of the aforementioned side effects was significantly different from the placebo in the blinded arm of the study (Table 1.2). In the open arm of the study, however, a high incidence for a variety of side effects was reported.

Acute hypersensitivity reaction to BoNTs is extremely rare, but erythematous skin reactions infrequently occur; the reaction usually clears within a few weeks. Theoretically, presence of human albumin in the toxin carries a small risk of slow virus disease. No such case has ever been documented following BoNT therapy, however. Patients with neuromuscular disorders are at risk of deterioration and increased severity of symptoms. BoNT treatment is not recommended in patients with myasthenia gravis or patients taking drugs which are known

to significantly impair neuromuscular transmission (e.g., aminoglycosides, neuromuscular blockers). BoNT therapy is also not recommended in pregnancy due to paucity of information. One animal study has shown that concurrent use of 4-aminopyridine, the drug which improves symptoms of multiple sclerosis, can reduce the effect of botulinum toxin A (Adler et al. 1996), but human data is not available. Absolute contraindications include hypersensitivity to BoNTs and presence of local infection.

Based on reports to the FDA, all botulinum toxins used in the USA carry a black box warning in their brochure indicating potential occurrence of rare and serious side effects including severe dysphagia, respiratory failure, and even death. This information needs to be shared and discussed with the patient before initiating treatment with any type of the BoNTs.

In my 25 years of experience with BoNT therapy in a sizeable number of patients, aside from few cases of transient moderate dysphasia that developed in my early years of practice, I have never witnessed a serious side effect. My practice and experience with BoNTs has been gratifying as 90 % of the patients report significant satisfaction that I document at each visit with global patient impression of change (GPIC). Despite this positive experience, which is shared by many others, one should not lose sight of the fact that botulinum neurotoxin is one of the most potent toxins in nature. Therefore, clinicians who are engaged in this practice should always ascertain that important issues pertaining to dose, dilution, intended type of toxin, and proper marking of the syringes are precise and according to the guidelines. A list of side effects of the toxin from manufacturer's FDA-approved brochure should be provided to the patient and ample time given for asking questions before initiating therapy. Approval from patient's insurance is needed prior to treatment so the patient does not receive an unexpected and expensive invoice. If a side effect develops, evaluating the patient by the treating physician within 24 h, even in nonurgent cases, is highly recommended in order to alleviate patient's anxiety and offer a plan of management. Serious side effects should be referred to emergency department and dealt with aggressively.

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Chapter 2
Analgesic Effects of Botulinum Neurotoxins: Data from Animal Studies

Abstract The availability of novel technologies has been crucial in the discovery and description of new pain receptors and modulators expanding our knowledge of the pathophysiology of pain. Data generated from animal models indicate that botulinum toxins can modify and subdue a variety of mechanisms that generate or maintain pain.

The first part of this chapter provides a brief overview of the pathophysiology of pain in light of some of the new developments. The second part provides a focused review of the literature on how botulinum neurotoxins improve and modify animals' response to pain as well as the therapeutic influence of these toxins on pain receptors, channels, and mediators.

Keywords Botulinum toxin • Botulinum neurotoxin • Botulinum toxin A • Botulinum toxin B • Calcitonin gene-related peptide • Substance P • Sodium channels • TRPV1 receptor • ATP receptor • DRG • Rexed layer • Peripheral sensitization • Central sensitization

Introduction

Over the past 15 years, there has been an outpour of data in the field of pain medicine based on investigations on animals and asymptomatic volunteers. These data have identified new, important pain receptors, promoted our knowledge on pain mediators/modulators, and refined our understanding of pain pathophysiology. Moreover, data emerging from animal studies and human volunteer literature have provided crucial information on how botulinum toxins can influence the pain mechanisms and alleviate pain by altering the function of nerve endings, dorsal root ganglia, and spinal neurons.

In this chapter, the pathophysiology of pain as it pertains to the function of peripheral nerves, DRG, and spinal neurons is discussed first, followed by presentation of the data on botulinum toxin's effect on pain pathophysiology from the literature on animal studies.

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Pathophysiology of Pain at Peripheral and Spinal Levels

Pain-inducing agents (heat, cold, chemical, mechanical) stimulate non-corpuscular, nociceptive free nerve endings and generate action potentials via activity of sodium channels. The generated action potentials, reflecting the nociceptive information, are conveyed to specialized peripheral and central neurons by unmyelinated C and small, myelinated Aδ fibers. C fibers are either peptidergic, using substance P (SP) and calcitonin gene-related peptide as transmitter, or non-peptidergic. The peptidergic fibers end in Rexed lamina I and outer part of Rexed lamina II of the superficial layers of the spinal dorsal horn, whereas non-peptidergic fibers terminate in inner lamina II, Fig. 2.1 (Priestley et al. 2002).

In chronic pain, nerve endings exude excess of pain mediators such as glutamate, substance P (SP), and calcitonin gene-related peptides (CGRP) and cause local inflammation. Local inflammation leads to accumulation of inflammatory agents such as bradykinin, cytokines, and prostaglandins. This cascade of events initiates peripheral sensitization of nociceptive nerve endings and the peripheral neuron of dorsal root ganglia (DRG) ultimately lowering the sensitivity threshold of peripheral nerves and neurons to future noxious stimuli. Peripheral sensitization gradually increases the excitability of central sensory neurons and leads to central sensitiza-

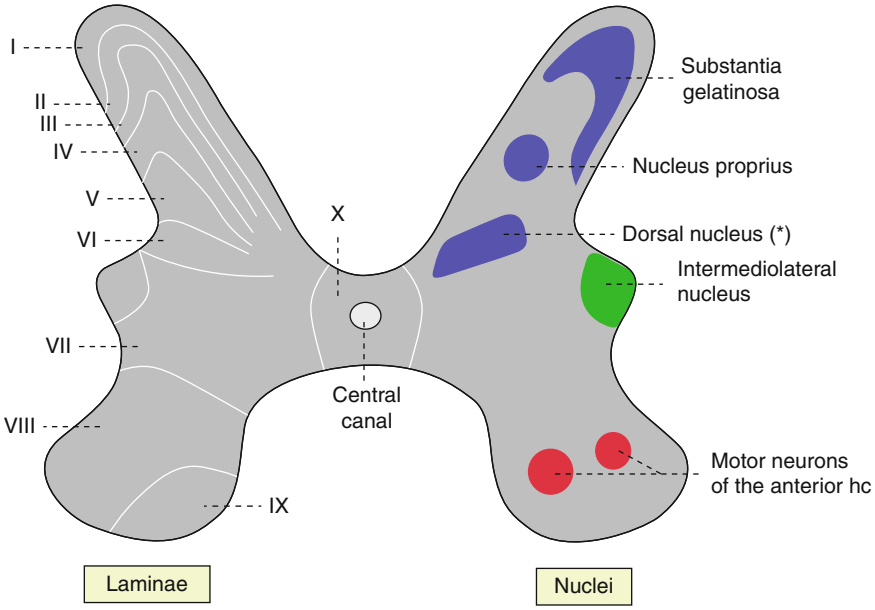

Fig. 2.1 Anatomical location of Rexed lamina and substantia gelatinosa (By User:Polarlys, traced from the German version and translated by Interiot (own work/selbst erstellt) [GFDL (http://www.gnu.org/copyleft/fdl.html), CC-BY-SA-3.0 (http://creativecommons.org/licenses/by-sa/3.0/), or CC-BY-2.5 (http://creativecommons.org/licenses/by/2.5)], via Wikimedia Commons)

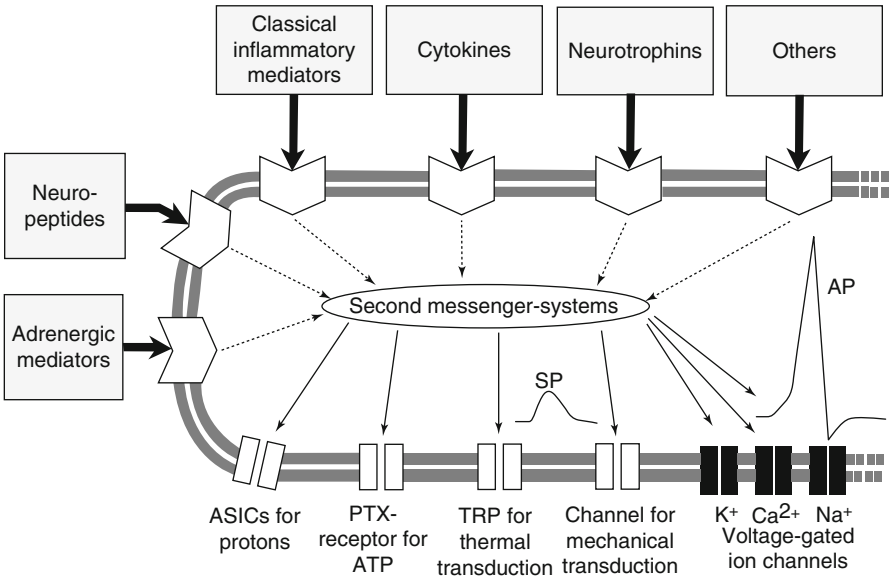

Fig. 2.2 Ion channels and receptors of peripheral nociceptor involved in transmission and modulation of pain signals (From Schaible (2011). Reprinted from Arthritis Research Therapy with permission from John Wiley and Sons, Inc.)

tion of the nociceptive sensory system. The first central nociceptive sensory neuron is located in the two most superficial layers of the posterior horn of spinal gray matter, Rexed areas I and II (Fig. 2.1). Rexed area II or substantia gelatinosa, so named for its paucity of myelinated fibers, modulates pain stimuli in addition to receiving pain signals from the periphery (Melzack and Wall 1965). The excitability of neurons in the superficial Rexed layers is determined by a variety of factors, among them activity of Na+ channels, local excitatory neurotransmitters such as glutamate, and a variety of excitatory and inhibitory receptors, some of them newly discovered (see Fig. 2.2) (Schaible 2007).

Na+ Channels

Na+ channels, the main generators of action potential, are present diffusely at every peripheral sensory level (receptor, axons, and DRG) and, hence, play a pivotal role in modulating neuropathic and nociceptive pain. A variety of Na+ channels have been described with Na 1.7, Na 1.8, and Na 1.9 most relevant to pain. The Na+ channels are also classified as tetrodotoxin sensitive (TTX-S) with fast activation/inactivation and tetrodotoxin resistant (TTX-R) with slow activation/inactivation. Na 1.7 is a TTX-S channel, whereas Na 1.8 and 1.9 are TTX-R type of sodium channel. Sodium channel mutations are associated with some of the most severe forms of human pain such as seen in erythromelalgia (Fischer and Waxman 2010).

Transient Receptor Potential (TRP) Channels

A major step in understanding the molecular physiology of pain was the discovery of transient receptor potential channels (TRPs) (Caterina et al. 1997). TRPs are expressed specifically in sensory nociceptive neurons. These receptors, made of vanilloid protein (TRPV), are cation-gated calcium channels. Produced by DRG neurons, these protein channels are then transferred by axonal transport peripherally to the nerve endings and centrally to the dorsal horn neurons (Rexed area II, substantia gelatinosa). There are several types of TRP channels designated as TRP1, TRP2, TRP3, TRP4, and TRP8, but TRPV1 plays the dominant role in neuropathic and nociceptive pain. The influx of cations, especially calcium, opens the TRPV1 channel leading to hyperexcitability of the peripheral and central neurons enhancing pain. Heat of over 42°, chemicals such as capsaicin, and low pH of <5.9 directly stimulate and open the TRPV1 channel. A large number of other agents also activate TRPV1 indirectly including inflammatory mediators such as prostaglandin E2, proteases, and nerve growth factor (NGF), with this indirect activation most likely carried through a second messenger (Schaible et al. 2011). The function of TRPV1 channel seems to be different for peripheral (DRG) and central (dorsal horn in SG) neurons. While TRPV1 in DRG neurons receives pain signals from the periphery and conducts the information to SG neurons, activation of TRPV1 in SG neurons releases glutamate locally and promotes central hyperexcitability (Kumamoto et al. 2014).

There is evidence that TRPV1 plays a significant role in production of inflammation-induced hyperalgesia. Inflammatory hyperalgesia is absent in TRPV1 knockout mouse (Davis et al. 2000), and TRPV1 expression is markedly enhanced in neuropathic pain and inflammatory hyperalgesia. Intrathecal injection of TRPV1 antagonist AS1928370 alleviates the neuropathic pain in mouse models (Watabiki et al. 2011). Another TPRV channel, TPRA1, is also upregulated in DRG and dorsal horn neurons by peripheral inflammation and is implicated in cold hyperalgesia caused by inflammation and nerve injury (Obata et al. 2005).

Role of ATP and Purinergic Channels

Purinergic receptors are ligand-gated Ca++ channels that respond to ATP stimulation. The recently discovered P2x3, ATP-responsive receptor channel is specifically expressed in sensory nociceptive neurons. These channels have both chemical and mechanical sensitivity. ATP applied to a blister base causes pain in human and induces pain behavior in animals (Snider and Mc Mahon 1998).

Nerve Growth Factor (NGF)

Nerve growth factor is a major factor in nociception (Snider and Mc Mahon 1998). The development of peripheral nerve endings, C fibers, DRG neurons, and nociceptive sensory spinal neurons is highly dependent on NGF. Specific NGF receptor,

tyrosine receptor kinase A (TrkA) is expressed highly in nociceptive neurons. NGF reduces the threshold for heat-generated pain by increasing activity of TRPV1 channels; long-term exposure to NGF increases production of SP and CGRP as well as expression of Na+, P2x3, and TRPV1 channels (Stein et al. 2009). NGF antagonists exert analgesic effects (Lane et al. 2010).

The Role of Spinal Cord GABAergic Neurons in Pain

The excitability of neurons in the superficial laminae of the spinal cord is controlled by GABAergic nerve endings that work upon GABA-A (ionotropic) and GABA-B (metabotropic) receptors attached to the surface of these dorsal horn neurons (Bardoni et al. 2013). The inhibitory input to these neurons comes from inhibitory spinal cord interneurons and from the descending inhibitory fibers. In the state of central sensitization and chronic pain, failure of this GABA system could enhance pain, while enhancing GABA activity could alleviate pain by reducing hyperexcitability of spinal neurons.

Inflammation

As stated earlier in this chapter, with exposure to chemicals and adverse (high or low) temperature and following nerve injury, pain mediators accumulate locally. This accumulation leads to vasodilation and development of inflammation in the damaged tissue. Inflammation, which is associated with lower tissue pH, starts a cascade of events that enhance pain through influencing the function of pain receptors via a variety of mechanisms. Inflammatory cells activate local production of NGF that enhances pain (see above). In acute inflammation, macrophages can directly invade DRG neurons and disturb its function (MacMahon et al. 2006). Lowering of tissue pH by inflammation triggers activity of a specific form of sodium channel (acid-sensing sodium channels) causing hyperexcitability of the neural tissue. Additionally, low pH activates ATP production, which in turn opens the purinergic channels and also activates TRPV1 channels leading to further excitation. The resultant effects are mechanical hyperalgesia and also thermal hyperalgesia due to stimulation of dermal nociceptors.

The Effects of Botulinum Neurotoxins on Pain Receptors, Pain Modulators, Neuroinflammation, DRG, and Spinal Neurons

Over the past 20 years, a large volume of literature has been published on the efficacy of botulinum toxins in modulating pain predominantly based on animal studies. The purpose of this section is not to provide an exhaustive review of the subject, but rather a brief summary of how different nociceptive

mechanisms are modified by BoNT resulting in alleviation of human pain. There is currently a significant interest in this subject as reflected in several recent reviews (Aoki 2005; Jabbari 2008; Aoki and Francis 2011; Jabbari and Machado 2011; Guo et al. 2013).

One of the major findings in this line of research was the discovery of significant anti-inflammatory effect for onabotulinumtoxinA (onaA) and subsequent alleviation of inflammatory pain (Cui et al. 2004). A formalin pain model was used as a test model to evaluate the effect of onaA on inflammatory pain and on local accumulation of pain mediators. The authors noted that subcutaneous injection of formalin in rat's paw produces a biphasic pain response. The first peak of pain develops within 0–5 min of injection and is caused by the direct chemical effect of formalin upon C fibers. The second peak, which occurs within 15–60 min of injection, is a more intense pain induced by tissue inflammation (Wheeler-Aceto et al. 1990). At this stage, a variety of inflammatory agents (neuropeptides, kinins) and pain mediators (glutamate, substance P, CGRP) accumulate at the site of injection. The second peak, unlike the first, is not associated with significant activity of C fibers and is believed to mainly represent central sensitization. Cui et al. (2004) pretreated rats with onaA for 2–12 days in order to observe the time frame of onaA's effect in formalin-induced pain. Four groups of rats received 3.5, 7, 15, and 30 u/kg of onaA diluted in 0.9 % saline into the hind paw subcutaneously. The control rats received the same volume of 0.9 % saline injected into the hind paw. The rats were then injected with 50 ml of 5 % formalin in the same paw. The immediate lifting/licking (check spelling) behavior was recorded 0–5 min postinjection and, again, at 15–30 min postinjection corresponding to the first and second peaks of formalin-induced pain. The rats were euthanized at the completion of the experiment, and the level of glutamate was measured in the injected tissue.

Pretreatment with onaA (5, 10, 15, 30 units/kg) 5 days before formalin injection significantly reduced the level of formalin-induced pain in a dose-dependent manner (Fig. 2.3). The second peak of pain (inflammatory peak) was most affected by the onaA pretreatment. The largest dose (30 units/kg) affected both peaks but rendered the animals too lethargic to make a reliable assessment. There was also a significant reduction in paw edema in onaA-treated animals. A significant reduction in tissue glutamate was noted in the BoNT-A-treated animals compared to animals who received saline only; the mean tissue glutamate level was 280.2 ng/ml for those injected with saline versus a mean of 208.4 ng/ml for those treated with 15 u/kg of toxin, $P < 0.05$. These results clearly demonstrated that onabotulinumtoxinA reduces local accumulation of the pain mediator glutamate associated with formalin-induced tissue inflammation and that onaA has both an anti-inflammatory and analgesic effect.

Recently, Marino et al. (2014) reported similar findings in formalin model of pain with intraplantar injection of BoNT-B. In mice, unilateral injection of BoNT-B (one unit) reduced the following reactions: (1) intraplantar formalin-evoked flinching, (2) intraplantar capsaicin-evoked plasma extravasation in the hind paw, (3) intraplantar formalin-evoked dorsal horn substance P (SP) release, (4) intraplantar

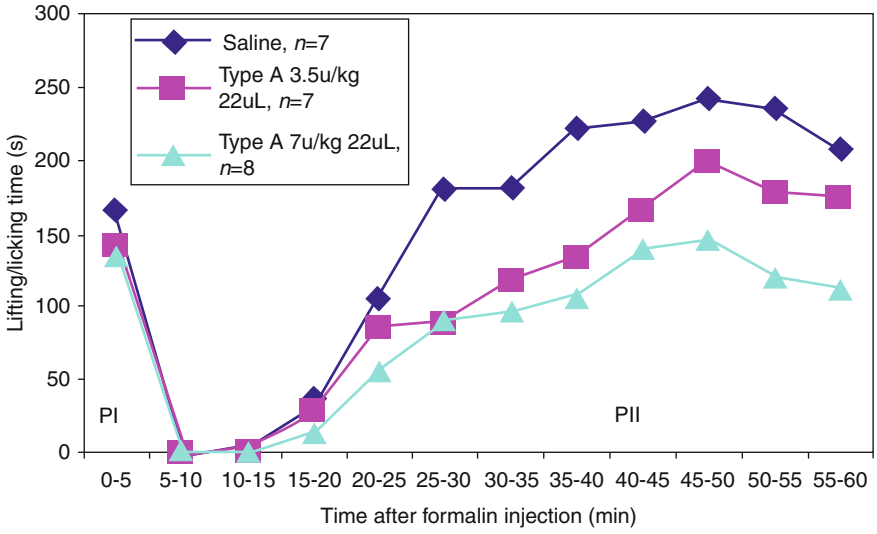

Fig. 2.3 Pretreatment with BoNT-A reduces formalin injection-induced paw pain in rats in a dose-dependent manner (Cui et al. (2004). The figure has been reproduced with permission from the International Association for the Study of Pain® (IASP))

formalin-evoked dorsal horn neuronal activation (c-Fos), (5) ipsilateral dorsal root ganglion (DRG) vesicle-associated membrane protein (VAMP), and (6) ipsilateral SP release otherwise evoked bilaterally by intrathecal capsaicin administration.

BoNT-A inhibits a family of G proteins including Rho guanosine triphosphatase which is essential for activation of interleukin-1, an important pro-inflammatory cytokine (Namazi 2008). Intraprostatic injection of BoNT-A inhibits cyclooxygenase-2 expression and suppresses capsaicin-induced prostatitis in animal models (Chuang et al. 2008).

In the sciatic nerve ligation-induced mechanical allodynia animal (both rat and mice) models, Marinelli et al. (2010) have demonstrated marked reduction of mechanical and thermal allodynia within 24 h after a single intraplantar or intrathecal (IT) injection of onabotulinumtoxinA. Intraplantar injection of 15 pg/kg in rat and 75 pg/kg in mice and IT injection of 75 pg/kg in rat improved allodynia; the results lasted for 80, 25, and 35 days, respectively.

Several investigators have shown that injection of BoNT-A into tissue inhibits release of SP and CGRP. Welch et al. (2000) studied the effect of botulinum toxins A, B, C, and F on SP release from DRG neurons that had been exposed to elevated extracellular potassium to enhance their calcium-dependent SP release. All toxins partially inhibited SP release, but this effect was most notable for BoNT-A (IC50 = 0.05) and least notable for BoNT-B (IC50 = 30). BoNT-A cleaves the SNAP25 within 2 h but inhibits SP release at hour 4. In another experiment (Lucioni et al. 2008), researchers showed that acute bladder injury after exposure to HCL resulted in marked release of SP and CGRP into the injured bladder tissue (1,235

and 1,655 pg/g, respectively, compared to 183 and 449 pg/g for controls, respectively; $P<0.001$). After injection of BoNT-A, the levels of SP and CGRP were reduced to 870 and 1,033 pg/g, respectively ($P<0.05$ and <0.01). Similar results with BoNT-A administration were observed on elevated SP and CGRP after chronic exposure to CYP.

In trigeminal neurons, SNAP25 is co-localized with CGRP, and the release of CGRP was blocked by application of BoNT-A. The calcium-dependent release of SP was also blocked by A, C, and D toxins, but not by BoNT-B (Meng et al. 2007). BoNTs failed to block capsaicin-induced elevation of CGRP from trigeminal neurons. In a later experiment, the same group of investigators administered an A/E chimera BoNT that specifically targets the sensory cells. Application of this novel form of BoNT subdued capsaicin activation of TRPV1 channel as well as the rise of CGRP (Meng et al. 2009).

Drinovac et al. (2014) studied the role of GABAergic system on the analgesic effect of BoNT-A in formalin model of inflammatory pain and in mechanical allodynia. These authors demonstrated that intrathecal (1 ug) or intraperitoneal injection of 0.6–0.8 mg of bicuculline (GABA-A antagonist) prevents antinociceptive effect of onabotulinumtoxinA in rats. Rats were given five to seven units of onabotulinumtoxinA to prevent/reduce the inflammatory pain induced by injection of formalin. The authors took these results as evidence for central effect of botulinum toxin A after peripheral injection. Furthermore, application of bicuculline (2 mg/kg) also prevented enhanced c-Fos expression induced by BoNT-A injection, providing more evidence in support of a central effect for botulinum neurotoxins. In a separate experiment, the authors demonstrated that intraperitoneal injection of bicuculline ($P<0.05$) reversed the reduction of mechanical pain induced by BoNT-A. Since injection of bicuculline into cisterna magna did not reverse the effect of botulinum toxin A, the authors concluded that the effect of botulinum toxin is at the spinal and not at the supraspinal level and partly mediated by inhibition of GABA effect centrally.

Botulinum toxins also alter and modify the function of other proteins and channels that are important in the initiation and maintenance of neuropathic and nociceptive pain. Femtomolar concentrations of BoNT type A inhibit sodium channels in rat's central and peripheral neurons (Shin et al. 2012). Overactivity of sodium channels plays a pivotal role in erythromelalgia, a human model of chronic neurogenic pain (Fischer and Waxman 2010). Injection of BoNT type A into rat jaw muscles decreased the discharge of muscle spindles, a major sensory input which can enhance central sensitization in chronic pain (Filippi et al. 1993). BoNT type A impairs sympathetic transmission (Rand and Whaler 1965) and consequently can interfere with maintenance of pain via decreasing sympathetic hyperactivity.

There is now some evidence that at least part of the analgesic effects of peripherally injected BoNTs is due to their direct influence upon the spinal neurons (Bach-Rojecky and Lackovic 2009; Mazzocchio and Caleo 2014). This is probably achieved through retrograde transfer and transcytosis.

Effects on Nerve Regeneration and Earlier Recovery

Mice suffering from neuropathic pain and allodynia secondary to sciatic nerve ligation demonstrate quicker recovery of walking pattern after intraplantar, intrathecal, or intraperitoneal injection of 15 pg/kg of onabotulinumtoxinA (Marinelli et al. 2010). The authors found structural modifications in the injured nerve that led them to conclude that treatment with onaA facilitates the recovery. The structural modification included expression of cell division cycle 2 and growth-associated protein 43 (GAP-43) regeneration-associated proteins. Expression of S100β protein and glial fibrillary acidic protein (GFAP) by immunofluorescence was used to illustrate the changes in the sciatic nerve.

Conclusion

Animal studies have demonstrated that botulinum toxins can disrupt pain mechanisms and alleviate pain-induced behavior in animals by influencing the function of pain receptors and pain mediators. The wide range of actions used by these toxins to exert their effect is encouraging and suggests a significant potential for botulinum neurotoxins to alleviate human pain.

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Chapter 3
Neuropathic Pain (NP)

Abstract Neuropathic pain (NP) is a common form of human pain, often poorly responsive to analgesic medications. This chapter discusses the pathophysiology and conventional treatment of common categories of neuropathic pain and reviews the literature on botulinum neurotoxin (BoNT) efficacy in neuropathic pain. The level of efficacy for BoNT treatment in each category is defined according to the published guidelines of the American Academy of Neurology. The data on type A toxin (mostly onabotulinumtoxinA, onaA) indicates efficacy in postherpetic neuralgia and probable efficacy in post-traumatic neuralgia, and painful diabetic neuropathy. Retrospective studies and anecdotal observations suggest efficacy in residual limb pain of amputees, complex regional pain syndrome, and chemotherapy-induced allodynia. Controlled studies are necessary to assess the efficacy of BoNTs in these conditions. Much remains to be learned about the most effective dosage and technique of injection, optimum dilutions, and differences among BoNTs in the treatment of neuropathic pain.

Keywords Botulinum toxin • Botulinum neurotoxin • Neuropathic pain • Pain • Allodynia • Postherpetic neuralgia • Post-traumatic neuralgia • Diabetic neuropathy • Complex regional pain syndrome • Phantom pain • Residual pain

Introduction

Neuropathic pain (NP) is defined as a pain caused by lesion or disease of the somatosensory system (Treede 2012). The site of disturbance or damage can be peripheral (peripheral nerve, plexus, or root) or central (spinal cord, brain stem, or thalamus). Typically, the pain has a burning, jabbing, and searing quality. Skin areas of allodynia (touch perceived as pain), hyperalgesia (enhanced pain after exposure to painful stimuli), and hyperesthesia or dysesthesia (enhanced or altered sensations to touch) are common.

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The pathophysiology of neuropathic pain is yet to be fully elucidated; the peripheral neuropathic pain (PNP) is currently believed to result from damage to peripheral nervous system with irritation of nerve endings and accumulation of nociceptive transmitters and modulators (substance P, glutamate, bradykinin, calcitonin gene-related peptide, and others). Accumulation of these agents produces local inflammation. Together, these two phenomena lower the sensory threshold of peripheral nerve endings to nociceptive stimuli (peripheral sensitization). Peripheral sensitization increases the number of nociceptive volleys into the spinal cord and leads to sensitization of sensory spinal cord neurons (central sensitization). The interplay between peripheral and central sensitization contributes to pain chronicity (Aoki and Francis 2011).

A number of mechanisms are now considered contributors to neuropathic pain (Table 3.1). Modifying these mechanisms is the basis of treatment strategies for NP treatment.

OnabotulinumtoxinA (onaA) has shown the potential to influence neuropathic pain in animals through a number of mechanisms: blocking the release of pain mediators from peripheral terminals and from dorsal root ganglia (Meng et al. 2007; Lucioni et al. 2008), decreasing local inflammation around nerve terminals (Cui et al. 2004), inhibiting sodium channels in peripheral and centred nervous system (Shin et al. 2012) discharge of muscle spindles (Filippi et al. 1993), and decreasing sympathetic transmission (Rand and Whaler 1965). The muscle spindle discharge can enhance central sensitization; increased sympathetic activity can maintain pain. The details of BoNTs' effects (particularly onaA) on experimental pain of animals and healthy human subjects are presented in Chap. 2.

Five examples of peripheral neuropathic pain (PNP) for which prospective and controlled data are available on BoNT efficacy are presented in this chapter. These include postherpetic neuralgia, post-traumatic neuralgia, painful diabetic neuropathy, complex regional pain syndrome, residual limb pain, and phantom pain. Case reports and videotapes are provided from the author's experience.

In this chapter and throughout the book, the level of efficacy for BoNTs is defined according to the guidelines of the therapeutics and assessment subcommittee of the American Academy of Neurology (AAN). These guidelines require two class I studies for level A evidence (effective or not effective). For level B evidence (probably effective/ineffective), one class I or two class II studies are required. Presence of only one class II study denotes level C (possibly effective/ineffective) evidence. Level U means efficacy is undetermined. Appendices 3.1 and 3.2 provide a summary of the AAN guidelines with descriptions of the study class and level of evidence (French and Gronseth 2008; Gronseth and French 2008). The Yale Medical Library's search system was used for literature search which encompasses a number of search programs including PubMed and Ovid.

Among the seven BoNT serotypes (A, B, C, D, E, F, and G), only types A and B have clinical utility. Three type A toxins (onabotulinumtoxinA, onaA; incobotulinumtoxinA, incoA; abobotulinumtoxinA, aboA) and one type B toxin (rimabotulinumtoxinB, rimaB) are approved by the FDA for use in the USA (Fig. 3.1). Table 3.2 illustrates the generic and trade names of these toxins, their manufacturer's name, and number of units/vial.

Table 3.1 Pathophysiological mechanisms of neuropathic pain

Level of the nervous system	Pathophysiological mechanisms
PNS	
Peripheral nerve	Release of pain-related mediators (BK, PG, TNFα, ILs, His, ATP, and potassium ions)
	Upregulation of TRP proteins in uninjured C fibers
	Dysregulation of the synthesis or the functioning of voltage-gated sodium channels
	Dysregulation of the synthesis or the functioning of potassium channels
Dorsal root ganglion	Increased activity in dorsal root ganglions
	Dorsal root ganglion infiltration by activated macrophages
	Increased synthesis of proinflammatory cytokines in dorsal root ganglions
CNS	
Spinal cord neurons	Functional reorganization (neuroplasticity) of dorsal horn nociceptive
Neurons	
	Increased release of glutamate and substance P
	Increased expression of Nav1.3 in dorsal horn second-order neurons
	Increased activity in voltage-gated calcium channels
	Selective apoptotic loss of GABA-releasing interneurons
	Reduction of KCC2 in lamina I neuron
	Intracellular changes induced by the activation of NMDA receptors or other receptors (i.e., glutamate metabotropic receptors) by excitatory amino acids released by primary afferents
	Microglial activation
Brain stem (descending pain-controlling systems)	
Loss of function in descending inhibitory opioidergic, serotonergic, and noradrenergic pathways	
Changes in the modulatory control of nociceptive pathways	
Brain	Functional reorganization (neuroplasticity) of thalamic and cortical (prefrontal and somatosensory) nociceptive neurons

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ATP adenosine-5′-triphosphate, *BK* bradykinin, *CNS* central nervous system, *GABA* γ-aminobutyric acid, *His* histamine, *IL* interleukin, *KCC2* potassium chloride co-transporter 2, *Nav1.3* voltage-gated sodium channel 1.3, *NMDA* N-methyl-D-aspartate, *NP* neuropathic pain, *PG* prostaglandin, *PNS* peripheral nervous system, *TNFα* tumor necrosis factor-α, *TRP* transient potential receptor

Technical Points

All toxins except incoA require refrigeration. With the exception of rimaA (which comes as an already prepared solution), all toxins need to be prepared with preservative-free saline. A dilution of 1–4 cc can be used in clinical practice. To prepare the solution, saline is drawn with a 20 or 21 gauge needle into a 2 or 4 cc syringe and then introduced into the vial. The vial is then gently shaken for a few seconds. In the case

Fig. 3.1 FDA-approved botulinum neurotoxins (From Chen and Dashtipour 2013 © 2013 Wiley Publications, reprinted with permission from Wiley)

Table 3.2 FDA-approved botulinum neurotoxins

Name given by FDA	Trade name	Manufacturer	Vial (units)
OnabotulinumtoxinA (onaA)	Botox	Allergan Inc.	100, 200
IncobotulinumtoxinA (incoA)	Xeomin	Merz Pharm	50, 100
AbobotulinumtoxinA (aboA)	Dysport	Ipsen Pharm	300, 500
RimabotulinumtoxinB (rimaB)	Myobloc (US)	US WorldMeds	2,500, 5,000, 10,000
	Neurobloc (Europe)		

of incoA, it is recommended to invert the vial two to three times. The solution is then drawn with the same needle into a 1, 2, or 4 cc syringe. For injection, a 27.5 or 30 gauge needle is used. Depending on the depth of injection, the length of the needle may vary from 0.5 to 1.5 in.; for subcutaneous injection, a 0.5-in.-long needle suffices. Per manufacturer's recommendations, the prepared toxin should be used within 4–6 h.

Botulinum neurotoxins (BoNTs) are now used widely in clinical medicine for a variety of indications such as treatment of dystonias, spasticity, and migraine. In pain medicine, only chronic migraine is an approved FDA indication. All other areas are currently considered off label, although for several of them, the literature strongly suggests efficacy. The four aforementioned neurotoxins are generally considered safe in the recommended doses. Rare and serious side effects, however, have been reported. It is hence prudent before administering any BoNT, to obtain a signed acknowledgement from the patient about having reviewed the list of potential side effects.

Postherpetic Neuralgia

Herpes zoster results from reactivation of varicella-zoster (VZ) virus usually in individuals who previously have had chicken pox and developed cell-mediated immunity after the infection. The reactivation takes place in cranial nerves or dorsal root ganglia with spread of the virus to sensory nerves and corresponding dermatome. Diabetic and immunocompromised patients are more prone to zoster infection.

The extent of pathology varies widely from patient to patient. There is often substantial reduction of epidermal nerve fibers (small unmyelinated fibers) and loss of subepidermal plexus. Reinnervation is slow and skin biopsy, even 10 years after the infection, shows incomplete innervation (Oaklander 2001). In one study, magnetic resonance imaging showed signal changes in the spinal cord and brain stem (56 %), and the cerebrospinal fluid demonstrated inflammatory cells in 61 % of the patients affected by acute zoster infection (Haanpaa et al. 1998). Varicella-zoster vaccination reduces development of PHN by 66.5 % between ages 60 and 80 (Oxman et al. 2005). Antiviral therapy reduces the risk of developing PHN (Wood et al. 1996). Concurrent steroid therapy does not reduce the risk of PHN but alleviates the initial acute pain (Whitley et al. 1996).

Pain associated with zoster infection may manifest before the rash (presymptomatic neuralgia), during the rash, or even later after the rash has cleared up. The typical PHN usually persists beyond 3 months after the zoster infection. The incidence of postherpetic neuralgia increases with age: 5 % for individuals younger than 60, 10 % between 60 and 69, and 20 % for age 80 or older (Yawn et al. 2007). Older age, severity of the initial acute pain (Thyregod et al. 2007), and presence of larger fiber neuropathy (A-beta fibers with loss of vibration) increase the risk of PHN (Baron et al. 1997).

Treatment

PHN is one of the most severe forms of human pain. Affected individuals cope with poor quality of life and are often disabled by severe bouts of pain (Oster et al. 2005). A variety of oral and topical medications are currently in use for treatment of PHN. Gabapentin and pregabalin, due to their safer side effect profiles, are often used as first drugs sometimes in combination with tricyclic agents. More severe

forms of pain will require adding opioid agents, corticosteroids, or application of anesthetic patches. Cohen (2013) reviewed the subject of PHN and its treatment in a recent communication (Table 3.3). Most medications depicted in Table 3.3 are also used for treatment of other forms of neuropathic pain. Unfortunately, a large number of patients with PHN fail to respond to currently available medications.

BoNT Studies in Postherpetic Neuralgia

Two double-blind studies have investigated the efficacy of botulinum toxin A in postherpetic neuralgia.

The first study by Xiao et al. (2010) assessed pain relief by visual analog scale (VAS) at 1, 7, and 90 days after subcutaneous injection of BoNT-A in 60 patients with PHN. Quality of life was measured by improvement in sleep hours. Patients were randomized and assigned blindly into three groups: BoNT-A, lidocaine, and placebo (20 in each group). The baseline level of pain and sleep disturbance was comparable between the three groups. The location of herpetic skin lesions was orofacial ($n=11$), cervical and upper extremity ($n=14$), thoracic ($n=18$), and lumbar and lower limbs ($n=17$).

A Chinese botulinum toxin A prepared by Lanzhou Institute was used for this study. The injecting solution was prepared by mixing 100 units of this toxin with 2 cc of preservative-free saline (5 units/cc). Injections were subcutaneous, grid-like, 1 cm apart, and into the region of tactile allodynia. Patients in the BoNT group had significantly better pain relief compared to the two groups on lidocaine and saline ($P<0.01$). BoNT analgesic response began at days 3–5, peaked at 1 week, and continued for 3 months. The improvement of sleep from BoNT was also superior to the lidocaine and placebo groups ($P<0.05$). Patients in the BoNT group also used significantly less opioids (22 % vs. 52 % and 66 %). Side effects consisted only of pain at the time of injection.

Apalla et al. (2013) conducted a prospective, double-blind, parallel study comparing the effect of BoNT-A (onaA) with placebo in 30 adult subjects with PHN. In the BoNT-A group, the toxin was diluted with 4 cc of normal saline and injected subcutaneously via a 30 gauge needle in a "chessboard manner." The dose per injection site was 5 units. A total of 100 units was used. The severity of pain was assessed by VAS (0–10) at baseline and then daily for the first 2 weeks, every 2 weeks until the 12th week, and every 4 weeks until the 24th week. The primary outcome was 50 % or more reduction in VAS score measured at week 4 compared to baseline. The secondary outcome was improvement of quality of sleep evaluated by a 5-point questionnaire (very bad to very good) recorded at the same time frames.

Maintenance of improved VAS scores beyond the first 4 weeks was also considered a secondary outcome. Significant VAS improvement was reported at 4 weeks and also over subsequent weeks (for the toxin group, $P<0.001$). Patients in BoNT also demonstrated significant improvement in quality of sleep and reduction of sleep scores along the same timelines.

Table 3.3 Medications commonly used for treatment of acute pain associated with herpes zoster

Medication	Dose	Dose adjustment	Maximum dose	Side effects
Opioid and nonopioid analgesics				
Oxycodone	5 mg every 4 h as needed	Increase by 5 mg four times daily every 2 days as tolerated	None specified, but should not exceed 120 mg daily except in consultation with a pain specialist	Drowsiness, dizziness, constipation, nausea, vomiting
Tramadol	50 mg once or twice daily	Increase by 50–100 mg daily in divided doses every 2 days as tolerated	400 mg daily; 300 mg daily if patient is >75 years of age	Drowsiness, dizziness, constipation, nausea, vomiting
Glucocorticoids				
Prednisone	60 mg daily for 7 days, then decrease to 30 mg daily for 7 days, then decrease to 15 mg daily for 7 days	None	60 mg daily	Gastrointestinal distress, nausea, vomiting, mood changes, edema, glucose intolerance, increased blood pressure
Anticonvulsants				
Gabapentin	300 mg at bedtime or 100–300 mg three times daily	Increase by 100–300 mg three times daily every 2 days as tolerated	3,600 mg daily	Drowsiness, dizziness, ataxia, peripheral edema
Pregabalin	75 mg at bedtime or 75 mg twice daily	Increase by 75 mg twice daily every 3 days as tolerated	600 mg daily	Drowsiness, dizziness, ataxia, peripheral edema
Tricyclic antidepressants				
Nortriptyline	25 mg at bedtime	Increase by 25 mg daily every 2–3 days as tolerated	150 mg daily	Drowsiness, dry mouth, blurred vision, weight gain, urinary retention
Topical therapy				
Lidocaine patch (5 %)	One patch, applied to intact skin only, for up to 12 h per day	None	One patch for up to 12 h per day	Local irritation; if systemic, absorption can cause drowsiness, dizziness

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This table provides examples and is not meant to be comprehensive (Modified from Dworkin et al. by permission of Oxford University Press)

The controlled and blinded study of Ranoux et al. (2008) which demonstrated efficacy of onaA in neuropathic pain (rated class I by AAN subcommittee) also included four patients with PHN. The specifics of these four patients, however, were not provided. This study is discussed in detail in the section on post-traumatic neuralgia.

Case Report 3-1

A 62-year-old female was referred to the Yale Botulinum Toxin Treatment Clinic for evaluation of severe right retroauricular pain. Patient specified the onset of pain to 2 years ago. At the onset, the pain involved both inside and behind the right ear. A course of antibiotics was not helpful. Few weeks later, with the appearance of typical skin lesions, zoster infection was diagnosed and treated with acyclovir. The skin lesions gradually improved, but the right retroauricular pain continued and grew in intensity. Some of the bouts of pain ended in severe headaches. The pain was described as jabbing and stabbing resulting in loss of sleep and marked apprehension in anticipation of the next bout. A variety of analgesic medications including gabapentin, pregabalin, and oxycodone were not helpful. The pain was often scored as 10 of 10 on visual analog scale and described as unbearable.

On examination, there was discoloration along with scars of zoster infection behind the right ear. A total of 60 units of onaA toxin was injected in a grid-like pattern behind the left ear subcutaneously at 20 points (3 units/point) using a 30 gauge needle (Video 3.1). The dilution was 100 units per 2 cc. Patient reported a sharp drop in pain frequency and intensity (VAS down from 10 to 3) 5 days after the injections. The pain then disappeared at week 2 postinjection and gradually reappeared at 2.5 months. Over the next 2 years, patient received similar treatments every 3 months. Each treatment resulted in significant reduction in pain. The last injection lasted 6 months with the returning pain reported as subtle (1 in VAS). Patient described no side effects. In an interview 2 years after treatment, the patient was very pleased with the outcome (Video 3.2).

Comment

The author has treated six patients with PHN with subcutaneous injections of onaA. The dose ranged from 60 to 200 units based on the extent of the involved skin. The treatment was very effective in five patients (i.e., case 1). In one patient with extensive zoster infection of the chest, two treatments of onaA with similar doses failed to alleviate the pain.

Based on the above two class I studies, BoNT-A treatment possesses level A efficacy (effective) for treatment of PHN. The role of other BoNTs needs to be investigated. Failure of some patients with PHN to respond to onaA may be related to extensive pathology possibly extending to CNS.

Post-traumatic Neuralgia

Pathophysiology

Peripheral trauma triggers a cascade of events which involve nociceptor receptor sites, peripheral nerve endings, dorsal root ganglia (DRG), spinal cord neurons, and central sensory neurons. Damaged nerve endings often accumulate pain mediators (glutamate, substance P), and new sprouts demonstrate increased density of sodium channels (Katz and Seltzer 2009) which increases peripheral nociceptive firing and generates ectopic discharges. New sprouts show increased sensitivity to cytokines, prostaglandin, and catecholamines. This peripheral sensitization increases the volume of nociceptive volleys which enter the dorsal root ganglia and spinal cord.

Histologic changes which develop after peripheral trauma in DRG and spinal cord indicate increased neural excitation. In DRG, there is overgrowth of sympathetic nerves and abnormal linkage of A and C fibers (McLachlan et al. 1993). In the spinal cord, dark cells appear in dorsal horns which presumably represent dying inhibitory neurons of glycinergic and GABAergic types (Garrison et al. 1991; Todd and Sullivan 1990). Demise of inhibitory neurons leads to enhanced excitation of central neurons. It has also been shown that after peripheral injury, many large alpha/beta afferents (usually ending in Rexed area III) grow and penetrate more superficial levels (Rexed laminae II and I of dorsal horn) and gain access to low-threshold pain afferents (Yaksh and Caplan 1997).

Treatment

Medical treatment consists mostly of administration of analgesic agents listed in Table 3.3. Additional treatments for persistent PTN include nerve block by single injection or infusion, transcutaneous electrical nerve stimulation (TENS), peripheral nerve stimulation (PNS), or spinal cord (dorsal horn) stimulation which leads to increased GABA release.

BoNT Treatment of Post-traumatic Neuralgia

Ranoux et al. (2008) screened 61 consecutive patients of whom 29 met the criteria of neuropathic pain and eligibility for BoNT treatment. These patients were enrolled in a randomized, prospective, double-blind study which investigated the efficacy of onaA in neuropathic pain. Nineteen patients were women. Twenty-five patients had post-traumatic neuralgia and four patients had postherpetic neuralgia. In the post-traumatic group, 18 patients had surgical trauma and 7 nonsurgical trauma to single nerves. The primary outcome was self-reported level of pain in the past 24 h on an 11-point scale of brief pain inventory (0–10) from a diary. Pain level was assessed

at baseline and at 4 and 12 weeks. Secondary outcomes included degrees of brush allodynia, mechanical sensation and pain threshold, thermal sensations and pain threshold, as well as neuropathic pain symptom inventory; all were assessed at aforementioned timepoints.

A neurologist not involved in the study administered the BoNT-A (onaA) solution intradermally at points 1.5 cm apart. The dilution was 100 units in 4 cc of preservative-free saline. The mean number of injections was 20 + 8.3. The dose ranged from 20 to 190 units.

The pain intensity started to decrease from week 2 ($p = 0.02$) in favor of onaA and remained improved until week 14 ($p = 0.03$). The average pain intensity assessed at each visit improved in the toxin group (0.007). Allodynia to brush also improved significantly, and pain threshold to cold was decreased in the BoNT group. Injections were painful, but no patient reported any side effects.

Patient 3-2

A 56-year-old woman was referred to the Yale Movement Disorder Clinic for evaluation of severe post-traumatic neuralgia, to be considered for BoNT treatment. Twelve years earlier, her car was forcefully rear ended after she braked hard in order to avoid hitting a car in front of her. The accident heavily bruised her right ankle and the lateral aspect of her right foot. The foot and ankle continued to ache, and an area of intense allodynia developed over the lateral malleolus extending up to the lower leg. A large number of medications failed to improve either the pain or the local allodynia. The most recent medications included Neurontin, pregabalin, tramadol, capsaicin ointment, and voltaren gel. In patient's words, "the physical, emotional, and psychological impact of my chronic pain defies description. Every night, I have to take Tylenol, Advil, Ambien and apply ankle soak, topical pain cream, and heat wrap in order to be able to sleep. With all this, many nights I am unable to sleep due to pain. Even the pressure of sheets would cause the pain to flare up. Sleeping on my side is impossible."

On examination, muscle strength was normal, but foot movements were slow and intensified the ankle pain. A large area of allodynia and hyperesthesia was present including the lateral aspect of the right foot extending 10 cm above the right ankle. The most intense allodynic region was over the lateral malleolus extending to 5 cm above (Fig. 3.2).

OnabotulinumtoxinA (onaA) was injected subcutaneously into the dorsolateral aspect of the right foot (50 units, 20 sites, grid pattern) including the region of lateral malleolus. Patient reported 30 % reduction of pain (7 on VAS) after the first injection and 90 % decrease after the second injection (VAS 1–2) 6 months later.

Patient noted, "the effect after the second injection was astounding. I stopped taking gabapentin and using pain wrap at night. I can now wear high-heel shoes and clothes that rub against my ankle. I am looking forward to wearing boots for the first time in 12 years!" (videotapes).

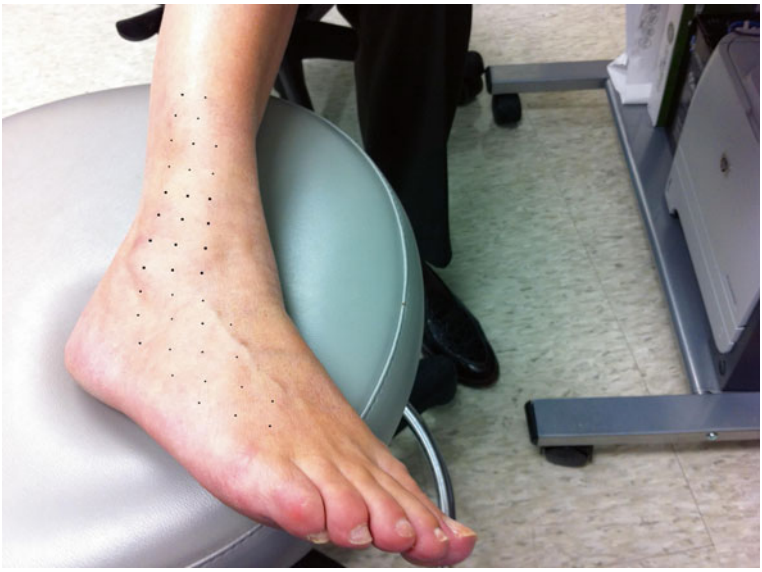

Fig. 3.2 Region of right foot allodynia in patient 3-2. The most intense area is over and around the lateral malleolus shown by *larger* and *darker dots*

An examination 3 months after the second injection showed marked reduction of allodynia which was now much less intense and limited to a small area above the lateral malleolus.

Clinical Comment

The level of evidence for efficacy of onaA for PTN is B (probably effective) based on one class I study. The case presented above is an example of PTN with severe allodynia showing a remarkable response to onaA after two treatments. A more significant response after the second or third injection with onaA has also been reported for chronic migraine (see Chap. 4). A number of patients with PTN may later develop complex regional pain syndrome (CRPS), a condition which is more difficult to treat. An important question is whether or not early treatment of PTN with onaA may prevent the development of CRPS in some patients.

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) often evolves from post-traumatic neuralgia. For reasons which are yet poorly understood, a traumatized limb affected by somatic pain gradually develops additional autonomic and trophic dysfunction. In

CRPS I, the causative factor does not damage or disrupt the nerve, whereas in CRPS II, the peripheral nerve is damaged. Causalgia, first described in detail by Weir Mitchell among soldiers with traumatized limbs during the American Civil War, belongs to the CRPS II category. Pain in CRPS has a burning and jabbing quality, and the involved limb has areas of allodynia and hyperesthesia. Autonomic dysfunctions can be in the form of coldness or warmth of the limb with hyper- or hypohydrosis. Trophic changes include skin atrophy, hair loss, and nail changes (Harden et al. 2013). Motor symptoms such as finger, hand, and arm dystonia and tremor may develop and cause further discomfort. Symptoms may progress proximally and result in pain and dystonia of the arm and shoulder muscles. In severe cases, loss of vascular supply threatens development of gangrene and may necessitate limb amputation.

Pathophysiology

For years, primary dysfunction of the sympathetic system was held responsible for the development of CRPS. This view is now modified in favor of neuroinflammation and deranged autoimmunity with small C fiber damage playing a pivotal role. Damage to C fibers could lead to neurogenic inflammation, ectopic firing, vasodilation (via axon reflex), and/or hypoxic/ischemic injury (Weber et al. 2001; Coderre et al. 2004). Evidence exists that in some patients, neural inflammation extends to the spinal cord. In one patient with long-standing CRPS, tissue examination of the dorsal horn demonstrated significant activation of microglia and astrocytes with neuronal loss (Del Valle et al. 2009).

Conventional Treatment

Treatment of CRPS is difficult and geared to relief of pain and modification of the course of the disease. Treatment of pain with tricyclic antidepressants, calcium channel blockers including gabapentin and pregabalin, serotonin/norepinephrine reuptake inhibitors, and locally delivered anesthetics is partially effective. Intranasal calcitonin (100–400 units) may relieve pain in some patients. In a blinded study, intravenous infusion of ketamine (NMDA antagonist) effectively reduced pain in 16 of 20 patients with follow-up of 6 months (Schwartzman et al. 2009). However, the recommended dose of 100 mg for 4 h/day for 10 days can be associated with significant hepatotoxicity requiring close liver function monitoring. Recently, a small double-blind crossover study of 12 patients suggested the efficacy of intravenous immunoglobulin (IVIG) (Goebel et al. 2010). In general, CRPS is considered a very difficult condition to treat.

BoNT Treatment of CRPS

Argoff (2002) reported alleviation of pain, skin color, and local edema in 11 patients with CRPS following intramuscular injection of onaA. In agreement with this observation, a recent single case report described marked reduction of allodynia after subcutaneous injection of onaA in a patient with CRPS and dorsal hand allodynia (Birthi et al. 2012).

In contrast, in a blinded, controlled, parallel study, Safarpour et al. (2010) found no statistically significant difference between onaA and placebo in eight patients with severe CPRS allodynia. The authors also reported failure of onaA in an open trial of additional six CRPS patients. In another publication, however, these same authors (Safarpour and Jabbari 2010) reported significant improvement of proximal pain, proximal and distal dystonia, and shooting arm pain in two patients with CPRS after intramuscular injection of onaA into painful proximal muscles (deltoid, trapezius, levator scapulae, supraspinatus, upper thoracic paraspinal, and flexor digitorum superficialis) with a total dose of 300 units. In one of these patients, concurrent exquisite dorsal hand allodynia also gradually improved after 2 years of repeated proximal intramuscular injections. A recent retrospective report of 37 patients by Kharkar et al. (2011) also indicated improvement of CRPS after intramuscular injection of shoulder girdle muscles.

Clinical Comment

The natural history of CPRS reflects a debilitating condition with poor prognosis. One long-term follow-up study found little improvement of symptoms with current methods of treatment (Schwartzman et al. 2009). The role of botulinum toxin treatment in CRPS is evolving, and at this point, the level of efficacy is U (undetermined) due to the lack of sizeable class I and II studies. The encouraging reports of open observations need to be examined by larger controlled studies. On the technical side, patients with severe allodynia (advanced CRPS) tolerate injections poorly. One important technical question is if combined subcutaneous and intramuscular injection would be more effective than subcutaneous or intradermal injection alone. Another equally important question is whether or not early and aggressive treatment with BoNTs would slow down the dismal course of CRPS.

Metabolic and Drug-Induced Painful Peripheral Neuropathies

A large number of metabolic derangements and medications affect the peripheral nerves. In some, pain is a major symptom. Total coverage of all painful neuropathies is beyond the scope of this chapter. The focus of this section is on painful diabetic

neuropathy, the only metabolic neuropathy for which blinded, placebo-controlled clinical trial results with BoNT treatment are available. No blinded data on BoNT treatment of drug-induced peripheral neuropathies is available. Because of its importance and frequency, neuropathic pain related to chemotherapy is briefly discussed with a representative case presentation from the author's experience with onaA.

Diabetic Neuropathy

Among metabolic disorders, diabetic neuropathy (DN) can be considered a model of metabolic neuropathic pain. Painful neuropathy is more common in type 2 diabetes with prevalence of 25–26 % (Boulton 2007) versus the 16 % reported for type 1 diabetes among the younger individuals (Barrett et al. 2007). The persistent pain often has a burning and aching quality. Examination shows reduced or lost sensory modalities consistent with DN but also areas of hyperesthesia and allodynia. Chronic pain causes anxiety and depression impairing the quality of life due to psychosocial distress and disrupted sleep.

Pathophysiology

For many years, hyperglycemia was considered the reason for the development of pain in DPN. Recent data suggests hypoinsulinism and abnormal insulin signaling as more relevant factors (Romanovsky et al. 2006). At the molecular level, sodium channels, nonselective calcium channels linked to transient receptor potential receptor (TRP), and receptors for nerve growth factors (Trks) are all expressed highly in DRG neurons and believed to have a role in the pain of diabetic neuropathy. More recently, CaV3.2 T-type voltage-gated calcium channels (T-channels) have been identified as key players in the sensitized (hyperexcitable) state of nociceptive sensory neurons (nociceptors) in response to hyperglycemia and suggested as the basis for painful symptoms of diabetic neuropathy (Orestes et al. 2013).

Treatment of Painful Diabetic Neuropathy (PDN)

The treatment strategy focuses on modifying the mechanisms which cause neuropathic pain (Table 3.1), the use of known drugs for neuropathic pain (Cohen 2013, Table 3.3), and control of hyperglycemia. Agents that increase hyperglycemia are to be avoided.

BoNT Treatment in Diabetic Neuropathy

Two placebo-controlled, blinded studies have investigated the efficacy of onaA in painful diabetic neuropathy.

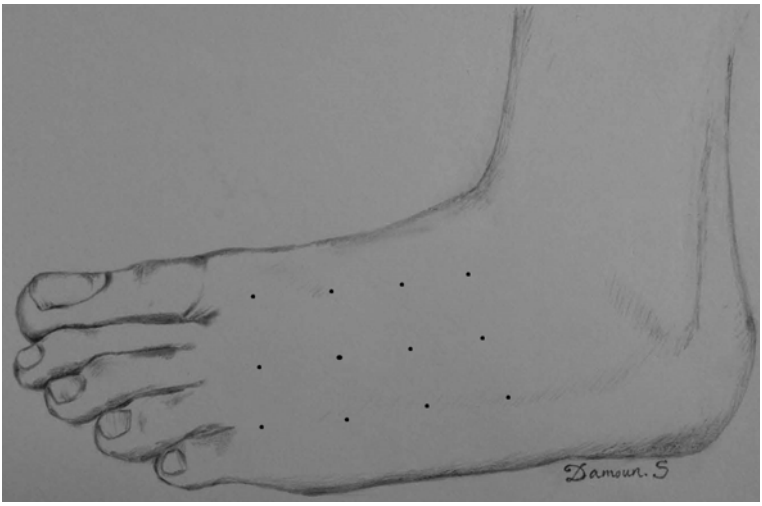

Fig. 3.3 Grid pattern of intradermal injection advocated by Yuan et al. (2009) (neurology) for treatment of painful diabetic neuropathy (Created by Damoun Safarpour; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

Yuan et al. (2009) conducted a double-blind crossover study in 18 patients injecting onaA or saline intradermally in the hyperesthetic and allodynic foot regions (4 units/site in the case of onaA) (Fig. 3.3). The pain reduction measured by VAS was significant in favor of onaA at 1, 4, 8, and 12 weeks ($p < 0.05$). OnaA administration improved sleep at 1 week (using Chinese version of the Pittsburgh sleep quality index, CPSQI) ($P < 0.05$). Quality of life assessed by SF36 also improved in more patients in the onaA group (compared to placebo), but the difference was not statistically significant.

In another blinded, placebo-controlled crossover study, Chen et al. (2013) assessed the efficacy of onaA in 18 patients with painful diabetic neuropathy. Sensory perception was assessed by using von Frey filaments (tactile threshold TT) and mechanical pain threshold (using weighted syringes) of bilateral medial and lateral feet obtained at baseline and at weeks 1, 4, 8, and 12 after treatment. At weeks 1, 4, 8, and 12, both tactile perception and mechanical pain decreased markedly in onaA group compared to baseline.

Comment

The studies cited above for allodynia of diabetic neuropathy are both class II. Two class II studies indicate a B level of evidence for efficacy (probably effective) for onaA in relieving the pain of DN. The efficacy of other type A toxins and type B toxin in DN deserves investigation. Other metabolic and drug-induced painful neuropathies also need to be studied.

Painful Neuropathy Related to Drugs and Chemotherapeutic Agents

There are no controlled studies assessing the efficacy of BoNTs in drug-induced and chemotherapy-related painful neuropathies. The case below describes author's experience with one of the two patients in whom treatment with onaA resulted in marked improvement of pain associated with chemotherapy-induced allodynia.

Patient 3-3

A 64-year-old man was referred to the Yale Botulinum Toxin Treatment Clinic for evaluation of severe burning pain of both feet. One year earlier, he had been diagnosed as having a myelodysplastic syndrome for which he had received stem cell transplant. The pain began a month after the transplant while he was receiving immune system-modifying agents (tacrolimus, CellCept, and prednisone). The pain first involved both upper and lower limbs equally but intensified in the feet over the succeeding months. He described the pain as frequent "electrical shocks" or "like a swarm of bees stinging you all at once." The most intense pain affected the dorsal and ventral aspects of the big toe and the adjacent dorsum of the foot bilaterally. The pain worsened at night and was described as "excruciating." Patient rated his pain in VAS as 10 out of 10. Treatment with a variety of analgesic medications including duloxetine, gabapentin, methadone, and oxycodone provided only minimal relief.

Neurological examination showed decreased light touch, pinprick, and vibration sense in the distal part of all extremities and absent ankle jerks. There was exquisite sensitivity to light touch in the dorsum and ventral aspects of the big toes and a small area on the dorsum of both feet close to the big toes which resulted in intense pain (severe allodynia) upon palpation. Each of these three areas, in each foot, was injected with 10 units of onaA subcutaneously. Six to eight sites were injected per area (1.5–2 units/site) for a total of 30 units per ft (Fig. 3.4). Within 2 weeks after this treatment, patient noted marked improvement. In evaluations performed at 4 and 8 weeks after treatment, patient reported his level of pain as 2 out of 10 "very low" in VAS. He expressed his level of satisfaction in PGIC (patient global impression of change) as "much improved."

Comment

Painful neuropathy related to chemotherapeutic agents is a major issue in clinical oncology. If controlled trials can demonstrate efficacy of BoNTs in alleviating this form of neuropathic pain, it would be very beneficial to these patients who are often on polypharmacy and not enthused to take additional pain medications.

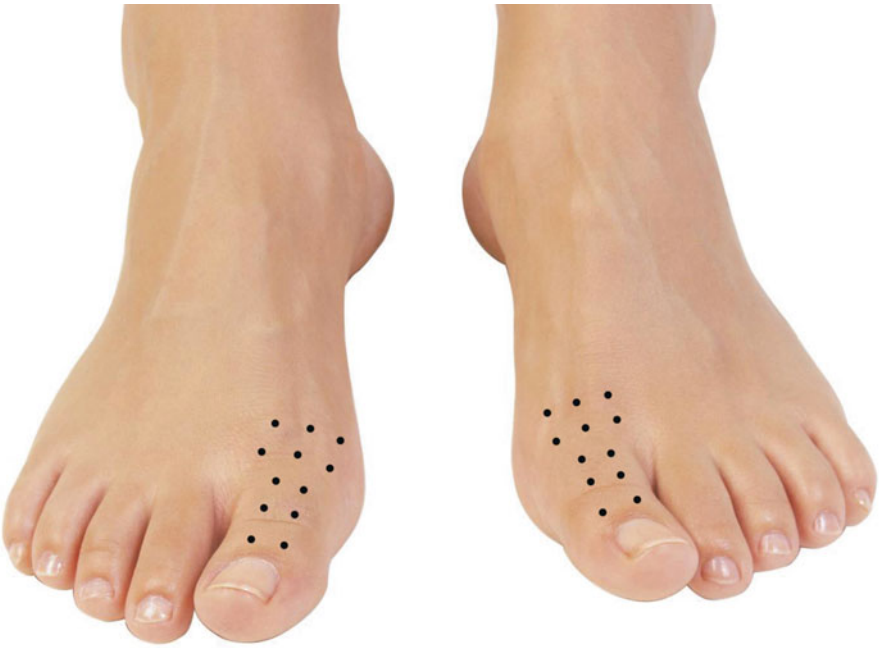

Fig. 3.4 Patient 3-3. Areas of intense allodynia (injected by onaA) affecting the big toes and dorsum of the foot developed following treatment with immune-modifying agents for cancer

Residual Limb Pain and Phantom Pain

With increasing frequency of military conflicts, pain associated with loss of limb has become a major medical management issue among soldiers. It is predicted that in the USA, the number of patients affected by this type of pain will exceed three million by the year 2050 (Zeigler-Graham et al. 2008). Pain associated with loss of limb can be a pain in the stump (residual limb pain, RLP) or felt in the region of the lost limb (phantom limb pain, PLP). The reported incidence of RLP after amputation is 22–43 % and for PLP is 66 % (Carlen et al. 1978; Jensen et al. 1983). The possible mechanism and pathophysiology of phantom pain is discussed in detail in a recent review (Hsu and Cohen 2013).

Pharmacological Treatment

A Cochrane review of literature (Alviar et al. 2011) concluded that based on blinded studies, morphine, gabapentin, and ketamine demonstrate trends toward short-term analgesic efficacy in PLP, while memantine and amitriptyline were ineffective. No data on long-term efficacy is available. The role of calcitonin, anesthetics, and dextromethorphan requires further clarification. In clinical practice, gabapentin is now used increasingly

as the first drug of choice for treatment of PLP due to its safer side effect profile. Since long-term efficacy of drugs against PLP is low (less than 5 % in one large review, Sherman et al. 1984), exploration of novel therapeutic approaches is urgently needed.

BoNT Treatment of RLP and PLP

Two clinical observations, each on a small number of patients, claimed BoNT administration into stump muscles improves phantom pain. In one study (Kern et al. 2004), four patients were injected with 2,500–5,000 units of rimabotulinumtoxinB into the arm and leg stumps (two patients each). Injections were performed at multiple trigger points. All patients reported improvement in stump pain, PLP attacks, and improvement of local allodynia. One patient noted significant improvement of sleep. Improvements lasted for "many weeks." In one patient, a 12-month follow-up showed almost total pain relief. In another study (Jin et al. 2009), the authors described significant improvement of phantom pain in three patients (two with accident injury and one with landmine injury) after EMG-guided administration of aboA (up to 500 units) into the stump muscles. All three patients reported level 3 (on a 0–3 scale) improvement on global clinical scale as well as substantial pain improvement on VAS. Pain improvement lasted 11 months. Patients were able to reduce their pain medications after BoNT treatment.

Unfortunately, these positive observations did not bear out in a recent prospective, parallel design, blinded study which compared the effect of onaA with that of combined lidocaine/methylprednisolone therapy (Wu et al. 2012). Investigators injected a total of 250–300 units of onaA or 10 mg Depo-Medrol in 1 % lidocaine in up to six tender points of 14 patients with RLP and PLP. There was no significant effect on phantom pain from any of the two agents. Both agents, however, significantly improved RLP and pain tolerance. OnaA's effect on RLP and pain tolerability was stronger than that of lidocaine/Depo-Medrol injection ($p=0.002$ vs. $p=0.06$ and $p=0.01$ vs. 0.07, respectively). The relief of RLP in both groups lasted for 6 months.

Comment

Phantom pain is a fascinating area for BoNT research. Efficacy, if confirmed, would imply that peripheral administration of BoNTs can influence allodynia caused by central pain. The blinded study cited above and open observations suggest efficacy of onaA for RLP. At this time, the level of efficacy of BoNT is U (undetermined) for both RLP and PLP due to the lack of class I or II studies.

Conclusion

Neuropathic pain is one of the most common forms of human pain. Failure of response to current analgesic medications is not uncommon. The data on type A toxin (mostly onaA) is encouraging and indicate efficacy or probable efficacy in

three major and common forms of neuropathic pain, namely, postherpetic neuralgia, post-traumatic neuralgia, and painful diabetic neuropathy. Controlled and placebo-controlled trials are necessary to assess efficacy of BoNTs in other painful metabolic and drug-induced neuropathies, complex regional pain syndrome, residual limb pain, and phantom pain. Much remains to be learned about the most effective technique of injection, most effective dose, optimum dilutions, and differences among BoNTs in the treatment of neuropathic pain.

Appendix 3.1 AAN Classification of Evidence

Class	Criteria	Level of evidence	Recommendation
I	Prospective, randomized, controlled, outcome masked, representative population with criteria A–E[a]	A: Two or more Class I studies	Established as effective, ineffective, or harmful
II	Prospective, matched cohort, representative population, masked outcome and meets A–E or RCT with one criteria in A–E lacking	B: At least one Class I or two Class II	Probably effective, ineffective, or harmful and recommended
III	Controlled trial, representative population, outcome independent of patient treatment	C: At least one Class II	Possibly effective, ineffective, or harmful, may be used at discretion of clinician
IV	Uncontrolled study, case series, case report, or expert opinion	U	Data inadequate or conflicting

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[a]Criteria A–D: A = primary outcome(s) clearly defined, B = exclusion/inclusion criteria clearly defined, C = adequate accounting for drop-outs and cross-over with numbers sufficiently low to have minimal potential for bias, D = relevant baseline characteristics or appropriate statistical adjustment for differences, E = for non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs meet 3 cited criteria

Appendix 3.2 AAN Classification of Recommendations

A- Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies)[a]
B- Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies)
C- Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies)
U- Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven

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[a]In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if (1) all criteria are met, (2) the magnitude of effect is large (relative rate improved outcome 5 and the lower limit of the confidence interval is 2)

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Chapter 4
Migraine and Other Primary Headaches

Abstract Primary headaches consist of migraine, tension-type headaches, and trigeminal autonomic cephalalgias (e.g., cluster headache). Migraine and tension-type headaches are common and, in chronic form, are major causes of disability. Prospective double-blind and placebo-controlled studies have confirmed the efficacy of onabotulinumtoxinA (onaA) in chronic migraine (class A evidence). Follow-up of patients in PREEMPT studies with five cycles of onaA injections (over 56 weeks) attests to the tolerability and safety of this drug in chronic migraine and demonstrates progressive improvement of patient's quality of life. In clinical practice, patients treated with onaA for more than 2 years describe their experience as very gratifying (attached videotapes). Studies using onaA in management of episodic migraine and chronic daily headaches have shown disappointing results and no evidence of efficacy. Investigations using botulinum neurotoxins (BoNTs) in management of tension-type headache have also provided negative results, but the results are confounded by selection of low-dose, suboptimal technique and selection of rigid primary outcome criteria. No blinded studies with BoNTs are available for trigeminal autonomic cephalalgias.

Keywords Episodic migraine • Chronic migraine • Tension headache • Chronic daily headache • Autonomic neuralgias • Cluster headache • Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA • OnaA

Introduction

Headache is a common human ailment with an annual prevalence of 90 % and lifetime prevalence of 99 % (Evans 2005). The Headache Classification Subcommittee of the International Headache Society (IHS) has classified headaches into primary and secondary categories (Headache Classification Subcommittee of HIS 2004, 2nd edition). The focus of this chapter is on primary headaches (migraine, tension

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headache, and trigeminal autonomic cephalalgias: cluster and others) for which data on BoNT efficacy is available.

Migraine

Introduction

Migraine is a common primary headache disorder that affects 18 % of women and 6 % of men (Lipton and Silberstein 2001). It is the most complex form of human headache due to the great variability of its symptoms. Migraine is a major financial burden to the society with an estimated annual cost of $4.2 billion for direct cost of care in the USA (Insinga et al. 2011).

Migraine headache is subclassified into migraine with aura (MWA) and migraine without aura (MWoA). The pain is characteristically pulsating, starts often unilaterally, and is frequently associated with photophobia, phonophobia, and gastrointestinal distress. Migraine's aura often involves the visual system with either enhancement of function (bright or zigzag lights) or loss of function (scotoma). Loss of function may also occur in the motor (hemiplegic migraine) or other sensory domains. Local scalp tenderness and allodynia (touch perceived as pain) are common in migraine and were reported to affect 43 % of 89 patients in one study (Ashkenazi et al. 2007). In another study, the incidence increased with the number of migraine attacks, 33 % associated with one to four attacks and 58 % associated with more than eight attacks/month (Mathew 2011). Allodynia usually starts ipsilateral to the side of headache, denoting activation of peripheral nociceptive pathways. Contralateral spread of allodynia indicates central sensitization to pain via third-order (thalamic) neurons (Burstein et al. 2000).

In episodic migraine, attacks occur less than 15 days per month. Chronic migraine is defined as headaches occurring 15 or more days per month, lasting more than 3 months with 8 or more days per month meeting the criteria for migraine without aura or responding to migraine-specific treatment (Headache Classification Subcommittee of HIS 2004). Chronic migraine includes approximately half of all chronic daily headaches and has an estimated global prevalence of 2 % (Natoli et al. 2010). It is the most costly form of migraine with nearly $200 per week more cost to the employers than episodic migraine (Serrano et al. 2013).

Pathophysiology

The aura phase of migraine corresponds to the electrical phenomenon of cortical spreading depression (SD) that often involves the occipital cortex (predominance of visual aura) (Lance and Goadsby 2005). Spreading depression marches through the cortex at the rate of 3–6 mm/min does not respect specific vascular territories (Cao et al. 1999). What triggers and initiates SD has remained elusive. It is believed that the release of extracellular potassium, nitric oxide,

adenosine, and others agents during cortical depression causes inflammation and vasodilation in the cortex and meningeal vessels (Waeber and Moskowitz 2003). This results in a sensitized trigeminovascular system which sends enhanced afferent impulses to the trigeminal ganglion, nucleus pontis caudalis, superior salivatory nucleus, and parasympathetic efferent fibers (Noseda and Burstein 2013). Excitation of the latter causes dural vasodilation. Emergence of nociceptive stimuli at different levels of the nervous system and the trigeminal nucleus causes head and facial pain.

The genetics of migraine was reviewed in a recent communication (Silberstein and Dodick 2013). First-degree relatives of patients with MWA and MWoA have 4 and 1.9 times the risk of developing the same type of migraine, respectively. Approximately, 52 % of female twins raised together or apart demonstrate co-occurrence. Aside from familial hemiplegic migraine which is monogenic (with three identified genes), the genetics of other forms of migraine is complex, and the information is still preliminary and evolving. Recently, mutation of CNK18 gene with complete loss of function of related K channel was detected in some patients with MWA (Lafreniere et al. 2010).

Reliable biomarkers for diagnosis of migraine are often sought. A recent communication reported that serum level of CGRP is 2.5 times higher in CM compared to asymptomatic controls and about 1.8 times higher than patients with episodic migraine or cluster headaches ($p < 0.05$) (Cernuda-Morollon et al. 2013).

Treatment

Treatment of migraine headaches includes strategies to abort acute attacks and, in case of frequent attacks, reduce the frequency of attacks by daily medications (preventive drugs). Several recent comprehensive reviews have discussed treatment strategies for migraine (Silberstien 2008; Mathew 2011; Diener et al. 2011). Treatment of mild migraine attacks includes the use of acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs). For more severe attacks not responding to these measures, triptans are often recommended. Triptans act on 5HT receptors in the trigeminal nucleus caudalis and in the dorsal horns of the upper cervical spine, hence interfering with the nociceptive cascade beginning to set in the trigeminovascular system (Goadsby and Knight 1997). Many patients with migraine, however, do not respond to triptans, and cardiovascular comorbidities often limit their use (Hoffmann and Goadsby 2014). For attacks refractory to oral medications, liberal hydration (IV fluids) and intravenous administration of dopamine receptor agonists (prochlorperazine), dihydroergotamine (DHE), or IV NSAIDs (diclofenac or ketorolac) are recommended (Gelfand and Goadsby 2012). One small study has shown that high flow oxygen may alleviate acute attacks of migraine (Ozkurt et al. 2012). Opiates, barbiturates, and short course of steroids are also used as abortive therapy by some clinicians, but supportive studies are lacking. Since most abortive medications are associated with significant comorbidities, development of effective preventive drugs with safe profile is urgently needed.

Preventive daily treatment of migraine is recommended when migraine episodes exceed six to eight headache days per month or if the patient has to use abortive medications more than eight to nine times per month (Silberstein 1997). Beta-blockers such as propranolol or metoprolol, topiramate, gabapentin, amitriptyline, and sodium valproate are commonly used for migraine prevention (Goadsby 2013). Venlafaxine and histamine are considered second-line preventive medicine.

For chronic migraine, double-blind studies are available on the efficacy of topiramate (two large multicenter studies; Lanteri-Minet et al. 2007; Diener et al. 2007), valproate, and levetiracetam (both small studies). Both double-blind multicenter US and European studies have demonstrated significant reduction of headache days and migraine days per month with topiramate (in the USA study, 3 days reduction with topiramate vs. 0.7 days with placebo). The effective dose was 100 mg/day. The double-blind/parallel valproate study (Yurekli et al. 2008) and the double-blind/crossover levetiracetam study (Beran and Spira 2011) encompassed 41 and 71 patients, respectively. Both studies showed effective reduction of headache days per month and headache severity in the BoNT group versus placebo. For levetiracetam, the primary endpoint—absence of any headaches—was not met, however, perhaps due to the rigidity of the criteria.

Botulinum Neurotoxin for Preventive Treatment of Migraine

Episodic Migraine

The first double-blind, placebo-controlled, prospective study (class II) investigating efficacy of onabotulinumtoxinA (onaA) in episodic migraine was published in 2000 (Silberstein et al. 2000). The authors investigated the effect of 25 and 75 units of onaA in 123 patients with two to eight migraine attacks per month. Patients with headache days exceeding 15/month (chronic migraine) were excluded. OnaA was injected into the procerus muscle (3 or 9 units) and bilaterally into corrugators (two on each side, 6 or 18 units), frontalis (two on each side, 6 or 8 units), and temporalis (one on each side, 6 or 18 units) muscles.

Primary efficacy was defined as a significant change from the baseline of migraine attacks. At 3 months, patients in the 25 unit group had significant reduction in headache frequency and headache intensity and 50 % reduction of headaches compared to baseline. No statistically significant change was noted in the 75 unit group, a finding attributed to their milder headaches at baseline. Subsequently, two large class I studies were conducted with onaA in EM investigating 238 and 418 patients (Elkind et al. 2006; Saper et al. 2007). Both studies failed to meet their primary outcome measure that was reduction of migraine frequency/month. Another small (60 patient) class II study of EM that considered 50 % or more reduction of migraine frequency as the primary outcome also failed to meet its primary endpoint (Evers et al. 2004). The total dose applied in

the aforementioned studies varied from 25 to 100 units. The American Academy of Neurology's subcommittee on guidelines based on the above four studies (two class I and two class II) assigned level B evidence (probably ineffective) to onaA for the treatment of episodic migraine (Naumann et al. 2008).

Two other class I studies which were published later and used larger doses of onaA confirmed the stance of AAN's subcommittee on episodic migraine (Relja et al. 2007; Aurora et al. 2007). The first study compared the effect of different doses of onaA (75, 150, 225 units) with placebo using the mean number of migraine days at day 180 as the primary outcome measure. All four groups (including the placebo group) improved with either onaA or saline (the placebo), and there was no significant difference between onaA subgroups and the placebo group (Relja et al. 2007). In the second study of 369 patients (Aurora et al. 2007), the authors compared the effect of onaA (mean 190.5 units) with placebo. The primary endpoint, defined as the mean change in migraine episodes over 30 days prior to day 180, was not met. Although the study failed to meet the primary endpoint, a subgroup analysis of patients with 12–14 headache days per month showed significant improvement in onaA group versus placebo ($p = 0.04$).

Chronic Migraine

In a small study, Freitag et al. (2008) compared the effect of fixed-dose (100 units) and fixed-site (glabella, frontalis, temporalis, trapezius, suboccipital) injections between onaA (20 patients) and placebo (21 patients) and reported promising results for chronic migraine. Patients with medication overuse were excluded. The primary outcome was the number of migraine episodes with each 4 weeks of the study. The secondary outcomes included the number of headache days and the headache index (a measure of both intensity and frequency). OnaA was statistically superior to placebo on both primary outcome ($p < 0.01$) and secondary outcomes ($p = 0.041$ and $p = 0.046$) and for headache index (HI) at 16 weeks ($p = 0.003$). Nevertheless, between 2002 and 2009, a number of large multicenter studies assessing efficacy of BoNTs in chronic migraine failed to meet their primary outcome. The major breakthrough in this area came with the publication of PREEMPT studies (I and II) in the summer of 2010 (Aurora et al. 2010; Diener et al. 2010). Each of these two multicenter studies evaluated approximately 700 patients (total 1,384 patients) who met the criteria for chronic migraine. Patients with medication overuse were included in both studies. The studies had a 24-week blinded arm followed by 32 weeks of open arm. The primary outcome for PREEMPT I was the number of migraine episodes and for PREEMPT II, the number of headache days, both evaluated at 24 weeks. A number of secondary outcomes were also evaluated at the 24-week time point. PREEMPT II met both its primary and secondary outcomes at all time points (Fig. 4.1). For the primary outcome, the change in headache days was 9 for onabotulinumtoxinA versus 6.7 for the placebo ($p < 0.001$). Although PREEMPT I did not meet its primary outcome, it met all its secondary outcomes. The pooled data (Dodick et al. 2010) from the two studies showed significant change from the baseline in favor of onabotulinumtoxinA in

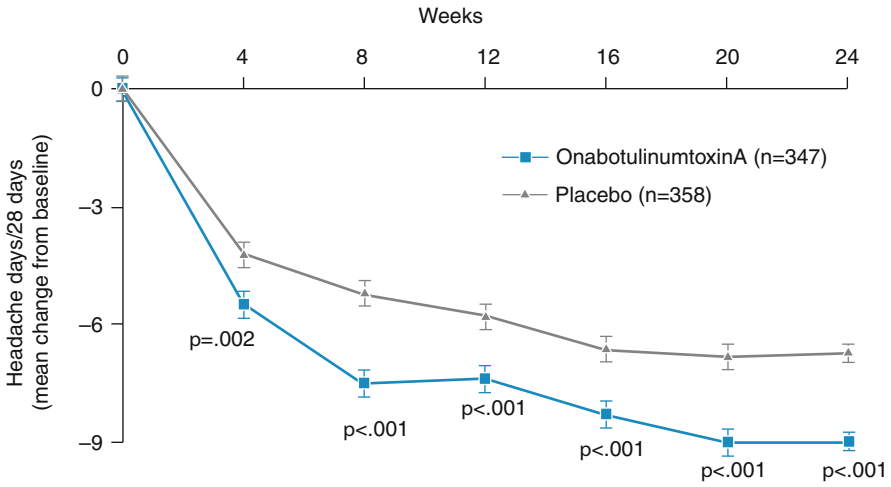

Fig. 4.1 Significant reduction in pain days from botulinum toxin group compared with placebo group over all time points of 24-month blinded arm of the study (From Diener et al. (2010). © 2010 SAGE Publications. Reprinted with permission from SAGE)

respect to the primary and all secondary parameters. Based on these studies, onabotulinumtoxinA was approved for the treatment of chronic migraine in the UK, Canada (summer of 2010), and in the USA (October 2010).

Subsequently, Lipton et al. (2011) studied the PREEMPT pooled data (1,384 patients) specifically in regard to the quality of life which was measured by both the Migraine-Specific Quality of Life Questionnaire (MSQ) and the Headache Impact Test (HIT). Both measures were significantly improved from the baseline in the onaA-treated group at 24 weeks providing strong evidence for quality of life improvement with onaA in chronic migraine.

BoNT Injection Technique in Chronic Migraine

A variety of injection techniques have been proposed for BoNT treatment of chronic migraine based on established studies and the practice of experienced BoNT practitioners. The technique used in PREEMPT studies (Blumenfeld et al. 2010), recommends 31 injection sites, a total dose of 155 units, and injecting of 5 units per site (Fig. 4.2). In some patients, an additional 40 units is allowed for a total of 195 units. A dilution of 100 units/2 cc was recommended. Silberstein from Jefferson's comprehensive headache clinic in Philadelphia endorses a technique similar to PREEMPT with more injection points over the frontal region (Silberstein et al. 2013).

Over the past 15 years, I have used an injection scheme at Yale which provides a high rate of success (nearly 90 %) in chronic migraine (Fig. 4.3). The total number of injections is 23, and the total dose is 165 units. In patients with

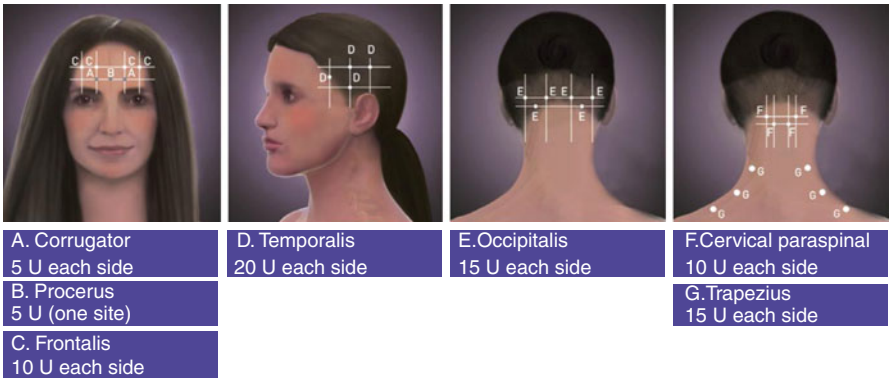

Fig. 4.2 Injection sites for treatment of chronic migraine based on PREEMPT studies (From Blumenfeld et al. (2010). © 2010 American Headache Society. Reprinted with permission from John Wiley and Sons)

Fig. 4.3 Injection sites and doses of onaA for chronic migraine per author's protocol at Yale. The emphasis is on fewer number of injections, higher dose in anterior temporal and posterior cervical muscles (Created by Tahereh Mousavi; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

large necks, an additional 30 units is injected into the cervical paraspinal muscles. In this technique, on each side, 5 units are injected into the corrugator muscle, 15 units into the frontalis muscle (5 units/site), 30 units into temporalis (15 units anterior and 15 mid-temporal), 10 units into occipitalis (1/site), and 30 units into the splenius muscles (10 units per site). An additional 5 units is injected at midline into the procerus muscle. The injection pattern emphasizes the importance of temporalis and posterior neck muscles in chronic migraine and does not include horizontal, shoulder trapezius muscles. Although Ashkenazi and Blumenfeld (2013) warn against development of weakness in cervical and trapezius muscles if the dose per injection site exceeds 5 units, I have never seen

weakness of these muscles following 10 units/site injection. This is probably because cervical paraspinal and trapezius muscles are very strong and multilayered muscles. Our technique has also the advantage of applying fewer injections of 23 versus 31 employed in PREEMPT studies.

The Issue of Medication Overuse in Chronic Migraine

Medication overuse is a common problem as many patients with chronic migraine have medication overuse problems. Inclusion of patients with medication overuse headaches in PREEMPT studies has raised questions by some investigators. Silberstein et al. (2013) studied the efficacy of onaA in a subgroup of PREEMPT study patients who had medication overuse in addition to chronic migraine (MO + CM). Of 1,384 patients in the PREEMPT study, 65.3 % met the criteria for medication overuse. At 24 weeks, similar to the patients in the main PREEMPT study, MO + CM patients demonstrated significant improvement of headache days (primary end point) (−8.2 vs. −6.2 with $p < 0.001$) and also met many secondary endpoints (frequency of migraine days, frequency of moderate to severe headache days, cumulative headache hours on headache days, headache episodes, migraine episodes, and percentage of patients with severe HIT-6 (all $Ps < 0.05$). Triptan intake was also significantly reduced in the onaA-treated group ($p < 0.001$). Authors concluded that onaA treatment is effective in patients with chronic migraine with MO.

Sandrini et al. (2011) studied the effect of onaA injections in 68 patients with chronic migraine without aura and with MO (35 placebo, 33 toxin). The study was double blind and placebo controlled with primary and secondary outcomes measured at 12 weeks. Patients received a total of 16 injections (100 units), 8 on each side (2 frontal, 2 cervical, 1 corrugator, 1 temporal, 2 trapezius). No significant difference was noted between the placebo and toxin in reduction of pain days (primary outcome). A subgroup analysis of the data, however, demonstrated that MO patients with pericranial tenderness had significantly lower number of pain days (primary outcome). The total dose of 100 units used in this study was probably too small; also, some important head regions (occipital) were not covered.

Long-Term Response to BoNTs in Chronic Migraine and Safety Issues

Although many BoNT practitioners with substantial experience in the treatment of migraine have long believed in the long-term efficacy and safety of onaA, until recently, no systematic data was available. In 2014, Aurora et al. published data on safety, tolerability, and efficacy of onaA (PREEMPT study) after five cycles of treatment (at 56 weeks). The mean change in frequency from baseline of headache days, migraine days, and moderate to severe headache days and 50 % or more change in headache days from baseline were all significantly lower ($p < 0.05$) in the onaA treatment group. The quality of life was further improved at 56 weeks (59 %) compared to 25 weeks

Fig. 4.4 Mephisto sign, elevation of the lateral part of eyebrows following injection of frontalis muscles in migraine. This finding is attributed to injections affecting lateral and medial brow elevators unequally (Created by Tahereh Mousavi; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

(44 %), measured by 5 or more points increase in the HIT-6. No cumulative undesirable effects were noted. Tolerability was excellent, and there were no serious safety issues.

Personally, I have been very impressed with the long-term efficacy of onaA in chronic migraine. A prospective observation (unpublished data) of my last 80 patients with over 2 years follow-up and treated with the methodology illustrated in Fig. 4.3, excluding cases of litigations and secondary gain, disclosed an efficacy of 90 %. In general, the second and third injections were more effective than the first. At least 80 % of the patients reported significant improvement in their quality of life (attached videos). Side effects were uncommon and included transient local bleeding, local neck pain, and transient frontal asymmetry including the Mephisto sign. The Mephisto sign refers to an elevation of the lateral part of the eyebrow (Fig. 4.4). Cho et al. (2013) recommend an additional, lateral frontal injection to avoid elevation of the lateral part of the eyebrow. I have not seen any serious side effects with onaA treatment of chronic migraine with over 3,000 injection sessions.

Imploding Versus Exploding Migraine

In a study of 63 patients with migraine, Jakubowski et al. (2006) found patients with imploding headaches to be better responders to onaA than those with exploding headaches. Among responders to onaA, 74 % had imploding headaches; among

nonresponders, 92 % had exploding headaches. Imploding headaches were described as those with pressure from outside the head (crushed, clamped, or stabbed by an external force). Exploding headaches were headaches felt as pressure built inside of the head. This is an interesting and perhaps an important concept. Distinction between exploding and imploding headaches is not always easy in patients with chronic migraine and requires focused questioning by examining physicians.

Patient 4-1

A 32-year-old female complained of frequent migraine attacks for 7 years. The attacks gradually increased in frequency despite taking triptans for acute attacks and a number of preventive medications. The last preventive drug before BoNT treatment was topiramate (100 mg daily). Patient had daily headaches with three to four severe migraine episodes per week. During the episodes, she had pounding/pulsating headaches with nausea and photophobia. She stopped working 2 years ago due to disabling headaches. After the second session of botulinum toxin treatment with onaA, the patient reported significant reduction in frequency and intensity of the headaches that improved even further with subsequent treatments.

A year after initiation of treatment with onaA, she was able to stop all preventive medications. Six months later, she resumed her work and became gainfully employed. At 2 years posttreatment evaluation, she reported few headaches, was fully functional, and expressed relief (Video 4.1). Video 4.2 shows her at 2 years post-onaA treatment during an injection session (using the PREEMPT scheme). Video 4.3 shows an injection session in a male patient with 3 years of onaA treatment and a 10-year history of debilitating migraine. Video 4.4 shows this patient's interview, 3 years after onaA treatment for chronic migraine. Videos 4.5 and 4.6 demonstrate our injection technique in a female patient with chronic migraine and an interview with the patient.

The Mechanism of Action of onaA in Chronic Migraine

Animal studies have demonstrated an analgesic effect for botulinum toxins via different mechanisms (see Chap. 2). These mechanisms include inhibition of the release of pain mediators (calcitonin gene-related peptide, glutamate, and substance P) from peripheral nerve endings and dorsal root ganglia (Aoki 2005; Meng et al. 2007; Lucioni et al. 2008). Furthermore, onaA reduces tissue inflammation and local accumulation of glutamate in the formalin model of pain (Cui et al. 2004). Peripheraly injected onaA has been shown to travel to sensory ganglia, and there is some evidence that it may reach central nervous system from the site of peripheral injection (Wiegand et al. 1976). In animals, experimentally induced spreading depression releases pain mediators and pro-inflammatory agents in meningeal and dural nerve endings; the same is probably the case in migraine (Noseda and Burstein 2013). Direct excitatory cortical connections to neurons of trigeminal nucleus and brain stem nuclei also lead to inflammatory changes and increased release of pain

mediators (especially CGRP). These changes lead to peripheral and central sensitization of the neural tissue (Aoki 2005).

It has been postulated that after injection, onaA reaches trigeminal and cervical nerve endings locally. The relief of migraine is via blocking the release of aforementioned pain mediators and reduction of peripheral and central sensitization (Ashkenazi and Blumenfeld 2013).

The effect of onaA on pericranial muscles may also partially explain its effect on chronic migraine. In CM, pericranial muscles are often tense and display increased tone. In tense muscles, intrafusal muscle fibers (muscle spindles) have a higher discharge rate. Increased non-nociceptive input to the central nervous system can worsen central sensitization as in this state, non-nociceptive input can be perceived as nociceptive by wide range function neurons (Roberts 1986). Muscle spindles are a major source of non-nociceptive input to the central nervous system. In animals, injection of onaA into the muscle markedly reduces the discharge of muscle spindles (Filippi et al. 1993).

Comment

Chronic migraine is a debilitating disease. Oral medications provide only partial relief. In a recent study, 57.3 % of the patients on oral preventive medications at 1 year and 34 % at 3 years still had chronic migraine (Manack et al. 2011). The data from PREEMPT studies and experience of physicians who treat large number of chronic migraine patients with BoNT show onaA as a very effective mode of treatment. It improves all aspects of chronic migraine including quality of life (Lipton et al. 2011) (videotapes). The treatment is most effective after administration of repeated doses, maintains its effectiveness over time (Aurora et al. 2014), and has an excellent safety profile. Its advantages over oral medication include more efficacy, better tolerability, and less frequent (every 3 months) treatment. After 1 year of treatment, at least half of the patients either reduced preventive medications, triptans, or both; some patients were able to stop all medications for migraine (author's personal experience).

The issue of the right primary outcome measure for clinical trials is an evolving matter. Logically, the most important primary outcome should be the one most appreciated by the patient suffering from migraine. Is it merely the number of pain days, as used in the PREEMPT studies; or the number of severe and moderately severe pain days, as initially used in the study of Silberstein et al. (2000); or the migraine index which not only takes pain frequency but also some measures of pain intensity into account? Some blinded studies of episodic migraine have found significant improvement of migraine index, although it was not the primary outcome (Silberstein et al. 2000; Vo et al. 2007). The feedback from most of my patients indicates that they consider both frequency and intensity important, and, for them, severe or moderately severe headache days are of prime concern.

The importance of the right technique and the right dose is also an evolving matter. PREEMPT studies provided us an excellent injection profile with an efficacy

supported by a large-scale study. As we observe, experience, and obtain more feedback from patients, we will ultimately find the optimum technique and dose to apply.

Tension-Type Headache (TTH)

Tension-type headache is the most common form of primary headache. Like migraine, it is more common among women. One epidemiological study gives and overall prevalence of 38 % (47 % among women) (Schwartz et al. 1998). Recently, Freitag (2013) published a comprehensive review of this subject. The pain of TTH typically affects the scalp and pericranial muscles, but contraction of the neck and jaw muscles is not uncommon. Although the pain is usually not as severe as the pain of migraine, severe tension headaches do occur and can be quite disabling accounting for loss of work days in 8–10 % of the affected patients. The most important differential diagnosis is episodic migraine without aura, especially if the associated signs (nausea, photophobia) are subtle. Sinus problems, temporomandibular joint disease, and pain arising from neck pathology (disc degeneration) can also be confused with tension headaches. Harsh family and work environments promote manifestation of TTHs. TTH is more common among individuals with higher levels of education. Tension-type headache, like migraine, can be episodic or chronic (headache days >15 per month). Chronic TTH is the second most common type of chronic daily headaches (after migraine) and occurs with the same prevalence of 2 % (as chronic migraine) in the general population (Freitag 2013).

Pathophysiology

Although stress and psychological factors play a major role in the development of TTH, headache specialists emphasize the contribution of central nervous system in the pathophysiology, especially in the chronic form.

Diamond and Dalessio (1986) proposed the following cascade of events as the pathophysiology of TTH implicating central mechanisms. Local responses in muscle provoke muscle contraction and activate a spinal reflex that polysynaptically activates the thalamic and cortical neurons. This leads to excitation of the descending reticulospinal system that in turn causes increased muscle tone and local muscle contraction through the gamma loop—muscle spindles activation. In chronic TTH, perhaps like migraine, both phenomena of peripheral and central sensitization are at work.

Treatment

Episodic TTHs can be treated with aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs). Supportive treatment includes behavior modification, psychotherapy, and biofeedback. For chronic tension-type headaches, tricyclic

antidepressants (particularly amitriptyline) are the drugs of choice (Freitag 2013). European guidelines also recommend the use of serotonin and norepinephrine reuptake inhibitors venlafaxine and mirtazapine (Bendtsen et al. 2010).

BoNT Treatment of Tension-Type Headache (TTH)

Six prospective double-blind, placebo-controlled studies have investigated the efficacy of BoNTs in TTH. Three studies were class I (Schulte-Mattler et al. 2004; Silberstein et al. 2006; Straube et al. 2008), and three were class II (Schmitt et al. 2001; Padberg et al. 2004; Rollnik and Dengler 2002). None of the aforementioned studies showed efficacy for onaA or aboA in tension-type headaches (Table 4.1). A close look at these studies demonstrates suboptimal dosing and rigid primary outcomes. For instance, none of the BoNT studies in TTH meet both the primary outcome (number of headache days) and the dose (155–195 units recommended for onaA) endorsement of PREEMPT study. Interestingly, the study of Silberstein et al. (2006) indirectly supports taking "headache days" as primary outcome in TTH because in their onaA-treated group the number of HD days (which was not primary outcome) was significantly reduced compared to the placebo group ($p = 0.03$).

At this juncture in time, this author strongly believes that a large, multicenter study is needed to demonstrate or refute the efficacy of BoNT treatment; such a study should preferably use the primary outcome measure (number of HD days) and dose/technique criteria of the PREEMPT II study.

Recently, Harden et al. (2009) studied patients with TTH secondary to cervical myofascial disease with trigger points. Injection of onaA into cervical trigger points decreased chronic TTH days in the onaA group ($p = 0.03$), but had no effect on the pain intensity.

Table 4.1 BoNT studies in Tension type headaches (TTH)

Authors	BoNT	Class	No#	Dose	POM	Results	Comment/limitation
Rollnik and Dengler (2002)	aboA	II	21	200	VAS HA days	–	Low dose. Mixed episodic and chronic
Schmitt et al. (2001)	onaA	II	60	20	WHYPI HD	–	Low dose, limited areas injected
Schulte-Mattler et al. (2004)	aboA	I	60	250	Area under HD curve	–	Low dose
Padberg et al. (2004)	onaA	II	40	100	VAS, HA days	–	Low dose, limited areas injected
Silberstein et al. (2006)	onaA	I	300	50/100/150	HD-free days	–	POM too rigid
Straube et al. (2008)	aboA	I	120	210/420	HD-free days	–	POM too rigid

POM primary outcome measure, *HD* headache, *WHYPIHD* West Haven-Yale Pain Inventory

Chronic Daily Headaches (CDH)

Chronic daily headaches are defined as headaches that occur 15 or more days per month (Silberstein and Lipton 2000). A majority of the affected patients have chronic migraine with the second most common headache being TTHs (Mathew et al. 1987). The efficacy of BoNTs was investigated in four double-blind, placebo-controlled studies (Ondo et al. 2004; Mathew et al. 2005; Silberstein et al. 2005; Dodick et al. 2005). One study (Dodick et al. 2005) actually reflected a subgroup of another study (Mathew et al. 2005) on patients with CDH who were on no prophylactic medications. All studies used the mean change of headache-free days per month as their primary outcome. The largest study enrolled 702 patients (Silberstein et al. 2005). The first three studies did not meet their primary outcome measure. The subgroup study of Dodick et al. (2005) however demonstrated a significant increase in number of headache-free days in the BoNT group compared to the placebo (10.7 days compared to 6.6 days). Based on aforementioned data, the Therapeutics and Assessment Subcommittee of ANA assigned a level U evidence (insufficient evidence to support or refute efficacy) for BoNT treatment in CDH (Naumann et al. 2008).

Trigeminal Autonomic Cephalalgias (TAC)

This category includes cluster headaches; paroxysmal hemicranias; short-lasting, unilateral neuralgiform headache attacks associated with conjunctival congestion and tearing (SUNCT); and short-lasting, unilateral neuralgiform headaches attacks associated with cranial, autonomic dysfunction (SUNA) (Silberstein and Vodovskaia 2013).

Cluster Headaches

Cluster headaches (CH) are attacks of severe or very severe, strictly unilateral pain, which affect the orbital, supraorbital, or temporal regions, lasting 15–180 min and occurring from once every other day to eight times daily. At least one cranial autonomic symptom is present during the attack. Unilateral, conjunctival congestion, nasal stuffiness, and/or runny nose is common. Alcohol consumption, physical exertion, or disturbance of sleep can all trigger acute attacks of CH. The prevalence is approximately 0.1 %, and it is more common among men (May 2013). The pathophysiology is believed to be intermittent dysfunction of posterior hypothalamus; new imaging studies and the clocklike periodicity of the symptoms support this assumption.

Treatment

For acute attacks, oxygen (7 l/min for 10 min), triptans, and IV dihydroergotamine are recommended. Preventive measures used for the management of chronic cluster headaches include administration of a short course of corticosteroids,

calcium channel blocker, lithium, sodium valproate, and topiramate (May 2013; Becker 2013).

BoNT Treatment of Cluster Headaches

Sostak et al. (2007), in an open-label study, investigated the effect of 50 units of onaA in 12 patients with refractory cluster headaches. Three of nine patients with chronic cluster headaches improved significantly. In one, the attacks totally ceased for 18 months. None of the three patients with episodic cluster headaches showed any improvement, however. No placebo-controlled studies of BoNT treatment are reported for cluster headaches or other types of headaches in the TAC category.

Conclusion

Double-blind, placebo-controlled studies of onaA have shown efficacy, tolerability, and safety of this neurotoxin in management of chronic migraine. In addition, patients have experienced significant and progressive improvement of quality of life after several cycles of treatment. Much of this achievement in chronic migraine can be credited to tireless energy and continuous contributions of PREEMPT investigators over the past 10 years. In this author' s experience, most patients treated with onaA consider this treatment as their most rewarding preventive measure and also describe a remarkable improvement in their quality of life.

In contrast, the data in tension-type headache and episodic migraine is disappointing. In regard to tension-type headaches, however, much of disappointment relates to suboptimal technique, insufficient dosage, and suboptimal choice of primary outcomes in the conducted studies. Modification of these measures in future studies may result in different outcomes. Transient autonomic cephalalgias are uncommon, and the role of neurotoxins in their treatment is open to investigation.

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Chapter 5
Botulinum Neurotoxins and Chronic Low Back Pain

Abstract Chronic low back pain is a common condition with diverse etiologies. It is a major cause of functional impairment and disability. In recent years, our understanding of the pathophysiology of low back pain has improved significantly especially in regard to the contribution of dorsal root ganglia and pain mediators. The treatment of chronic low back pain is challenging. Most drugs have limited or short-term efficacy, and many produce undesirable side effects. In animal models, botulinum neurotoxins (BoNTs) have shown analgesic effects through different mechanisms. In human, onaA is effective in chronic migraine, and data suggests efficacy in other forms of neuropathic pain. Using the same dose and technique (multilevel injection into erector spinae), one class II (double blind, placebo controlled) and one prospective, 16-month, open-label study have provided evidence of possible efficacy (level C) in chronic low back pain. Future studies should focus on etiologically distinct subgroups of patients with chronic LBP and take advantage of using the dose and techniques that have already shown promising results.

Keywords Botulinum toxin • Botulinum neurotoxin • Low back pain • Chronic low back pain • OnabotulinumtoxinA • AbobotulinumtoxinA

Introduction

The annual incidence of clinically significant low back pain (pain level of 4 or more on a 10-point scale) with functional impairment is approximately 10–15 % (Carragee et al. 2004). Epidemiological studies indicate that 75–80 % of all people suffer from low back pain some time during their lifetime (Andersson 1999).

Chronic low back pain (cLBP) is defined as pain in the low back lasting beyond 6 months. Approximately 8–10 % of all low back pains evolve into chronic pain. Chronic low back pain is a major cause of disability and early retirement. In the UK, it accounts for 13 % of absenteeism from work (Speed 2004) and imposes an annual burden of 6.65 billion pounds on the economy (Maniakadis and Gray 2000). In the

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USA, almost a quarter of century ago, the economic burden was estimated to be $50–100 billion dollars/annum (Fromyer and Cats-Baril 1991). Among German athletes, Schmidt et al. (2014) have reported a 1-year prevalence of 57 % and a lifetime prevalence of 66 % with the highest lifetime prevalence of 77 % noted among volleyball players.

Human low back is associated with a complex anatomy and physiology. All major anatomic elements of lumbosacral area (skin, muscles, bones, discs, dura, ligaments) have rich innervation and, when disturbed, are capable of producing low back pain. Direct involvement of neural elements (nerve roots) by compression or inflammation can also cause cLBP.

Botulinum neurotoxins have an analgesic effect and are reported to alleviate pain in a number of human pain conditions (Jabbari and Machado 2011). Since BoNTs are introduced through a muscular route and muscles of low back are major contributors to low back pain, the anatomy of low back muscles is reviewed here in some detail.

Anatomy of Low Back Muscles

The lumbosacral area contains a number of muscles arranged at different levels. These muscles stabilize the spine and allow movement of the low back in different directions (flexion, extension, rotation).

Erector spinae (ES) are the most superficial of the low back muscles. At lumbar region, the ES consists of a single muscle mass with three distinct groups: medially located spinalis, laterally located iliocostalis, and longissimus which is between these two (Fig. 5.1). The lower fibers of these muscles attach to the sacrum and iliac crest. Rostrally, the three muscles separate from each other approximately at L1–T12 vertebral level. The fibers of iliocostalis attach to T7–T12 ribs. The fibers of lumbar spinalis and longissimus attach rostrally to the transverse and spinal processes of lumbar and thoracic vertebrae. Unilaterally, ES provides lateral flexion and rotation to the opposite side. Bilaterally, these muscles extend the spine. The nerves for erector spinae originate from dorsal division of the spinal nerves.

Quadratus lumborum (QL) and multifidus muscles are located deeper than ES muscles (Fig. 5.1). QL is often implicated in low back pain. QL is rostrally attached to the lower level of the 12th rib and the transverse processes of the first four lumbar vertebrae. Its fibers end distally via aponeurosis to the lumboinguinal ligaments and attach to the medial part of iliac crest. Unilateral contraction of OL produces ipsilateral flexion of lumbar spine, whereas bilateral contraction helps with extension of the spinal column. Quadratus lumborum is innervated by the ventral rami of the 12th thoracic and upper three or four lumbar spinal nerves. Blood supply is derived from the lumbar arteries, lumbar branches of iliolumbar artery, and branches of subcostal artery.

Multifidus muscle fills up the groove in either side of the spinal processes of the vertebrae from the sacrum to the coccyx. The multifidus is composed of thin fasciculi which arise from the sacrum (as low as the fourth vertebrae), aponeurosis of the origin of sacrospinalis muscle, posterior medial surface of the ilium, and posterior

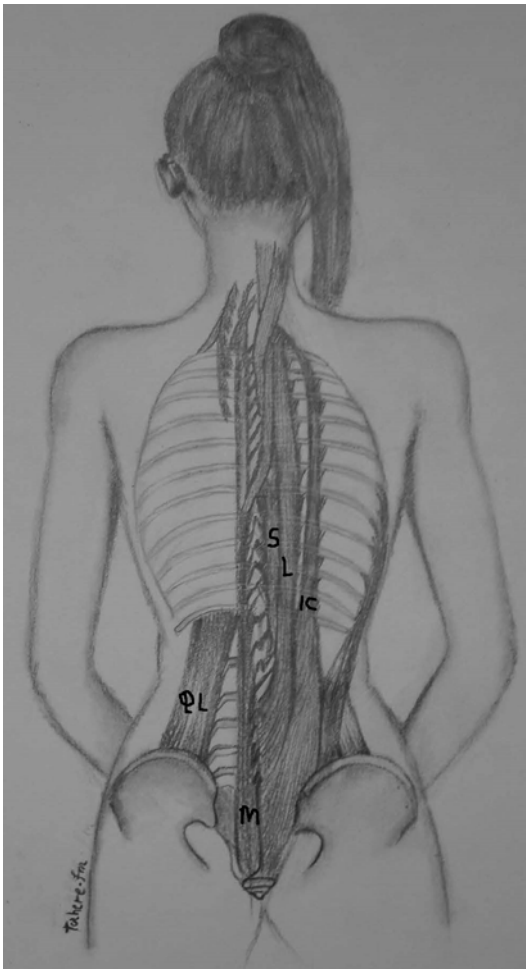

Fig. 5.1 The major muscles of low back: superficial layer (ES shown on the *right*,) and deep layer (quadratus lumborum marked *QL* and multifidus marked *M* and shown on the *left*). Spinalis (medial marked *S*), longissimus (*middle* marked *L*), and iliocostalis (lateral marked *IC*) join at T12–L1 level and make a single mass of erector spinae at the lumbar region (Created by Tahereh Mousavi; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

sacroiliac ligament. In the lumbar region, its fibers attach to mamillary processes of all lumbar vertebrae. Deeper fibers connect to L2–L4 lumbar vertebrae and work to stabilize the joints at each segmental level. At the lower lumbosacral region, more superficial multifidus fibers are close to the skin due to the thinness of the overlying ES in this region. Multifidus muscles, like facet joints, are innervated by the medial branch of the dorsal ramus of the spinal nerves.

Pathophysiology of Chronic Low Back Pain

Muscle strain and disturbance play a major role in the pathophysiology of mechanical low back pain. Major low back muscles such as ES and QL are richly innervated. Irritation of nerve endings may lead to accumulation of pain mediators (glutamate,

calcitonin gene-related peptide, and substance P) at the periphery causing peripheral sensitization. In patients with anatomically tight compartment for ES muscles, the compressed muscle can cause pain and discomfort especially during exercise, the lumbar compartment syndrome (Nathan et al. 2012).

Recently, the role of dorsal root ganglia (DRG) in chronic disc disease leading to low back pain has attracted much attention. It has been shown that DRG is very sensitive to pressure, and even light compression can cause long periods of repetitive firing (5–25 min) in DRG neurons (Howe et al. 1977). The ruptured disc material, due to proximity to DRG, can influence DRG neurons and upregulate expression of pain mediators and inflammatory agents to produce or enhance pain. In rats, experimental disc puncture at L5–L6 level causes persistent upregulation of calcitonin gene-related peptide (CGRP) in lumbar DRG neurons for the entire 8-week course of the study and a transient (2 weeks) increase in expression of inflammatory agents (interleukin-6, nerve growth and tumor necrotizing factors) in DRG (Miyagi et al. 2011). In a similar disc injury experiment in rats, after injury, there is upregulation of tetrodotoxin-sensitive sodium channel (NaV1.7), in L1–L5 DRG neurons. NaV 1.7 channels are associated with sensory transmission in sensory nerves (Sadamasu et al. 2014). Disc injury related to injection of Freund adjuvant into L5 disc results in increased expression of CGRP, substance P, and nerve growth factor both in DRG and the thalamus lasting for 8 weeks (Jung et al. 2011). A sizeable number of DRG neurons that innervate vertebral bodies are also CGRP positive (33 % of those innervating L5 vertebra) which suggests a role for this arrangement in bone-generated low back pain (Ohtori et al. 2007).

Facet joint disease is another condition often associated with chronic low back pain. Wakai et al. (2010) have shown that many DRG neurons have dichotomized axons which project both to facet joints and to low back muscles. These could be the source of referred pain. Approximately 17 % of all DRG neurons innervating the facet joints have other axons that extend to the lower back muscle.

The role of sympathetic nervous system in maintaining pain and its chronicity has long been suspected based on anatomical studies showing massive sprouting of sympathetic fibers into DRG after peripheral injury (McLachlan et al. 1993). Normally no sympathetic fibers are inside DRG, and noradrenergic innervation is present only in the adjacent blood vessels. Following peripheral injury, inflammation develops in DRG and sympathetic ganglia with influx of macrophages and T cell lymphocytes into DRG. This leads to the release of cytokines and increases discharge of DRG neurons. Sympathectomy or removal of sympathetic ganglia decreases the influx of macrophages and T cells into DRG and, consequently, decreases the magnitude of inflammation (McLachlan and Hu 2014). Sympathectomy attenuates the excitability of dorsal root ganglion neurons and pain behavior in a lumbar radiculopathy model (Iwase et al 2012). In chronic low back pain caused by root or DRG injury, sympathetic nervous system hyperexcitability may play a role in the maintenance of pain (sympathetically maintained pain).

In chronic pain states, peripheral sensitization (PS) due to accumulation of pain mediators and inflammatory agents leads to central sensitization (CS) that is believed to contribute to pain chronicity. This CS occurs at multiple levels of CNS

starting with the spinal cord neurons and followed by the brain stem, thalamic, and cortical levels. There is evidence from molecular biology, electrophysiological investigations, and neuroimaging studies that pathological conditions associated with chronic low back pain are capable of inducing central sensitization. In conditions such as herniated disc or trauma, DRG and spinal nerve injuries lead to the generation of ectopic discharges in DRG neurons causing hyperexcitability of spinal cord sensory neurons. Light compression of DRG by experimentally induced nucleus pulposus increases evoked responses in the posterior thalamic neurons for a minimum of 40 min (Nilsson et al. 2013). Functional MRI of patients with chronic low back pain compared to asymptomatic age-matched volunteers has shown augmented activation in premotor, supplementary motor, insula, and anterior cingulate cortex in patients with cLBP (Kobayashi et al. 2009).

Medical Treatment of Chronic Low Back Pain

In clinical practice, a large number of analgesic agents are used for the treatment of chronic low back pain; these include non-anti-inflammatory analgesics (aspirin, acetaminophen), nonsteroidal anti-inflammatory agents (NSAID), tricyclic and tetracyclic antidepressants, muscle relaxants, cyclooxygenase-2 inhibitors, antispasticity agents (tizanidine), anticonvulsants (gabapentin, pregabalin), serotonin/norepinephrine inhibitors (duloxetine), opioid-like agents (tramadol), strong opioids (oxycodone, OxyContin), and topical anesthetic agents. Tricyclic antidepressants cause a 20–40 % reduction over placebo in short follow-up (4–8) weeks, but their long-term effect is not known (Staiger et al. 2003). The anticholinergic side effects are also of concern in older patients. Prospective and control studies with some other agents (non-NSAID analgesics, NSAID, muscle relaxants, and cyclooxygenase inhibitors) have shown either no or marginal improvement over placebo in chronic low back pain (Van Tulder et al. 2000, 2003; Nussmeier et al. 2005; Coats et al. 2004; Ostelo et al. 2005; Solomon et al. 2005). In a 12-week study (Vorsanger et al. 2008), both 200 mg and 300 mg of tramadol moderately improved low back pain compared to placebo ($p = 0.052$ and $p = 0.009$); the disability index, sleep quality, and patient assessment score also improved as secondary measures ($p = 0.012$). Topical NSAID diclofenac has shown some promise in reducing osteoarthritic pain, but systematic studies in chronic low back pain are lacking. In acute and subacute low back pain, one prospective, open-label study has suggested efficacy of lidocaine patch to improve pain and quality of life, and these positive effects were associated with high score in patient satisfaction (Gimbel et al. 2005). Controlled studies in chronic low back pain with lidocaine patch are not available. The most recent Cochrane review of literature on the effect of opioids on pain and function of patients with low back pain encompassed 15 blinded studies and 5,600 patients during the period of 2007–2012 (Chaparro et al. 2014). Both tramadol (weak opioid function) and strong opioids improved chronic low back pain and function over placebo (moderate for pain, mild for function). Two studies found a comparable

effect in chronic low back pain for opioids with tricyclic antidepressants. No significant side effects were noted. None of the studies addressed long-term efficacy and safety. The long-term use of opioids is confounded by the development of addictive behavior.

In a recent review of chronic low back pain, Uhl et al. (2014) recommended tricyclic antidepressants (nortriptyline 25–150 mg daily), tramadol ER (100–300 mg daily), and lidocaine patch (5 %, one to three patches topically up to 12 h) as the first line of medical treatment. In view of limited supportive literature, the long-term efficacy of tramadol ER and lidocaine patch in treatment of cLBP is not well established. Despite medical therapy, most patients with chronic low back pain continue to experience pain and are not satisfied with their level of pain management.

Physical therapy (PT) is aimed to reduce pain, and therapists can educate patients to perform passive and active movements which potentially may prevent progression of low back pain and disability. While PT is commonly used in management of cLBP, well-designed studies are scant and methodological problems and paucity of high-quality investigations prevent drawing conclusions regarding the precise efficacy of physical therapy (Calvo-Muñoz et al. 2013).

Massage and heat and cold applications are temporarily effective for pain but show no long-term benefits. The few available high-quality studies advocate that spinal manipulative therapy (SMT) has no advantage in management of chronic low back pain (Rubinstein 2011). A recent review of yoga in chronic low back pain (ten randomized trials) suggested strong evidence for short-term and long-term effect on pain and moderate effect on pain-related disability (Cramer et al. 2013).

Transcutaneous electrical nerve stimulation (TENS) has been found to be ineffective based on two negative class I studies (level A evidence, AAN criteria—Appendices 3.1 and 3.2) (Dubinsky and Miyasaki 2010). Acupuncture data in low back pain are hard to interpret due to heterogeneity of participants and suboptimal quality of most studies. Improvements in pain and function are reported in some controlled studies, but the effects are transient (Rubinstien et al. 2010). Studies of ultrasound and shock therapy are limited, and available evidence suggests no appreciable effect on pain or functionality (Seco et al. 2011). Epidural injections with anesthetic agents (with or without steroids) improve pain flairs in cLBP, but the effects are generally transient. A recent review of the literature on this subject found 15 blinded, placebo-controlled studies with best results reported for radiculopathies due to disc herniation and spinal stenosis (Parr et al. 2012).

Surgical treatment of low back pain has produced mixed results. Spinal fusion alleviates pain and improves function in patients with degenerative spine disease, but the positive effects may not last long. Minimal spinal surgery without open surgery (with interbody fusion) in selected patients has produced good short-term results. Longer observations are needed, however (Spoor and Öner 2013).

A Cochrane review of six high-quality publications provided strong evidence that behavioral therapy had a moderate effect in decreasing pain, but no noticeable effect on patients' functional status or behavioral health. The review concluded that both the type of patients that benefit from behavioral therapy and the type of behavioral therapy which is most effective still need to be determined (Van Tulder et al. 2001).

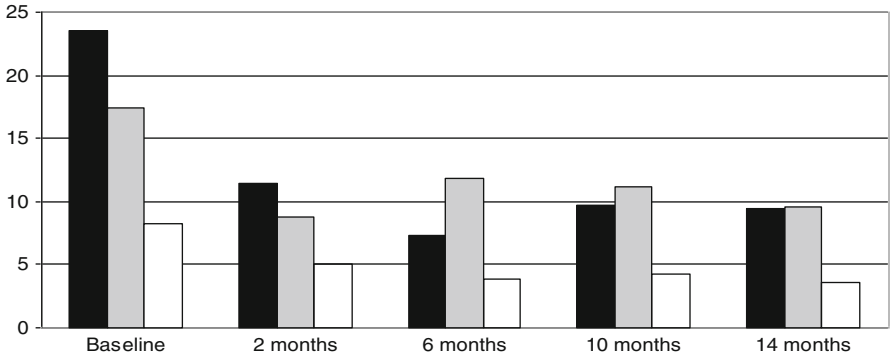

Fig. 5.2 Open-label study of onaA in cLBP with 14 months follow-up: *OLBPQ* Oswestry Low Back Pain Questionnaire (range 0–50), *PIQ* Pain Impact Questionnaire, *VAS* visual analog scale (range 0–10 cm). Compare to baseline *P* values for all three measures (<0.05). Mean pain days (PIQ), *dark*; OLBPQ, *gray*; and VAS, *white*, values before treatment and at 2 months after each treatment (injections are given at baseline and for most patients at 4, 8, and 12 months). Pain days and VAS are assessed over the preceding 28 days (Jabbari et al. 2006. © 2006, John Wiley and Sons)

Evidence for Efficacy of BoNTs in Chronic Low Back Pain

Two studies published from the Walter Reed Army Medical Center (WRAMC) first addressed the issue of BoNT efficacy, tolerability, safety, and quality of life in chronic LBP. The first study was double blind and placebo controlled (Foster et al. 2001). The second one was open label and prospectively assessed multiple treatment results (every 4 months) over a period of 14 months (Jabbari et al. 2006). Both studies used a similar protocol in respect to technique, dosing, and rating scales. The technique was based on the hypothesis that treatment results may not be optimal unless the whole length of erector spinae (ES) muscles in the lumbar region is exposed to and influenced by BoNT therapy. Hence, regardless of the location of pain or tender/trigger points (if present), injections were performed at five lumbar paraspinal levels (into lumbar ES) with a total dose of 200 units for unilateral LBP (blinded study) and 400–500 units for bilateral LBP (open study) (Fig. 5.2). Both studies used onabotulinumtoxinA (onaA). The third study performed by a different group reported on efficacy of aboA in a group of patients with chronic low back pain due to myofascial pain syndrome.

Study 1 (Foster et al. 2001)

Class II (using AAN criteria, Appendices 3.1 and 3.2). In this first blinded and placebo-controlled study of a BoNT in chronic low back pain, investigators randomized 31 subjects, 15 into the BoNT group and 16 into the placebo group. The inclusion criteria consisted of LBP of more than 6 months duration, unilateral or predominately unilateral LBP (level of 4 or more at visual analog scale (VAS)),

failure to respond to at least two major medications, and patients of 18 years or older. The exclusion criteria consisted of known hypersensitivity to onaA; pregnancy or planned pregnancy; presence of neuromuscular junction disorders; being on medications known to cause neuromuscular junction dysfunction; MRI evidence of severe disc disease, canal stenosis, or acute lesions of lumbosacral area requiring urgent medical or surgical intervention; and anesthetic or corticosteroid injections to the lumbosacral spine within 12 weeks of enrollment. Patients who were involved in litigation, seeking significant disability for low back pain, or with evidence of secondary gain were also excluded. The mean age of the study group was 46.4 years for onaA group and 47 years for the control group (range 20–73). The mean duration of pain was 8.1 years for the BoNT-A group and 5.7 years for the control group (range 6 months to 30 years). Patients were instructed to continue their analgesic medications during the study but not to change the dose, while avoiding new analgesics altogether. They were also instructed to make no changes in their physical therapy regimen as prescribed by routine clinical practice.

In the BoNT group, each patient received a total of 200 units of onabotulinumtoxinA (onaA) into the erector spinae (ES) on the side of unilateral or predominately unilateral pain. The ES muscle was injected at 5 points, L1, L2, L3, L4, and L5 levels, 40 units per level regardless of pain location. The dilution used was 100 units/cc. The baseline level of pain and degree of disability were documented by using the visual analog scale (VAS) and the Oswestry Low Back Pain Questionnaire (OLBPQ). Evaluations were performed at baseline, 3 and 8 weeks using VAS, and at baseline and 8 weeks with OLBPQ. The primary outcome measure was 50 % or more reduction in pain as defined by VAS at 8 weeks.

At 3 weeks, 11 of 15 subjects who received onaA (73.3 %) had >50 % pain relief versus 4 of 16 (25 %) in the control group ($p=0.012$). At 8 weeks, 9 of 15 (60 %) subjects in the onaA group and 2 of 16 (12.5 %) in the control group expressed relief ($p=0.009$). A repeat OLBPQ at 8 weeks showed significant improvement of quality of life in 10 of 15 (66.7 %) in the BoNT group versus 3 of 16 (18.8 %) in the control group ($p=0.011$). None of the patients experienced any side effects. It was concluded that paraspinal administration of onabotulinumtoxinA at five lumbar levels into ES is safe and can relieve pain and improve the quality of life in patients with predominantly unilateral chronic low back pain.

Study 2 (Jabbari et al. 2006)

Prospective, open label with repeated injections, 14 months. In this prospective study, the effect of BoNT-A on chronic LBP was investigated over a period of 16 months. The cohort consisted of 75 patients with chronic LBP refractory to medical or surgical treatment. The inclusion and exclusion criteria were the same as those of Study 1 with the exception of including patients with bilateral low back pain. The dose and technique were also similar to Study 1, with a minor modification (an extra dose of 10–20 units was administered more laterally into the bulk of

the erector muscles at the level of most discomfort). The patients had a mean age of 46.1 years (range 21–79) and mean pain duration of 9.2 years (range 7 months to 50 years). Of the 75 patients, 21 were female and 84 % of the entire cohort had bilateral pain. Other factors noted among the cohort included previous back surgery (n:14), root pain (n:20), epidural steroid injections (n:19), and narcotic analgesic use (n:36). Magnetic resonance imaging (MRI) showed a variety of low back pathology (50 %), but none were severe or acute. The most common pathologies consisted of chronic degeneration of the spine, canal stenosis, and chronic disc protrusions. Patients were instructed not to change their analgesic medications and continue with their physical therapy during the course of the study. Pain intensity (VAS), pain frequency (pain days measured in the Pain Impact Questionnaire (PIQ), Oswestry Low Back Pain Questionnaire (OLBPQ)), and patient level of satisfaction were assessed at baseline, 3 weeks, and at 2, 4, 6, 8, 10, 12, and 14 months. OnaA was injected into the paraspinal muscles at four to five levels (between L1 and S1) unilaterally or bilaterally depending on individual patient's pattern of pain. The dose per site was 40 units with exceptional patients receiving an additional 40–50 units at one level (more laterally) if the local area of pain extended laterally. The total dose per session ranged from 200 to 500 units. Re-injections were performed at 4 months if pain returned. Most patients had re-injections every 4 months. At 3 weeks, 40 patients (53 %) and, at 2 months, 39 patients (52 %) reported significant pain relief. The change in mean VAS, mean OLBPQ, and PIQ was significant compared to the baseline at 2 months after each injection period ($p<0.005$) compared to baseline and remained so over subsequent treatments. Among initial responders, 91 % continued to respond over the length of the study (Figs. 5.1 and 5.3). Nine of 20 patients (45 %) with root pain reported diminished root pain after treatment. After the first treatment, three patients (4 %) had mild flu-like symptoms which lasted 2–5 days. No other side effects were noted.

Study 3 (De Andres et al. 2010)

The authors enrolled a total of 28 patients (20 females) with chronic myofascial pain in the low back region. All patients had distinct trigger points which upon pressure evoked intense referred pain. The involved muscle distribution was as follows: psoas (18.5 %), quadratus lumborum (18.5 %), and psoas plus quadratus lumborum (63 %). The study was designed to evaluate prospectively and blindly the efficacy of onabotulinumtoxinA versus saline or bupivacaine. Twenty-seven patients completed the study. All patient received unilateral onaA injections into quadratus lumborum and iliopsoas (IS) muscles. On the contralateral side, 13 patients received bupivacaine (0.25 %), and 14 subjects received NaCl (0.9 %). The injected onaA solution was 100 units/cc. Each muscle (QL or IS) received 50 units fluoroscopically, injected deep into the muscle at one site.

Inclusion criteria were as follows: mechanical low back pain longer than 6 months duration; age 20–70; existence of bilateral trigger points with associated referred

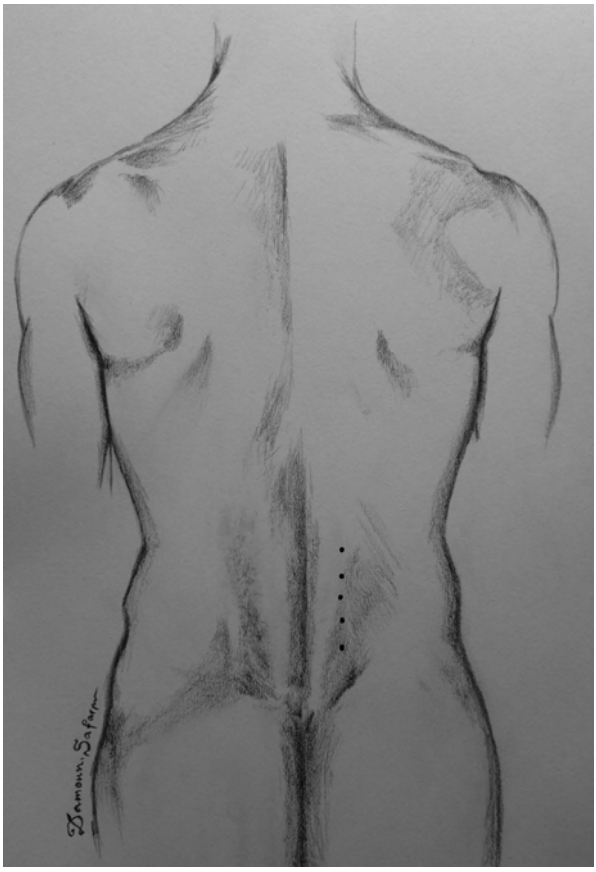

Fig. 5.3 Recommended locations of BoNT injection for chronic low back pain (Created by Damoun Safarpour; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

pain in the iliopsoas muscle, quadratus lumborum muscle, or both; and no response to conservative medical and physical therapy. Patients with previous back surgery, spondylolisthesis, facet joints arthropathy, known or suspected hypersensitivity to BoNTs, neurologic deficits in the painful area, neuromuscular junction or motor neuron diseases, diagnosis of fibromyalgia, and inflammation or infection of the injection sites were excluded.

The primary outcome was the difference between VAS score on the side of BoNT injection and the side of saline or bupivacaine injection at 15, 30, and 90 days. Authors used five different questionnaires to evaluate the effects of treatment on daily life activities and psychological status of the patients (Hospital Anxiety and Depression scale [HAD-A and HAD-D], Lattinen, Oswestry, and Spielberger State-Trait Anxiety Index).

OnaA administration did not significantly reduce VAS scores compared with contralateral NaCl or bupivacaine injections. Nonetheless, a trend toward significance was seen only in the BoNT group in respect to VAS score. The authors, however, concluded that administration of onaA provided the subjects with significant pain relief but cautioned against its cost.

Table 5.1 Yale Study: Assessment of efficacy of abobotulinumtoxinA in chronic low back pain

	Week 0 Visit 1	Week 4 Telephone	Week 6 Visit 2	Week 8 Telephone	Week 10 Telephone	Week 12 Visit 3	Week 14 Telephone	Week 16 Visit 4
Eligibility, consent	X							
History/ physical	X		X			X		X
VAS	X	X	X	X	X	X	X	X
ACPA's QoL scale	X		X			X		X
SF-36	X		X			X		X
PGIC		X	X	X	X	X	X	X
Oswestry scale	X		X			X		X
Side effects		X	X	X	X	X	X	X
Injection	X							

VAS visual analog scale, *ACPA's QoL scale* American Chronic Pain Association's Quality of Life Scale, *SF-36* Short Form-36 quality of life questionnaire, *Oswestry scale* oswestry low back pain disability questionnaire, *PGIC* patient global impression of change

Yale Ongoing BoNT/Low Back Pain Protocol

There is an ongoing, investigator-initiated, single-center protocol at Yale to assess the efficacy and safety of abobotulinumtoxinA (aboA) in patients with chronic low back pain, funded by Ipsen Pharmaceuticals. A total of 90 subjects will be enrolled allowing for 12 % dropout. The inclusion criteria consist of age over 18 years, uni- or bilateral low back pain of more than 6 months duration, failure to respond to pain medications, and a pain level of >4 in VAS. Exclusion criteria are as shown in Ipsen brochure and similar to those of the aforementioned WRAMC studies. Subjects with a history of prior back surgery are excluded. aboA is injected into erector spinae muscles unilaterally or bilaterally (depending on their pain pattern). The total dose per site is 500 units (approximately equal to 200 units of onaA). Each lumbar ES is injected at levels L1, L2, L3, L4, and L5 and with100 units of aboA per level. Table 5.1 shows rating scales and frequency of evaluations in this study. The primary outcome of the study is the proportion of patients with VAS <4 in aboA group compared to placebo at week 6. So far, 33 patients have been enrolled, and 22 patients have completed the study. Table 5.1 shows the design of the ongoing Yale study for assessment of efficacy and safety of abobotulinumtoxinA in chronic low back pain.

Patient 5-1

A 57-year-old Caucasian male suffered from chronic low back pain for 10 years. The pain began insidiously, gradually increased in intensity, and became daily over the past 2 years. The pain concentrated in the lower lumbar region. He described no

radicular pain. Episodes of severe exacerbations were frequent and disabling. Severe episodes were rated as 10 out of 10 on VAS scale. He used a large number of analgesic medications over several years with no relief. His last pain medication was gabapentin (800 mg three times daily) and Cymbalta (90 mg daily). The patient was taking oxcarbazepine (600 mg twice daily) and lamotrigine (200 mg twice daily for depression). Lumbosacral magnetic resonance imaging disclosed no significant abnormality and only mild degenerative changes. Neurological examination including assessment of cognition, cranial nerve, motor, sensory, and cerebellar functions, speech, and gait was normal.

AbobotulinumtoxinA (aboA), 500 units on each side (100 units per each lumbar level), was injected into the erector spinae muscles under EMG guidance (Video 5.1). Patient was evaluated monthly with VAS and patient global impression of change for 4 months. Two weeks after the initial treatment, he reported absence of low back pain. VAS scores at months 1, 2, 3, and 4 were at 0, 1, 1, and 2 levels, respectively. At 4 months, he reported his experience with aboA treatment as very satisfactory (Video 5.2, patient interview). There were no side effects.

How Does the Administration of Botulinum Toxin Improve Low Back Pain?

The exact mode of action of botulinum toxin A in chronic low back pain still remains to be determined. Based on animal and human research data, several plausible mechanisms exist:

1. In muscles, both A and B toxins produce relaxation via inhibiting the release of acetylcholine in the neuromuscular junction. This could explain some of the pain relief especially when low back pain is associated with muscle spasms. Furthermore, decreased muscle tone is often associated with a reduction in muscle bulk as well documented when BoNTs are used in hyperactive movement disorders. This decrease in muscle bulk (especially in the ES muscle) may be helpful when back pain is attributed to anatomically tight compartment (lumbar compartment syndrome Nathan et al. 2012).
2. As described under pathophysiology of cLBP, many causative factors, especially protruded disc, produce marked accumulation of pain mediators (CGRP, substance P) and inflammatory agents (cytokines) in DRG causing its hyperexcitability and leading to peripheral sensitization (PS). In animal studies, peripherally injected rimabotulinumtoxinB blocks release of substance P from DRG and dorsal horn neurons and reduces dorsal horn neuronal activation (c-Fos) evoked by formalin injection (Marino et al. 2014). Furthermore, local trauma and ruptured disc initiate local accumulation of glutamate, a potent pain mediator, which also can enhance PS (Harrington et al. 2000). In the formalin model of pain, pretreatment of rat's paw with local administration of onaA (a week before formalin injection) significantly reduces local accumulation of glutamate and local

inflammation relieving the pain related to formalin application (Cui et al. 2004). In human, injection of five units of onaA into the temporalis muscle following introduction of 0.2 cc/1 mol of glutamate markedly reduces glutamate-generated pain within hours of administration (da Silva et al. 2014).

3. It has been shown that both development of inflammation in DRG and increased pain mediators within it are enhanced by extensive sprouting of sympathetic fibers into DRG after peripheral nerve injury (McLachlan et al. 1993), and sympathectomy or removal of sympathetic ganglia can reduce accumulation of inflammatory agents and pain mediators in DRG caused by disc protrusion (McLachlan and Hu 2014). In this regard, Rand and Whaler (1965) have shown that peripheral injection of onabotulinumtoxinA impairs sympathetic transmission and, hence, has the potential to reduce pain mediators and inflammatory agents.
4. The aforementioned effects of BoNTs can all reduce central sensitization (CS) via their primary suppressing effect on peripheral sensitization (PS). Moreover, intramuscular administration of onaA may reduce central sensitization via its suppressing effect on muscle spindle discharge (Filippi et al. 1993). Muscle spindles are one of the major sources of non-nociceptive input to the central nervous system reporting muscle length to CNS. In chronic pain disorders with established CS, wide range function spinal cord neurons perceive non-nociceptive stimuli as nociceptive (Robert 1968). Reducing the input from muscle spindles can reduce central sensitization.

Comment

Chronic low back pain is a complex disorder with heterogeneous causes and still poorly understood pathophysiology. The preliminary data, mainly from WRAMC studies, indicate that at least half of the patients with chronic low back pain, regardless of etiology, respond well to injection of onaA into erector spinae muscles. The technique uses 40 units at each of five lumbar levels (total of 200 units for one side). The 16-month follow-up study with three to four cycles of injection (using the same dose and technique) have supported the long-term efficacy of this technique, good patient tolerability, and safety of onaA treatment in chronic low back pain.

Although the investigators were worried about possible weakening effects of onaA in applied doses, none of the studied subjects in either of the two studies (blinded and open) complained of muscle weakness or impaired ambulation. However, the studied population in the WRAMC protocol included many (almost half) younger, muscular, and otherwise healthy military subjects with mechanical chronic low back pain. Therefore, the safety data in this study may not necessarily apply to older, thin, and fragile subjects with chronic low back pain; when treating such older, fragile patients, initial approach should be more conservative. The positive effect of WRAMC protocol was rated as C level of evidence (possibly effective) (one class II study) by AAN assessment subcommittee (Naumann et al. 2008).

The positive effect of onaA on cLBP is probably multifactorial pertaining to some the mechanisms outlined above.

The study of De Andres et al. (2010) showed only a trend of significance in the onaA group compared to the anesthetic and saline groups. The results of this study cannot be compared with that of the WRAMC protocol due to the significant differences between the two populations in regard to: (1) the study cohort (their patients all had MFPS with distinct trigger points) and (2) the injections pattern (QL and multifidus vs. ES injection in the WRAMC study), and (3) the total dose and number of sites injections (50 units total and 1 injection site versus 200 units with 5 injection sites in the WRAMC studies).

This author's experience with many patients whom he treated for chronic low back pain (mostly with onaA) during the past 15 years agrees with the results of WRAMC studies, i.e., approximately half of the patients report significant pain relief and marked improvement of quality of life (Video 5.1, patient interview). Video 5.2 demonstrates EMG-guided BoNT-A injection in the patient of Video 5.1. Much work still needs to be done in the area of cLBP with BoNTs. Due to the heterogeneity of chronic low back pain's etiology, future studies should focus on etiologically distinct subgroups of cLBP. Perhaps, it would be advantageous to use WRAMC's protocol first in such studies since it has already shown some promise in this area.

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Chapter 6
Botulinum Toxin Treatment of Plantar Fasciitis (Plantar Fasciopathy)

Abstract Plantar fasciitis/fasciopathy (PF) is a common problem which affects two million people in the USA and 10 % of runners. The symptoms of heel pain and foot discomfort can interfere with daily functions and are often disabling in the chronic form of PF. Commonly used treatments for symptoms of plantar fasciitis include stretching, taping, night splints, orthosis, nonsteroidal anti-inflammatory medications, iontophoresis, steroid injections, ultrasound extracorporeal and intracorporeal shock waves, acupuncture, and cryosurgery. With most of these approaches, improvement is short lived, and some approaches (i.e., shock wave therapy) are very painful and often require prior nerve block. Furthermore, injection of steroids can cause rupture of the plantar fascia. Clearly, an effective and safe therapeutic approach without substantial side effect is very much needed for PF. Local injection of botulinum toxin A is a relatively novel treatment for PF. The results of two double-blind, placebo-controlled studies have supported its efficacy (level B). A comparator-blinded study has shown that BoNT-A is more effective than betamethasone in relieving pain and improving function at 6 months. Furthermore, the positive effect of ona- and abobotulinumtoxinA lasted often beyond 6 months, and the injections caused no side effects. In this chapter, various therapeutic approaches for management of PF are presented with emphasis on botulinum toxins and their advantages.

Keywords Plantar fasciitis • Plantar fasciopathy • Heal pain • Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA • AbobotulinumtoxinA

Introduction

Plantar fasciitis (PF), also referred to as plantar fasciopathy, is a clinical condition caused by degeneration, inflammation, and micro-tears of foot's plantar fascia; plantar fasciitis is a major cause of heal pain. It is a common ailment among individuals whose work involves substantial foot activity (Thomas et al. 2010). Approximately

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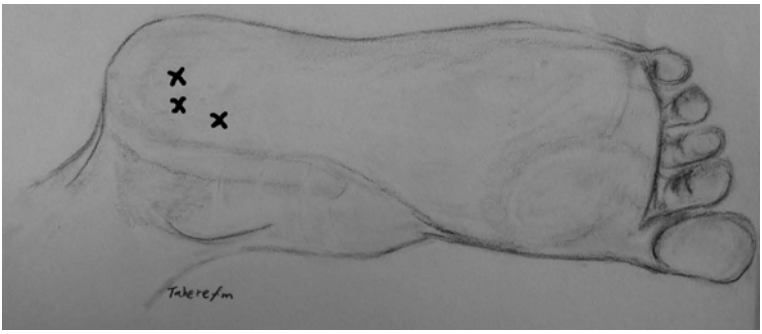

Fig. 6.1 The usual location of pain in plantar fasciitis (Created by Tahereh Mousari; Published with kind permission of © Bahman Jabbari 2014. All Rights Reserved)

10 % of runners have symptoms of PF (Chandler and Kibler 1993). In the USA, PF affects two million people and accounts for a million visits to physicians' offices annually (Berbrayer and Fredericson 2014). Many patients, however, improve spontaneously after months of discomfort. PF may progress into a chronic form with refractory pain, challenging management in 10 % of the patients (Janister et al. 2014).

Two recent publications (Tahririan et al. 2012; Berbrayer and Fredericson 2014) have updated the clinical spectrum of and treatment options for plantar fasciitis. The pain usually affects the medial side of the heel at the insertion area of plantar fascia (Fig. 6.1). Some patients may experience pain at the middle of the foot (middle of the central band of the fascia), while in others, the pain may spread to the entire foot including the toes. The pain is most noticeable during the initial steps of walking or running. The pain is enhanced by long periods of inactivity preceding activity; weight bearing also worsens the pain. In the chronic form (lasting beyond 6 months), calcaneal pain may be experienced at rest and prevent sleep. One third of the patients complain of bilateral pain. On examination, the foot looks normal, and no weakness is detectable, but approximately 80 % of the patients experience associated tightness of the Achilles tendon (Singh et al. 1997). In some patients, the skin over the medial calcaneal tuberosity is tender, and this tenderness is exaggerated on dorsiflexion of the toes or when standing on tiptoe (Young et al. 2001).

Anatomy of Plantar Fascia

In a recent communication, (Stecco et al. 2013) described the anatomy of plantar fascia and its relationship to the Achilles tendon and adjacent muscles in detail. The authors studied anatomy of the foot in 11 cadavers (mean age 72; 6 males and 5 females). Serial transversal sections were obtained every 2 cm from the cutis to the interosseous muscles in order to microscopically examine the relationships between the PF, skin, and muscles. Beneath the skin and the underlying fat pad of the foot, PF appears as a glistening, pearl-colored structure extending from the calcaneus to the metatarsophalangeal (MP) joints. The length of PF is approximately 12 cm from the medial tuberculum to the MP joint. The thickness of PF diminishes significantly

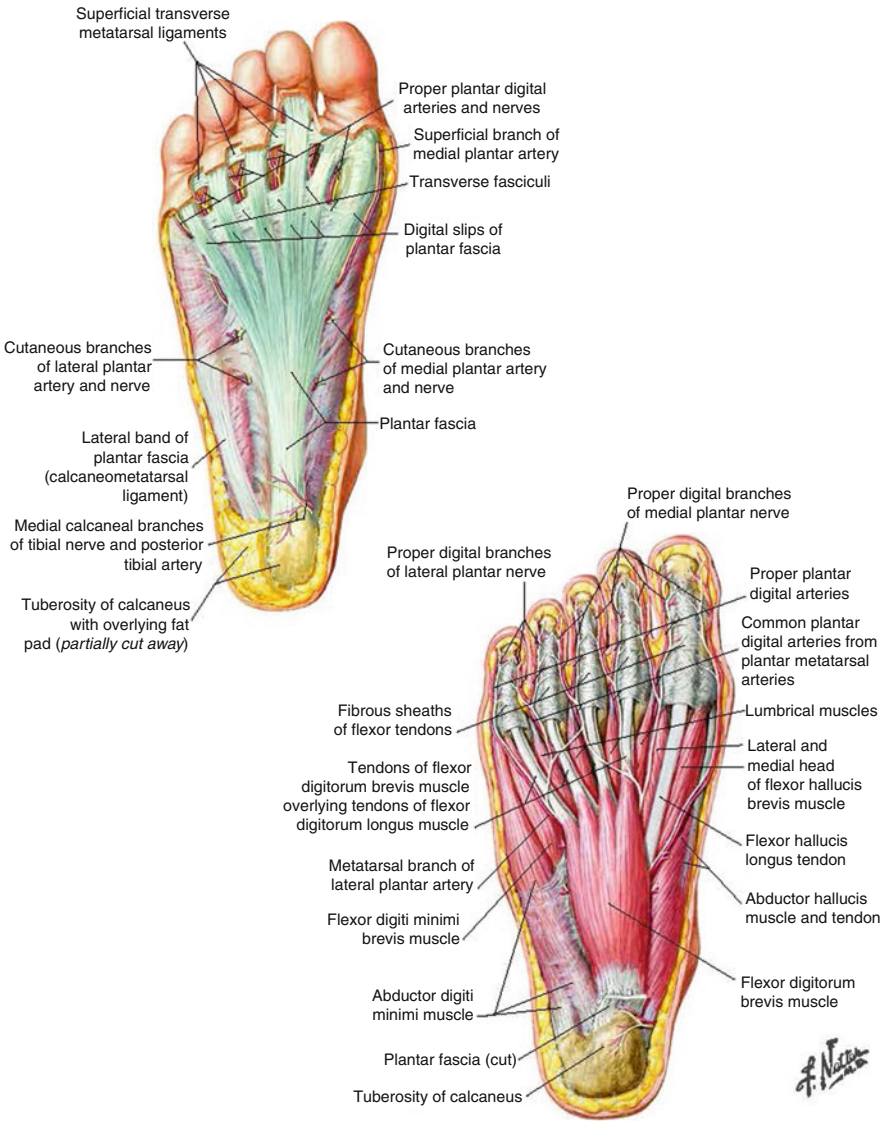

Fig. 6.2 Anatomy of the plantar fascia and the subfascial muscles (From Netter collection. Netter illustration used with permission of Elsevier, Inc. All rights reserved. www.netterimages.com)

as it extends toward the MP joints. At 2 cm from the insertion of the calcaneus, PF is 3.15 mm thick at its center and 1.56 mm laterally. At 10 cm from the insertion point, PF's thickness is 1.41 mm at its center and 0.66 mm laterally.

Most PF fibers are arranged longitudinally, but some fibers are oblique, and a few are transverse; the fibers close to the proximal and distal insertions may have transverse arrangement. PF is arranged into three longitudinal fiber groups: medial, central, and lateral (Fig. 6.2). At the heel, PF fibers are attached to the medial part of the calcaneum (medial tuberculum), cover the heel as a thin layer, and continue into the

Achilles tendon. Beneath PF are the deep fascias of the foot which embed three major foot muscles, the flexor hallucis, the flexor digitorum brevis, and the flexor digiti minimi. Septa from PF penetrate the deep fascia and connect at different points with all three muscles. Close to the metacarpophalangeal joints, PF divides into five segments each attaching to a metacarpophalangeal joint. The fibers of PF are rich in collagen type 1 but also contain hyaluronan which helps PF fibers to easily glide and work like a shock absorber. Plantar fascia is innervated by the terminal branches of the tibial nerve and medial calcaneal and medial and lateral tibial nerves. Plantar fascia is well innervated specially in its medial and lateral parts; it contains an abundance of Pacinian and Ruffinian corpuscles suggesting a role for it in the sole's proprioception (Stecco et al. 2013).

Pathophysiology of Plantar Fasciitis

The plantar fascia serves both astatic and a dynamic purpose. The static function deals with weight bearing; it supports the arch of the foot. The fascia contracts and elongates during walking allowing the medial arch to flatten and elevate—the so-called wind glass phenomenon (dynamic phase).

Despite the fact that PF is a clinically well recognized, the details of its pathophysiology remain elusive. Most recent data indicate the pathological changes are more in the form of degeneration (fasciopathy) rather than inflammation (fasciitis) of the fascia, although some elements of the latter are also present. Repetitive trauma to the fascia invariably is a major contributing factor to PF; PF is also more common among overweight individuals. Heel spurs are also common in association with plantar fasciitis suggesting a relation to PF's pathophysiology.

The role of triceps surae muscles in the pathophysiology of PF is increasingly recognized. Contraction of plantar flexor muscles and loss of flexibility of these muscles are proposed as risk factors for the development of plantar fasciitis (Cheung et al. 2006; Kibler et al. 1991). This view is supported by a recent detailed anatomopathological evaluation of PF which demonstrated a high correlation between Achilles tendonitis and PF. Radiologically, a PF thickness of 4 mm or more correlates with clinically active PF. In the study of Stecco et al. (2014), 5 of 27 patients with Achilles tendonitis had a PF thickness of 4.5 mm or more versus none of those in whom radiological data did not support the presence of Achilles tendonitis and PF.

Treatment of Plantar Fasciitis

Recently, Berbrayer and Fredericson (2014) reviewed the literature on current treatment of plantar fasciopathy/fasciitis and provided an evidence-based account of

efficacy of several therapeutic approaches. Depending on the quality of the studies, the level of efficacy was simply rated as low, medium, or high. Treatment modalities for acute (less than 3 months duration), subacute (3–6 months duration), and chronic (>6 months duration) were described individually.

In this section, the information on treatment of plantar fasciopathy/fasciitis, for the most part, is derived from Berbyer and Fredericson's review. Following this section, a review of the literature on BoNT treatment of plantar fasciitis will be provided using the level of evidence and efficacy (A, B, C, U) according to the guidelines of the American Academy of Neurology (Appendices 3.1 and 3.2).

Acute Phase

The recommended treatment in this stage consists of stretching exercises, foot orthosis, soft tissue trigger point manual therapy, calcaneal taping, iontophoresis, and treatment with nonsteroidal anti-inflammatory agents (NSAID).

Stretching Exercises

Three randomized trials are available with different types of stretching exercises employed in the studies: Achilles stretching and stretching of planter fascia that can be performed with either weight bearing or non-weight bearing and intermittent versus sustained. Stretching is usually performed several times daily and provides 2–4 months relief in the acute phase. The review concluded that stretching is effective in reducing pain and improving function in the acute phase.

Foot Orthosis

Foot orthosis is commonly used in patients with PF. Both over-the-counter and customized orthotics can be used. In a multicenter study of 236 patients, foot orthosis (prefabricated) plus stretching was found to be superior to stretching alone ($P = 0.022$) (Pfeffer et al. 1999). Foot orthosis can be used in all stages of PF.

Soft Tissue Trigger Point Manual Therapy

Retrospective studies suggest temporary reduction of pain in the acute phase using soft tissue trigger point manual therapy.

Iontophoresis

Two double-blind, placebo-controlled studies are available. In the first study of 40 ft from 31 patients, dexamethasone iontophoresis was found superior to placebo and relieved pain for 2 weeks; no long-term benefits were noted, however (Gudeman et al. 1997). In the second study (Osborne and Alison 2006), 43 feet from 31 subjects were studied in three groups: iontophoresis (1) with 0.5 % acetic acid, (2) with 4 % dexamethasone, and (3) with placebo. The investigators found acetic acid to be more effective than steroid iontophoresis and relieved pain for 2–4 weeks.

Calcaneal taping was shown to be effective in reducing pain in two prospective blinded studies (Lynch et al. 1998; Hyland 2006). However, this is a very short-term remedy due to skin breakdown that develops after prolonged taping.

Nonsteroidal, Anti-inflammatory Agents

Only one double-blind, placebo-controlled study is available pertaining to the use of NSAIDs in PF. Donely et al. (2007) studied 29 patients with PF. All patients were using a heal cord stretcher and night splints. NSAID was added to their ongoing treatment. Modest improvement of pain was noted by adding NSAID to the ongoing treatment (low level).

Subacute Stage

Steroid therapy and acupuncture are both considered options for this stage. Placebo-controlled studies are scarce. Mc Millan et al. (2012) showed the efficacy of ultrasound-guided dexamethasone over placebo at 4 weeks after treatment ($P = 0.03$). Several open studies also showed a short-term pain relief from prednisone in PF. A major issue with steroid therapy is rupture of the plantar fascia that occurs in 10 % of the patients following injection.

Acupuncture

Zhang et al. (2011) studied two groups of subjects (28 in each) blindly with two different techniques of acupuncture (one used as control). One group received acupuncture in acupoint pc7 a location known to affect heel pain. For the group, acupoint Hegu that has some pain properties was used. The primary outcome was perception of significantly lower heal pain at 1 month post acupuncture. A second study (Karagounis et al. 2011) compared acupuncture with NSAID treatment, and primary outcomes were measured at 1 and 2 months. Neither study met their

primary end point, but both showed considerably more reduction of pain in the acupuncture group.

Chronic Phase

Treatment options for the chronic phase include night splint, extracorporeal shock wave treatment, intracorporeal shock wave treatment, cryosurgery, percutaneous needle fasciotomy, plasma-rich platelet, and botulinum toxin therapy.

Night Splint

Night splint may be helpful in patients who suffer most of their heal pains in the morning. EZ step night splint in combination with NSAID helped 85 % of the patients in one study of patients with PF (Al-Bluwi et al. 2011).

Shock Wave Treatment

A meta-analysis of 11 extracorporeal shock wave treatment studies (ESWT) in plantar fasciitis (four randomized and controlled) (Dizon et al. 2013) showed efficacy of this technique in reducing pain in PF. One of the four controlled studies projected significant pain reduction at 12 months posttreatment. Intracorporeal shock wave treatment (ICST) is a more recent methodology where shock waves are applied directly to calcaneal spur under fluoroscopy. High-energy ECST requires nerve block since it is very painful. Dogramaci et al. (2010) assessed the efficacy of ICST in 50 patients with PF in a blinded, placebo-controlled study. Excellent and good results were significantly higher in the ICST group compared to the placebo group (92 % versus 24 % $P=0.02$). Complications consisted of hematoma, infection, and fascial rupture.

Cryosurgery

This is a minimally invasive, percutaneous technique which uses the tip of a cryoscope to freeze and destroy intracellular elements of the nerve in PF without destroying epineurium and soft tissue or forming neuromas. No blinded studies are available. One prospective study of 59 patients (Allen et al. 2007) demonstrated significant improvement in heel pain ($P<0.0001$) in 90 % of the patients at 1 year post-procedure. The major side effect was appearance of pain in the other foot regions which resolved in 3–4 weeks.

Platelet-Rich Plasma

This is a new therapeutic modality which aims to reduce degeneration and promote healing by local introduction of platelet-rich plasma which contains an abundance of cytokines. A recent review of the few available prospective studies showed no clear evidence of efficacy in PF (Vannini et al. 2014).

BoNT Treatment of Plantar Fasciitis

The first prospective, placebo-controlled, blinded investigation on efficacy of BoNTs in plantar fasciitis was conducted at the Walter Reed Army Medical Center (WRAMC) in 2005 (Babcock et al. 2005). This study investigated efficacy of onabotulinumtoxinA in 27 subjects (a total of 43 ft) with chronic plantar fasciitis. All patients had chronic PF with the duration of their symptoms exceeding 6 months. Subjects were recruited from the departments of neurology and physical medicine of WRAMC. Those with pending litigation and secondary gain and those who were on narcotics were excluded. The dilution used was 100 units/cc. OnabotulinumtoxinA (onaA) was introduced through a 0.75 inch needle into two points. The first point, the tender area in the medial aspect of the heel near the calcaneal tuberosity, received 40 units. The second point, between posterior line of the heel and middle of the foot, received 30 units. The total dose of onaA per foot was 70 units (Fig. 6.3). Controls received the same volume of normal saline solution at the same sites. Patients with bilateral symptoms received an injection of onabotulinumtoxinA in one foot and an injection of saline solution in the contralateral foot.

Pain visual analog scale, Maryland Foot Score, pain relief visual analog scale, and pressure algometry response were assessed before injection, at 3 weeks, and at

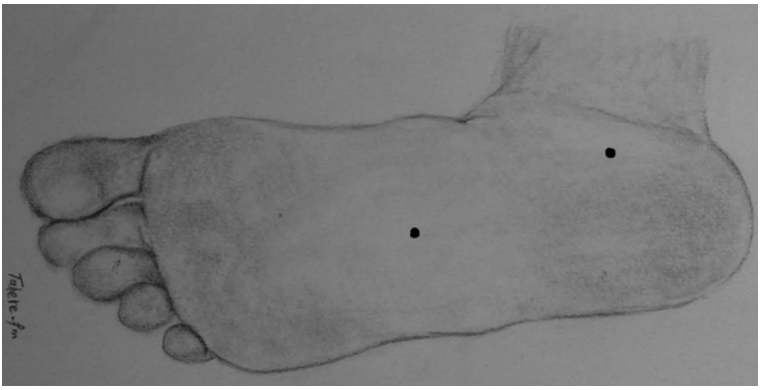

Fig. 6.3 Site of BoNT injection for treatment of plantar fasciitis (Created by Tahereh Mousari; Published with kind permission of © Bahman Ja-bbari 2014. All Rights Reserved)

8 weeks. The primary outcome was improvement of the visual analog scale for pain. The study revealed statistically significant changes in the treatment group. Compared with placebo injections, the botulinum toxin A group improved in all measures: pain visual analog scale ($P<0.005$), Maryland Foot Score ($P=0.001$), pain relief visual analog scale ($P<0.0005$), and the pressure algometry response ($P=0.003$). No side effects were noted by either the patients or the physicians.

In the same year, Placzek et al. (2005) reported on the effects of a single injection of botulinum toxin A in an open-label study of nine patients. All patients had PF and had failed at least two of these four treatments: physical therapy, custom/prefabricated orthotics, acupuncture, and extracorporeal shock therapy. A total dose of 200 units of aboA was injected subfascially in four directions through one puncture introduced at the origin of the plantar fascia. This single injection resulted in significant reduction of pain VAS scores from 2 weeks after injection to week 52 (weeks 2–39 $P=0.01$, week 52 $P=0.04$).

Huang et al. (2010) have conducted the second randomized double-blind study on 50 patients with chronic unilateral plantar fasciitis. Patients received either 50 units of onabotulinumtoxinA or a comparable volume of saline using ultrasonographic guidance. Outcome measures consisted of changes in VAS, gait assessment (the maximal center of pressure velocity during the first-step loading response), and measurement of the thickness of the plantar fascia and the fat pad. Assessments were made at baseline, 3 weeks, and 3 months after the injection.

At 3 weeks and 3 months, both VAS score and plantar fascial thickness (measured by sonography) decreased significantly ($P<0.001$) in the symptomatic foot. Injection of onaA caused no foot pad atrophy. No side effects were noted. The authors concluded that botulinum toxin A was safe and effective for treatment of chronic plantar fasciitis but recognized a need for long-term studies to confirm the findings.

Comparator Study

Díaz-Llopis et al. (2012) compared the efficacy and quality of life among patients using BoNT treatment or corticosteroid plus local anesthetic for their chronic plantar fasciitis. The study was single blind with 28 patients enrolled in each of the two groups. In the botulinum toxin group, the authors injected onabotulinumtoxinA into the plantar fascia using the same methodology and dose described by Babcock et al. (2005). The other group was given corticosteroid (betamethasone) plus local anesthetic (0.5 mL of 1 % mepivacaine) in the calcaneal tuberosity, the same area where botulinum toxin was injected in the first group. A number of different measures were used to evaluate the changes in pain and function in response to the two therapeutic approaches. At 1 month, both treatments improved all measures significantly, but onaA relieved pain more than betamethasone ($P=0.06$). At 6 months, the measures continued to improve further in the onaA group, while most of the improved values faded in the betamethasone group. Improvements with botulinum toxin vs.

corticosteroid were recorded as follows: pain 19.10/−6.84 ($P=0.001$), function 16.00/−8.80 ($P<0.001$), footwear 13.48/−7.95 ($P=0.004$), and self-perceived foot health 25.44/−5.41 ($P<0.001$).

Patient (6-1)

A 73-year-old gentleman, a tennis player, noted discomfort at the bottom of his feet approximately 8 years ago. The discomfort was particularly noticeable after playing a few games of tennis, and over months, it gradually developed into pain. The pain localized to the heels and around the medial part of both feet, and it often interrupted his game of tennis.

Over the years, the patient tried a variety of pharmacological and non-pharmacological measures for management of his heel pain. Stretching, orthosis, and night splints offered little help. Nonsteroidal anti-inflammatory drugs had minimal effect. A couple of sessions of acupuncture "helped some," but the effect lasted only a few days. Treatment with steroids did not help.

Following an Internet search and coming across BoNT literature and plantar fasciitis, the patient decided to visit the Yale Botulinum Toxin Clinic for an evaluation. His neurological examination including cognition; cranial nerve, sensory, motor, and cerebellar functions; speech; and gait was normal. He rated his pain during "bad days" as eight out of ten on VAS. He pointed to the regions of pain in his feet that mainly involved the heels but also extended to the center of the feet bilaterally.

Following an assessment of the distribution of the pain, onabotulinumtoxinA was injected into the bottom of both feet using the methodology of Babcock et al. (2005). A total of 70 units was injected (40 and 30 units at two points) (Fig. 6.3). Within days, the patient reported significant improvement of his heel pain; the pain relief lasted for 7 months. The second treatment with the same dose also produced pain relief for 7–8 months. For the third treatment, since emerging literature had suggested that tense triceps surae contribute to development of PF, an additional 30 units was injected into the soleus muscle. The patient came for his fourth treatment 9 months later and reported a longer period of relief and was very satisfied with the onaA treatment (Video 6.1: patient interview before the fourth treatment). He reported no side effects. Video 6.2 shows the technique for the fourth treatment that also includes injection into the soleus muscle.

How Does BoNT Improve Pain in PF?

Botulinum toxins influence and relieve pain via different mechanisms, largely through inhibition of pain mediator (calcitonin gene-related peptide, substance P, glutamate) release and anti-inflammatory effects (see Chap. 2). Additional

mechanism may be related to their effect on the major foot muscles such as flexor digitorum brevis and flexor pollicis brevis located beneath the fascia. Relaxation and diminished tone (possibly associated with decreased muscle bulk) of these muscles could decrease the tension of the fascia contributing to both generation and maintenance of pain. It is possible that injection close to the heal might also influence and relax the distal part of the soleus muscle. As discussed above, it is believed that increased tone of the Achilles tendon is significantly associated with PF and may even cause or enhance PF symptoms.

Comment

The current literature suggests that both onaA and aboA decrease pain and improve function in patients with chronic plantar fasciitis. The level of evidence is B (probably effective) for BoNT-A, based on two class II studies (Guidelines of AAN—Appendices 3.1 and 3.2). This is encouraging since treatment of chronic PF is difficult. Most results with pharmaceutical agents, NSAID or steroids, are short lived, and procedures (iontophoresis, acupuncture) are of short duration of benefit. Other therapeutic procedures such as shock therapy are themselves painful, and yet others may cause serious side effects (i.e., rupture of fascia after steroid therapy). Furthermore, the effect of botulinum toxin in PF usually lasts 6 months or longer.

For years, we used the technique designed and the dose proposed by our group while working at the WRAMC (Babcock et al. 2005). More recently, however, based on data emphasizing the increased tension of Achilles tendon, we have modified the technique by injecting an additional 20–30 units of botulinum toxin into the soleus muscle with good results (video, patient interview). Hopefully, as we learn more about the pathophysiology of plantar fasciitis, we can increase our success rate via designing better techniques and using more appropriate doses. The current literature's confirmation of the safety of BoNT in treatment of PF is in agreement with our experience.

Conclusion

Plantar fasciitis affects a large number of individuals (two million in the USA) and, in its chronic form, is a disabling condition. Current treatments for the chronic form of PF often cause temporary relief and have undesirable side effects. Botulinum neurotoxin A (ona and abo) provides pain relief and improves function; the beneficial effects last longer than other available therapies. Importantly, the approach is safe and well tolerated by patients. While we strive to identify better therapies, botulinum neurotoxin A is a useful option in management of PF.

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Chapter 7
Botulinum Toxin Treatment of Piriformis Syndrome

Abstract Piriformis syndrome is characterized by chronic buttock pain exacerbated by long periods of sitting. It is believed to be due to the irritation of nearby sciatic nerve (or one of its major divisions) by a tense and overactive piriformis muscle. Current treatments consist of stretching exercises, oral medications, and anesthetic or steroid injections; these approaches are only partially effective. Two double-blind, placebo-controlled studies have strongly supported the efficacy of onabotulinumtoxinA in management of piriformis syndrome. Two comparator studies favored onabotulinumtoxinA and abobotulinumtoxinA treatment over steroid injections in respect to both pain relief and duration of relief in piriformis syndrome. Limited open studies suggest that type B toxin (rimaB) is also effective. Botulinum neurotoxins provide a safe and effective treatment for relief of pain in piriformis syndrome.

Keywords Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA • AbobotulinumtoxinA • RimabotulinumtoxinB • Piriformis syndrome

Introduction

Piriformis syndrome (PS) is defined as a clinical condition characterized by irritation of the sciatic nerve caused by a tense and overactive piriformis muscle. The term piriformis syndrome was coined in 1947 by Robinson. Due to the difficulty in finding an exact pathology in many patients and lack of clear neuroimaging and electrophysiological data, some specialists have challenged the existence of this syndrome (Stewart 2003; Tiel 2008). It is currently believed, however, that the syndrome exists and is a cause of buttock pain and sciatica.

The true incidence of piriformis syndrome is not known. One investigator estimated that 6 % of all cases of sciatica represent PS (Hallin 1983). Based on this estimate, PS would affect a large number of people in the USA annually and, hence, pose a significant challenge for clinicians.

The factors that cause tension and contraction of the piriformis muscle, in most cases, are unknown. Trauma to the pelvis and gluteal area is considered a plausible etiology. Less common causes include disease of the sacroiliac joint, intragluteal

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Table 7.1 Clinical maneuvers employed to establish diagnosis of piriformis syndrome

Beatty maneuver (1994): patient lying in lateral decubitus position and actively abducting the extended thigh
Pace maneuver (1976): patient sits on a table and adducts the thigh against the examiner's hand
Freiberg maneuver: with patient in supine position and legs extended, the examiner passively internally rotates the whole leg
FAIR maneuver: with patient in supine position, the examiner passively flexes, adducts, and internally rotates the thigh

injections, myositis, hematoma, abscess, regional neoplasm, hypertrophy, and spasm of the piriformis muscle. Pain is the major symptom and it is often present during sitting or squatting. The pain mainly felt in the buttock may radiate down the thigh, or it may be felt in the low back region. On examination, pressure over the area of the sciatic notch may induce pain. In a review of 50 previously published papers on piriformis syndrome, Hopayian et al. (2010) found buttock pain (50–95 %), pain aggravated by sitting (39–97 %), and external tenderness near the greater sciatic notch (59–92 %) as the most common presenting symptoms of the syndrome. The "piriformis sign" is described as a tonic external rotation of the leg and is observed in 38.5 % of the patients (Durrani and Winnie 1991). A small number of patients may demonstrate mild muscle weakness related to sciatic nerve dysfunction. Diminished knee and ankle jerks occur infrequently. Certain maneuvers that generate buttock pain are considered supportive of the diagnosis of piriformis syndrome (Table 7.1). More details of clinical signs in piriformis syndrome are published in recent reviews (Kirschner et al. 2009; Miller et al. 2012; Jankovic et al. 2013; Michel et al. 2013).

In 2002, Fishman et al. proposed the following criteria for diagnosis of PS:

1. Positive Lasegue sign, flexion of the thigh when the leg is extended at 45°
2. Buttock pain during FAIR maneuver
3. Tenderness to touch at the sciatic notch or prolonged peroneal H-reflex when elicited during the FAIR maneuver

Absence of neuropathy or myopathy in electrodiagnostic studies is also supportive of diagnosis. Others have challenged some components of these criteria indicating that Lasegue sign is nonspecific and peroneal H-reflex is not that reliable (Campbell and Landau 2008).

Anatomy

Originating from the anterior border of the second, third, and fourth sacral bone segments and the superior margin of the greater sciatic notch, the piriformis muscle is triangular in shape. It attaches to the superior margin of the greater trochanter after passing (infero-latrerally) through the greater sciatic foramen. The muscle is

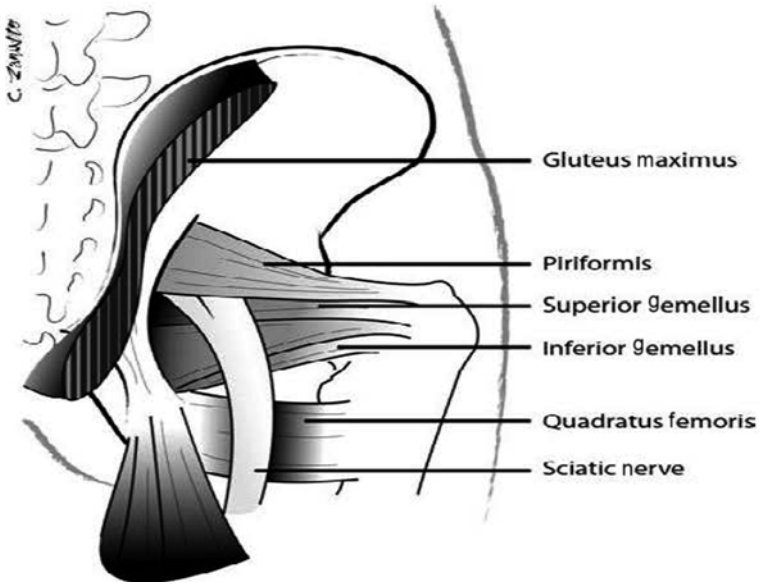

Fig. 7.1 Anatomy of piriformis muscle (From Miller et al. (2012). Reprinted with permission from John Wiley and Sons)

located deep in the thigh and is under the massive bulk of the gluteus maximus muscle. Superior and inferior gemellus muscles lie inferior to the piriformis (Fig. 7.1). The ventral rami of S1 and S2 nerve roots join and form the piriformis nerve which innervates the muscle. The piriformis muscle is an external rotator of the *extended* leg and an adductor of the *flexed* leg (Rodrigue and Hardy 2001).

The sciatic nerve is in close proximity of the piriformis muscle. Ventral rami of L4 to S3 nerve roots join and form the sciatic nerve at the inferior edge of the piriformis muscle (Fig. 7.1). This proximity makes the nerve vulnerable to pressure from an overactive muscle. Six variations of the anatomical relation of the sciatic nerve to the piriformis muscle have been described (Fig. 7.2). The most common variant noted in about 90 % of cases is characterized by the passing of the entire nerve trunk just under the inferior border of the piriformis muscle (Fig. 7.2, variant 1). In approximately 10 % of cases, other variants are seen. Natsis et al. (2014) painstakingly examined the relation of the piriformis muscle to the sciatic nerve in 147 cadavers. Currently, the precise contribution of the uncommon variants to the development of piriformis syndrome is not established. Some authors have suggested that when the nerve trunk or one of its branches (i.e., the peroneal) go through the muscle (variants 2 and 4, Fig. 7.2), the nerve becomes more susceptible to piriformis contraction. Future studies with focus on clinico-anatomical correlation and with more refined neuroimaging techniques could verify or refute these claims.

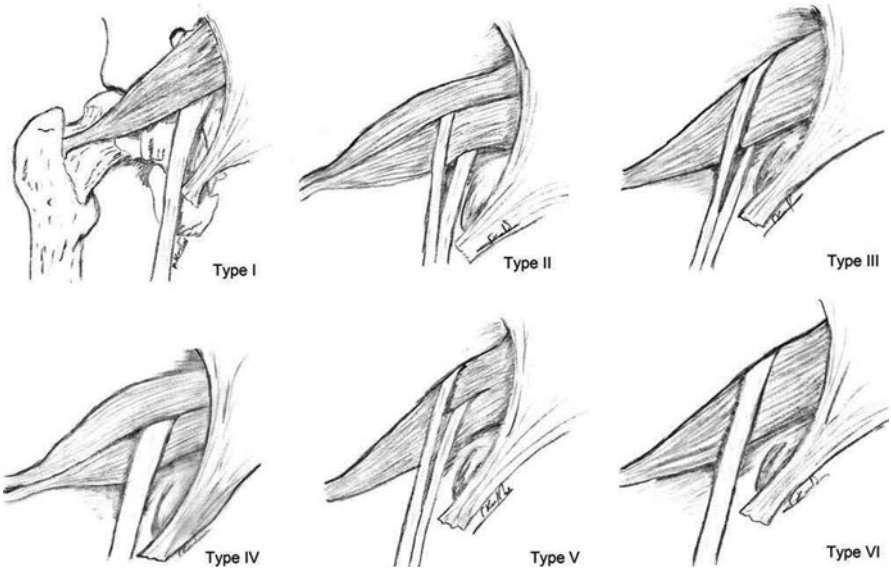

Fig. 7.2 Anatomical variations of sciatic nerve in relation to piriformis muscle (From Natsis et al. (2014). *Surgical Radiologic Anatomy*. 2013 Jul © 2014, Springer-Verlag France. Reprinted with permission)

Pathophysiology of the Piriformis Syndrome

There are currently two schools of thought regarding the mechanism of pain development which is the main symptom of the piriformis syndrome. One group considers the piriformis syndrome as a form of entrapment disorder in which pressure from the tense and contracted muscle against the sciatic nerve or its branch, the peroneal nerve (which in some individuals goes through the muscle), causes pain and discomfort in the buttock. Others postulate that PS is caused by an anomaly intrinsic to the piriformis muscle. The nature of this anomaly could be a large piriformis muscle or a tense and hyperactive one (dystonic?) or both. The two proposed mechanisms (entrapment vs. intrinsic muscle disorder) are not mutually exclusive and may coexist. Unfortunately, the data from neuroimaging and electrophysiology in piriformis syndrome are scant and not helpful in confirming or disputing any of these two possibilities.

From an electrophysiologic standpoint, Fishman et al. (2002a) hold the view that a prolongation of the peroneal H-reflex (3SD or more) when tested with the patient in FAIR position (activating the piriformis muscle; see Table 7.1) is helpful in diagnosis of piriformis syndrome. This view has been challenged by Campbell and Landau (2008) based on their own experience and support from the literature noting that peroneal H-reflex test is technically very difficult to perform and often is not obtainable in asymptomatic subjects.

Treatment of the Piriformis Syndrome (PS)

Treatment of PS consists of non-pharmacological measures such as physical therapy as well as medical and surgical approaches (Papadopoulos and Khan 2004; Kirschner et al. 2009; Jankovic et al. 2013). Physical therapy, as the first approach, focuses on stretching exercises of the piriformis muscle. A part of the program includes FAIR maneuver which, at the beginning, may be uncomfortable due to the associated induced pain. Gulledge et al. (2014) presented a refined stretching technique which lengthens the piriformis muscle. Heat and ultrasound therapy may enhance the effects of the stretching exercises (Krishner et al. 2012). Common analgesic agents, nonsteroidal anti-inflammatory drugs, and muscle relaxants focused on neuropathic pain (gabapentin and pregabalin) may be tried.

When oral medications fail and chronic pain interferes with daily tasks, injection of anesthetic agents or corticosteroids into the piriformis muscle can relieve pain. Unfortunately, high-quality studies are not available to define the efficacy of such injections in the piriformis syndrome. In a large retrospective study, however, Fishman and coworkers (2002b) reported their 10-year experience with over 500 PS patients who received these injections. In most patients, injections were done via anatomical landmarks and without EMG guidance. Each patient received 1.5 ml of 2 % lidocaine mixed with 0.5 ml (20 mg) of triamcinolone. The injecting needle was 3.5 in. long (gauge 23–25). Patients were followed every few months up to 48 months; significant improvement of pain was noted in 71 % of the patients. The duration of pain relief after steroid injections is unclear and deserves further investigation.

Currently, surgical treatment of piriformis syndrome is rarely performed and is limited to those cases in which magnetic resonance imaging defines a distinct pathology (tumor, abscess, vascular anomaly).

Botulinum Toxin Treatment of Piriformis Syndrome

Fanucci et al. (2001) should be credited for the first report suggesting the positive effect of BoNT treatment specifically in piriformis syndrome. In an open-label observation, patients received 200 units of onaA into the piriformis muscle under CT guidance. A response was considered significant if preinjection pain induced by forceful flexion/internal rotation of the involved leg resolved after injection. Twenty-six of 30 patients experienced pain relief 5–7 days after treatment with onaA. The four patients who did not get any relief from pain received a second injection which then terminated their pain.

Double-Blind, Placebo-Controlled Studies

Two double-blind, placebo-controlled studies have strongly suggested efficacy of onabotulinumtoxinA in management of piriformis syndrome:

Fishman et al. (2002a), using the criteria cited above for diagnosis of PS, blindly studied three groups of subjects with intramuscular injections under electromyographic guidance. Group 1 consisted of 26 who received onabotulinumtoxinA (onaA). In group 2, 37 subjects received triamcinolone 20 mg in lidocaine 2 % (T/L). In group 3, 24 subjects received normal saline. Patients were examined every 2 weeks after injection for a total of 12 weeks. A significant response was considered as a 50 % reduction in pain intensity (using VAS), compared to baseline at one or both of the last two evaluations. A significant response was noted in 65 % of the onaA group, 32 % of the T/L group, and 6 % of the placebo group ($P=0.001$ and $P=0.005$). No side effects were noted.

Childers et al. (2002) conducted a prospective, placebo-controlled, double-blind, crossover study with onaA and saline in nine patients with piriformis syndrome. After an initial injection of 100 units of onaA into the piriformis muscle under fluoroscopic guidance, pain was assessed over an 8-week period with visual analog scale. This was followed by a second injection after a 4-week washout period. Patients served as their own controls. The authors noted significant decrease in pain, measured by VAS, from day 4 to day 32 post-onaA injection day ($P<0.05$) and significant improvement of daily routine activities from day 5 to day 59 after onaA injection. No subject reported any side effect.

Comparator Studies

In addition to the above-cited study of Fishman et al. (2002a) which had a comparator arm, two other comparator studies have compared the effects of BoNT injection with steroid injections.

Porta (2000) compared the effect of onabotulinumtoxinA (100 units) with methylprednisolone (80 mg) in 40 subjects with myofascial pain syndrome (MPS), 23 of whom carried the diagnosis of piriformis syndrome. Changes in the visual analog scale were used as the primary criterion. At day 30 postinjection, onaA reduced pain more than triamcinolone ($P=0.06$). At day 60, onaA was significantly more effective than triamcinolone (VAS 2.3 vs. 4.9, $P<0.0001$). It is hard to determine the specific effect of onaA on piriformis syndrome (PS) since the results of this study were presented for the entire group which included another 17 subjects without MPS.

In an open-label comparator study, Yoon et al. (2007) compared the effect of abobotulinumtoxinA (150 mg, 20 subjects) with dexamethasone (5 mg mixed with 1 % Novocaine, 9 subjects) injected into the piriformis muscle. The level of pain was assessed with VAS and changes in routine daily activity were assessed with SF36 at baseline and 4, 8, and 12 weeks.

The mean VAS pain score was significantly lower in the subjects who had received onabotulinumtoxinA compared to baseline at 4, 8 and 12 weeks ($P<0.001$). At 4 weeks, several subsets of SF36, general health, social function, physical function, and vitality also improved significantly in the aboA group ($P<0.05$). On the other hand, the dexamethasone group showed no improvement, and in fact the nine patients in this group had to be taken out of the study at 4 weeks due to continued pain, requiring other methods of pain management.

Retrospective Data

Michel et al. (2013) treated 250 patients affected by PS with onabotulinumtoxinA and assessed the response to pain by the visual analog scale. The pain reduction using VAS was reported as "very good/good" in 77 %, "average" in 7.4 %, and "poor" in 15.6 % of subjects.

The data on the effect of botulinum toxin B (rimabotulinum toxin) in piriformis syndrome is limited to two small open studies. In one study, Lang (2004) reported on 20 patients with PS. Injection of 5,000 units of BoNT-B resulted in a significant reduction of pain at 2, 4, and 12 weeks after treatment. In another prospective, open-label study using different doses of rimabotulinumtoxinB (rimaB), Fishman et al. (2004) noted excellent response and pain relief in 24 of 27 patients following BoNT-B injection. Among the different doses used, the most effective was 12,500 units.

Technical Points

With the patient lying on the healthy side and the affected leg on the top with both the knee and the hip joints flexed, the point of entry of the injecting needle should be located at one centimeter below the middle of the line which connects the greater trochanter to the posterior rim of the iliac crest Michel et al. (2013) (Fig. 7.3). A hollow, 75–100 mm, dual-purpose needle is used for both the EMG recording and injection. The needle is inserted deep into the muscle traversing through the gluteus maximus toward the underlying piriformis muscle. The piriformis muscle is activated by lateral rotation of the leg. After identification of the muscle by EMG, using the aforementioned approach, BoNT-A is injected into the muscle through the hollow core of the needle.

I used 100 units of onaA diluted in 1 cc of preservative-free saline and injected (under EMG guidance) half of the solution in the identified location and the other half an inch more superficially. Ultrasound-guided injections could add more precision (Childers et al. 2002).

The Mechanism of Botulinum Toxin Action in Piriformis Syndrome

The analgesic effect of botulinum toxins in piriformis syndrome is most likely through both neural and muscular mechanisms. In the neural route, BoNTs inhibit the release of pain mediators (calcitonin gene-related peptide, substance P, and glutamate) from peripheral nerve endings and dorsal root ganglia (Welch et al. 2000; Mika et al. 2011; Marino et al. 2014), hence decreasing the phenomena of peripheral and central sensitization, essential to maintaining chronic pain (see Chap. 2 for details). In the muscular route, blocking acetylcholine at the neuromuscular

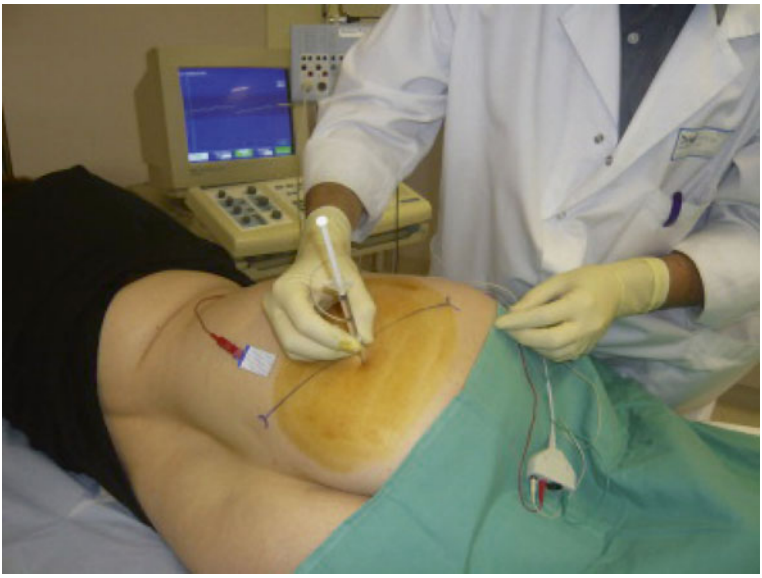

Fig. 7.3 Technique of piriformis muscle injection (Reproduced from Michel et al. (2013). Copyright © 2013 Elsevier Masson SAS. All rights reserved)

junction reduces muscle spasm, contraction, and pain if primary muscle disorder is a major contributing factor. Furthermore, reduction of muscle bulk which follows BoNT injection into the muscle can reduce pain by relieving pressure upon the sciatic nerve traversing in a tight compartment.

Comment

The data from blinded studies strongly suggest efficacy of BoNT-A in alleviating the pain of PS (two class II studies, level B evidence (probably effective); AAN guidelines, Appendices 3.1 and 3.2). Comparator studies have shown that BoNT-A (onaA and aboA) is more effective than steroids in relieving PS-related pain. The positive experience of Michel et al. (2013) in a large number of patients is encouraging. In our experience, with EMG guidance, approximately 50 % of the patients with PS respond favorably to onaA injections.

The correct or proper technique of injection and the most appropriate dosage are evolving and likely to change with more experience in the field. Current techniques seem to be working well but still finer points require clarification. For instance, one of the points to clarify is whether it is better to inject the total dose into the muscle at one point or divide the dosage in half and inject it at two different sites and/or depths.

The optimal dose of the botulinum neurotoxin for relieving the pain of PS remains to be established. Most reports use 100–200 units of onaA; 100 units often

works well in my experience. Would a lower dose of onaA also work? In the case of aboA, Yoon et al. (2007) had success with 150 units. If one equates one unit of onaA with 2.5 units of aboA (currently equated, but in reality the units are not truly interchangeable), then 150 units of aboA would be close to 60 units of onaA, a dose which is considerably lower than the reported effective dose of onaA and may be worth trying in future studies. Reports on the efficacy of rimaB await confirmation by blinded studies.

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Chapter 8
Botulinum Toxin Treatment of Myofascial Pain Syndrome and Fibromyalgia

Abstract Myofascial pain is one of the most common forms of human pain characterized by spontaneous and pressure-induced pain in muscle trigger points. Treatment of myofascial pain syndrome is partially successful with conventional analgesics, but a large number of patients remain unsatisfied.

Botulinum neurotoxins (BoNTs) can relieve myofascial pain by blocking the release of acetylcholine and pain mediators (substance P, glutamate, calcitonin gene-related peptide) from presynaptic vesicles. Ten double-blind, placebo-controlled studies have been published in this area; some of these strongly support the palliative role of BoNTs in myofascial pain syndrome. Using onaA and abobotulinumtoxinA, the successful studies emphasize the importance of a flexible rather than a fixed pattern of injection and injection of more than five trigger points in moderate or severe cases. Although the literature remains controversial, there is hope that future studies taking advantage of our current knowledge derived from positive studies can provide further support for the role of BoNT in management of myofascial pain syndrome.

Fibromyalgia is a systemic disease characterized by diffuse muscle pain, fatigue, headaches, mood disorders, sleep disturbance, bowel disorders, and endocrine dysfunction. Lack of controlled data prohibits the use botulinum toxins for treatment of fibromyalgia.

Keywords Myofascial pain syndrome • Trigger points • Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA (onaA) • AbobotulinumtoxinA (aboA) • IncobotulinumtoxinA (incoA) • RimabotulinumtoxinB (rimaB)

Myofascial Pain Syndrome (MPS)

Introduction

Myofascial pain syndrome (MPS) is a common pain disorder and a major source of work interruption and disability. It is characterized by focal pain felt in the area of trigger points. Trigger points include tight muscle bands (taut band) with sensitivity

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to touch both to induce pain (local or referred) and muscle twitch response. Trigger points can be active or latent (inactive). Active trigger points produce spontaneous pain and after being pressed whereas latent TPs may generate pain only when they are pressed upon. Latent TPs can be activated by prolonged exercise, low-load repetitive muscle activity, persistent stress, and prolonged ischemia of the muscle (Celik and Mutlu 2013).

The criteria of Simon's et al. (1999) for trigger points is generally accepted and used in clinical practice. It consists of: (1) presence of a palpable taut band in a skeletal muscle, (2) presence of a hypersensitive tender spot in the taut band, (3) local twitch response provoked by the snapping palpation of the taut band, and (4) reproduction of the typical referred pain pattern of the trigger point in response to compression. These criteria have shown good inter-examiner reproducibility and reliability (Gerwin et al. 1997).

Myofascial pain syndrome is reported with a variable prevalence of 30–93 %, is common in patients with decreased motor activity, has peak age presentation between ages 30–50 years, and is more common among women (Fricton et al. 1985; Gerwin 2001; Han and Harrison 1997; Simons et al. 1999).

Anatomy and Pathophysiology of Myofascial Pain Syndrome (MPS)

The trigger points in patients with MPS consist of hypersensitive indurated muscle fibers called "taut bands." Taut bands show an increased number of spontaneous, small-amplitude ongoing end plate potential discharges at rest (end plate potential) indicating a rich acetylcholine content (Simons et al. 2002, 2008). Increased level of acetylcholine in these muscle bands makes them sensitive to touch and elicits the "twitch response" (Ferguson et al. 2004).

Exactly how trigger points develop in the muscles of patients with MPS is unclear. The integral theory of Simons et al. (1999) proposes ischemic/metabolic derangement of the muscle and local failure of energy. Hypo-perfused muscle develops areas of low pH that inhibit acetylcholine esterase and lead to local accumulation of acetylcholine.

Development of trigger points in the muscle causes spontaneous or pressure-induced local muscle pain and referred pain. Pain may be partly related to low pH, increased local accumulation of protons (H+), and acid-sensing channels in the extracellular fluid of trigger points affecting terminal nerve endings.

The mechanism of pain induction in MPS has been investigated by Shah et al. (2005, 2008). These investigators have shown increased levels of pain mediators such as substance P and CGRP and of inflammatory mediators such as cytokines in both active and latent trigger points (less in latent). Local accumulation of pain mediators and inflammatory elements leads to peripheral sensitization of nerve endings and dorsal root ganglia. Continued peripheral sensitization causes central sensitization of spinal cord neurons leading to pain chronicity (Aokie and Francis 2011).

Treatment

The treatment of myofascial pain syndrome is focused on deactivation of active trigger points. A number of pharmacological and non-pharmacological approaches have been employed. Non-pharmacological approaches include massage, compression, stretching (Travell and Simons 1992; Esenyel et al. 2000), superficial heat (74.5 C), laser therapy (Uemoto et al. 2013), ultrasound with continuous mode 1.25–1.5 w/cm^{2j} (Blikstad and Gemmell 2008; Srbely et al. 2008), and TENS employing pulse duration of 100–110 uS/frequency—70–80 HZ for 25 min (Santiesteban 1985; Rachlin 1994).

Recently, in a double-blind, placebo-controlled study, Tekin et al. (2013) reported efficacy of dry needling causing both short-term relief of pain and improved performance of daily activities ($p<0.0$ %) in patients with MPS. Another open and prospective study found a positive effect of dry needling comparable with physical therapy in deactivation of trigger points (Rayegani et al. 2014). Acupuncture has also been reported to be partially effective in a controlled study (Sun et al. 2010).

The pharmacological approach encompasses a large number of agents used either alone or more often in combination. These include nonsteroidal anti-inflammatory drugs (NSAID), muscle relaxants, antidepressants, and antiepileptic analgesic agents. Trigger point injections with anesthetic agents and steroids are also often used. Despite the availability of a wide range of treatment modalities for deactivation of trigger points in MPS, it is generally believed that current strategies offer only transient pain relief (Desai et al. 2014; Zhou and Wang 2014). Novel therapeutic modalities with acceptable safety profile and infrequent side effects are needed to provide more sustained relief.

BoNT Treatment of Myofascial Pain Syndrome (MPS)

With increasing recognition of the analgesic effects of BoNTs in human subjects (Jabbari and Machado 2011), there is a high level of interest among clinicians at academic and nonacademic settings to use this mode of therapy for alleviating muscle pain including the pain associated with MFPS. This interest is reflected in a recent increase in the number of reviews published on this subject (Gerwin 2014; Adelowo et al. 2013; Zhou and Wang 2014; Desai et al. 2014).

Double-Blind, Placebo-Controlled Studies

Ten studies have investigated the effect of BoNTs in deactivating trigger points and relieving the pain of MPS (Table 8.1):

Twenty years ago (1994), Cheshire and colleagues first suggested the efficacy of onabotulinumtoxinA (onaA) in MPS based on a small double-blind crossover study. Six patients (four women), 35–50 years of age, participated in and completed the

Table 8.1 Randomized, controlled trials of botulinum neurotoxins in myofascial pain syndrome

Author	Class	No	Location	Primary outcome (PO)	Drug and dose	Results
Cheshire et al. (1994) $p<0.05$	II	6	Cervical	VAS at weeks 2, 4, 8	onaA: 5–25/tp	PO met
Wheeler et al. (1998)	II	26	Cervical thoracic	Pressure algometer at weeks 1, 3, 6, 8, 12	onaA: 50 and 100 u/tp	PO not met
Freund and Schwartz (2000) $p<0.01$	II	26	Cervical	VAS, ROM, at 4 weeks	onaA: 20 u/tp	PO met
Wheeler et al. (2001)	II	50	Cervical trapezius	Pressure algometer, NDI at weeks 0, 4, 8, 12, 16	onaA: 50 u/tp	PO not met
Ferrante et al. (2005)	II	142	Cervical/shoulder	VAS, PPT, SF36 weeks 1, 2, 8, 12	onaA: 10, 25, and 50 u/tp	PO not met
Ojala et al. (2006)	III	31	Cervical	VAS, VRS, PPT at week 4	onaA: 5 u/tp Total: 15–35 U	PO not met
Gobel et al. (2006)	I	144	Upper back	Proportion of patients with mild or no pain at week 5	aboA: 40 u/tp Total: 400 U	PO met P=0.002
Qerama et al. (2006)	II	30	Infraspinatus	VAS at weeks 3 and 28	onaA: 50 u/tp Total: 50 U	PO not met
Lew et al. (2008)	II	29	Cervical	VAS, NDI, SF36 at 2 months	onaA: 50 u/tp Total: 200 U	PO not met
Benecke et al. (2006)	I	153	Cervical/shoulder	Proportion of patients with mild or no pain at week 5	aboA: 50 u/tp Total: 400 U	PO not met

PO primary outcome measure, *VAS* pain intensity in visual analog scale, *ROM* range of motion, *onaA* onabotulinumtoxinA, *aboA* abobotulinumtoxinA, *NPAD* neck pain and disability scale, *GAI* global assessment of improvement, *PPT* pain pressure threshold, *VRS* verbal reporting score, *tp* trigger point, *NDI* neck disability index, *PF* pain frequency, *ns* not significant
Study class is designated according to the guidelines of the American Academy of Neurology (Appendices 3.1 and 3.2, Chap. 3)

8-week-duration study. Compared to saline, patients who had injections of onaA into trigger points of trapezius and cervical paraspinal muscles showed significant ($p<0.05$) reduction of pain (using VAS) and perception of unpleasantness (by patient account) at 2, 4, and 8 weeks. The dose of onaA was 50 units diluted in 4 cc of normal saline and equally divided between two and three sites.

Wheeler et al. (1998) studied 33 patients with myofascial pain syndrome affecting cervical and upper thoracic paravertebral muscles. Patients were randomized into three groups: high-dose (100 units) and low-dose (50 units) onabotulinum toxin

and saline. Injections were introduced into a single trigger point identified by palpation-evoked referred pain. If patients had several trigger points, only the one causing the most pain was injected. Patients' response was measured by pressure algometer, patient's global assessment of pain, as well as neck and pain disability scale before injection and at weeks 1, 3, 6, 9, 12, and 16 postinjection. A positive response was defined as total absence of pain with all three measures in three consecutive evaluations. No significant difference was found between the three groups. Nonetheless, both onaA and saline improved pain significantly compared to the baseline values. Eleven patients received a second injection of 100 units. Among these patients, those whose first injection also consisted of 100 units of onaA had better pain control (details were not provided).

In another study (Freund and Schwartz 2000), the effect of onabotulinumtoxinA (14 subjects) was compared with that of saline (12 subjects) in myofascial pain syndrome. Five trigger points were injected in each patient. Assessments included VAS, total neck range of motion (ROM), and Vernon-Mior objective function index. All were assessed before injection and at weeks 2 and 4 postinjection. Subjects who received onaA demonstrated significant ($p < 0.01$) pain relief (assessed by VAS) and improved neck range of motion at 4 weeks posttreatment.

In a more recent study, Wheeler et al. (2001) evaluated 50 patients injected with onabotulinumtoxinA at multiple trigger points at the discretion of the physician. The total number of injected sites (mean and range) is not clear from the publication. Most patients were injected into trapezius (36) and low cervical (12) regions. The mean dose was 231 units with 50 units as 1 standard deviation. Evaluation methods included pain algometer, patient and physician global assessment of pain, neck and pain disability scale, as well as both physical and mental SF36 (weeks 0, 4, 8, 12, 16). Both onaA and saline groups showed significant improvement in all assessments (except SF36), but the difference between the drug and placebo groups was not significant.

Ferrante et al. (2005) conducted a large single-center study on 132 patients with MPS. Subjects were randomized into four groups (three onaA groups and one saline) and studied blindly over 16 weeks. In the toxin groups, investigators injected 10, 25, and 50 units into the trigger points (up to five). Before treatment, all patients were taken off their pain medications and were put on a new tripartite regimen: amitriptyline (10–75 mg), ibuprofen 800 mg every 6 h, and propoxyphene/acetaminophen as a rescue drug. Pain relief and quality of life were assessed by VAS (past 24 h), pain algometry (sensitivity to pressure), and SF36 questionnaires at 1, 2, 4, 6, and 12 weeks. No significant differences were noted between any of the four groups in respect to any of the assessed parameters. In all four groups, including the placebo group, patients demonstrated significant improvement of their pain (assessed by VAS and pain algometer) and used less rescue medication compared to their baseline values before treatment, however ($p < 0.001$).

In another study (double-blind, crossover), Ojala et al. (2006) assessed the efficacy of onaA in 31 patients with MFPS. Patients had two injections, 4 weeks apart. onaA injections consisted of five units into each trigger point; the total dose injected

varied between 15 and 35 units. Pain intensity was assessed by VAS. There was no difference between onaA and saline in respect to pain relief, but both alleviated pain significantly compared to the baseline level ($p<0.001$); >60 % of the subjects reported 30–50 % pain reduction over the course of the study.

Qerama et al. (2006) compared injection of 50 units of onaA into a single trigger point with saline in 30 patients. Pain level was measured at baseline and day 3 and day 28 after injection by VAS and trigger point pressure sensitivity. No difference was detected between onaA and saline. Subjects in both groups, however, experienced significant reduction in pain (>30 %) compared to baseline.

In 2006, Gobel et al. conducted a well-designed, double-blind, placebo-controlled, multicenter study in 145 subjects who had moderate to severe pain affecting the neck and shoulder muscles. Injections of saline or aboA (40 units per point) were made into the ten most tender trigger points. The primary outcome was the proportion of patients with mild or no pain at week 5 compared to baseline. At week 5, significantly more patients (51 %) in the aboA group reported mild or no pain compared to the patients in the placebo group (26 %; $p=0.002$). During the period between week 5 and the study's last evaluation, patients in the aboA group experienced significantly more days per week without pain ($p=0.036$) and significantly more days per week with no or mild pain ($p=0.023$) compared with patients in the placebo group.

In another small blinded study (Lew et al. 2008), 15 subjects with onaA injections were compared with 14 subjects who received saline injection. The dose of onaA was 50 units/trigger point. The maximum dose was 200 units injected into four trigger points, with no more than two trigger points per side. Assessments included VAS for pain, quality of life by SF36, and neck disability index (NDI) performed at week 1 and months 1, 2, 3, 4, and 6. No significant difference was noted between onaA- and saline-treated subjects although all assessed values showed some improvement in the onaA group over the duration of the study. The authors concluded that patients in both groups noted improvement in assessed parameters over baseline, but the details and magnitude of improvements were not reported.

Finally, (Benecke et al. 2006) performed a prospective, double-blind, multicenter study with aboA in patients with neck and shoulder MPS using the identical inclusion/exclusion criteria and dosage (40 units/trigger point, ten trigger point injected) used in Gobel's study (2006). Their study, however, used a fixed-dose design (trapezius, four points, two/side; neck paraspinals, four points, two/side; temporalis, two points, one/side). The primary outcome was the same as Gobel's study, i.e., the proportion of patients with no pain or mild pain at week 5 postinjection. Although subjects who received aboA demonstrated less pain compared to the placebo group during the entire duration of the study (12 weeks), at week 5 (time for primary outcome assessment), this improvement was not statistically significant. At weeks 9 and 10, however, aboA significantly reduced pain compared to the placebo ($p<0.05$).

Comparator Studies

In a blinded and crossover study, Graboski et al. (2005) compared the efficacy of onaA injection into trigger points (25 units/point and up to 8 points) with bupivacaine (0.5 %) and dry needling in 18 patients with MPS. Both modes of therapy significantly reduced pain compared to baseline ($p = 0.006$), but no significant difference between the two was noted as to the degree of pain control. Dry needling did not alleviate pain. The duration of action was also approximately the same for both onaA and the anesthetic agent (4 weeks), but there was a trend in favor of onaA for longer duration. Authors found the substantially higher cost of BoNT treatment ($500 for onaA vs. $1 for bupivacaine) prohibitive to recommend it for routine use in MPS.

These results agree with the observations of (Kamanli et al. 2005) who in a single-blind study compared the effect of lidocaine with onaA and dry needling in 78 patients with MPS. At 4 weeks, the effect of onaA and lidocaine in pain relief was comparable; both markedly reduced pain (<0.005). The problem with both of these studies is a short follow-up of 4 weeks which does not properly address the longer (usually ≥3 months) duration of BoNT effect which is a significant advantage of BoNTs in clinical practice.

Patient 8-1: Myofascial Pain Syndrome with Two Trigger Points in One Muscle

A 38-year-old gentleman with history of 10 years competitive wrestling during his younger years complained of localized pain in the left upper back for the past 5 years. The pain was localized to the left infrascapular region and was both spontaneous and exercise induced. The area was sensitive to touch and upon pressing caused referred pain radiation toward the lower part of the scapula. The pain was described as aching and deep, but at times also had a burning quality. On examination, two trigger points could be identified in the upper subscapular region; pressing upon them induced referred pain. Twenty units of onabotulinumtoxinA was injected into each trigger point. Within 1 week, the patient reported marked reduction of pain (a change in VAS from 8 to 1). He required reinjection every 6 months that produced the same satisfactory response over a follow-up period of 3 years (Fig. 8.1).

Patient 8-2: Multiple Trigger Points in Multiple Muscles

A 62-year-old gentleman, construction worker, developed neck, shoulder, and upper back pain, gradually increasing in intensity over the past 2 years. His past medical history was significant for an episode of tetanus that followed a foot injury 12 years

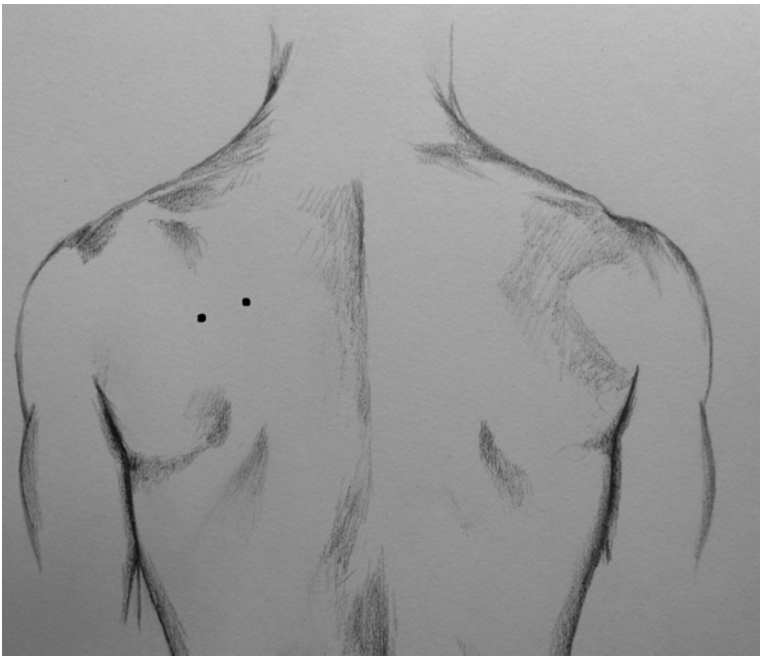

Fig. 8.1 The sites of trigger point injections in patient 8-1 (Created by Damoun Safarpour; Published with kind permission of © Bahman Jabbari 2014. All Rights Reserved)

ago. He was aggressively treated for the tetanus and recovered. For his current pain problem, his medications consisted of gabapentin, tramadol, and lidocaine patch applied daily. He was not satisfied with the level of pain control, however. The muscle pain interfered with his daily activities and kept him up at night. On examination, there were a number of trigger points scattered within the right trapezius, deltoid, splenius capitis, as well as the supra- and infrascapular muscles identified by thumb pressure and induction of referred pain. OnabotulinumtoxinA was injected into 20 trigger points located in the aforementioned muscles. The dose per trigger point was 20 units with a total dose of 400 units per session. The patient reported significant reduction of pain with a six-point reduction in VAS (baseline VAS of 8–9 changed to 2–3) within 2 weeks. The patient is very satisfied with the BoNT therapy that he believes has made his pain bearable. No side effects were noted over the 6 years of treatment with multiple trigger point injections every 3–4 months.

The Mechanism of Action of BoNT in MPS

The pain-alleviating effect of BoNTs in MPS probably involves different pathways. As described above under pathophysiology of MPS, acetylcholine is increased locally in the taut muscle bands of the trigger points, and its high level contributes

to hypersensitivity of muscle fibers, muscle twitch, and muscle contraction. Furthermore, the extracellular fluid around the trigger points contains elevated levels of pain mediators (substance P and CGRP) and inflammatory markers such as cytokines (Shah et al. 2005, 2008). These agents are all able to generate pain via peripheral sensitization of nerve endings and maintain the pain via ensuing central sensitization (see Chap. 2).

Botulinum neurotoxins block the release of acetylcholine at the neuromuscular junction and inhibit the release of pain mediators such as substance P and calcitonin gene-related peptide (Welch et al. 2000; Marino et al. 2014). Furthermore, in the formalin model of pain, pretreatment with onabotulinumtoxinA blocks the inflammatory peak of pain and reduces the accumulation of glutamate in the tissue after formalin injection (Cui et al. 2004). Action of botulinum neurotoxins through these different pathways collectively can alleviate the pain of MPS.

Comment

Despite the fact that most of the controlled and blinded studies in myofascial pain syndrome did not meet their primary outcome (Table 8.1), more careful examination of these studies inspires hope and suggests that BoNTs may help patients with MPS if the injection is well designed and the dosage is properly selected.

Among the ten reported studies, the one conducted by Gobel et al. (2006) with a flexible design, advocating injection of ten trigger points in patients with moderate to severe MPS, could serve as a model. This large, multicenter, class I study which was carefully conducted has become the cornerstone of efficacy of BoNT-A (aboA) in MPS. The carefully conducted multicenter study of (Benecke et al. 2006) is a replication of Gobel's study, but it used a fixed injection design. Its conclusion merely implies that a fixed dosage design does not work for Gobel et al.'s (2006) protocol. The study of Ferrante et al. (2005), comparable in size to Gobel's study (large number of patients) sheds negative light on the efficacy of BoNT (in this case onaA) in MPS. It is fundamentally different from Gobel's study since investigators injected only a limited number of trigger points (no more than five). We and others (Gerwin 2014; Zhou and Wang 2014; Desai et al. 2014) believe that the limited number of injections is a major issue which significantly and negatively impacts the response to BoNT treatment in the moderate to severe forms of myofascial pain syndrome.

Other negative studies have significant limitations in terms of design, the dose of BoNT applied, and the conclusions. The study of Ojala et al. (2006) used two injections, 4 weeks apart. Since the effect of BoNTs often lasts 3 months, assessment of response to the second injection would be invalid. Furthermore, the dose of five units per trigger point is probably too small to be effective.

Other negative studies have found BoNT efficacy statistically similar to placebo, but, in these studies, both BoNT and placebo alleviated pain significantly compared to baseline pain (Wheeler et al. 1998; Ferrante et al. 2005; Querma et al. 2006). As emphasized by Gerwin (2014), in this scenario, the only possible conclusion is that the study showed a large placebo effect precluding proper assessment of BoNT efficacy.

Further confounding factors can be inclusion of subjects with secondary gain, pending litigation, and those seeking disability or already on disability from MPS. Careful screening and exclusion of such patients is more likely to improve the results.

In conclusion, to establish a role for BoNT in treatment of MPS, a large multicenter study using a flexible injection design with ten or more trigger points in moderate or severely affected patients is needed. The proportion of patients with no pain or only mild pain at week 5 postinjection would be a reasonable outcome measure. The dose per trigger point is still a matter of debate. We suggest using 40 or 50 units of aboA per trigger point, 20 units for onaA or incoA, and 800–1,000 units for rimaA. The aforementioned dose/trigger point for aboA has been used successfully in Gobel's study. This dose is comparable with the dose of 20 units/trigger point of aboA in several reported studies (Miller et al. 2009; Safarpour and Jabbari 2010; Cheshire et al. 1994). In a review of the literature for efficacy, the reviewer should be cognizant of the dose differences between different BoNT-A toxins. This was overlooked in one recent review where the authors erroneously concluded that the dose of BoNT-A/trigger point did not make a difference in producing a positive response in MPS (20 units of onaA in Cheshire's study had the same analgesic effect as 40 units of aboA in Gobel's study). These dose values are very comparable and not significantly different as the authors suggested (Zhou and Wang 2014).

Fibromyalgia

Fibromyalgia is a common clinical condition which affects 2 % of the population in the USA. The cardinal feature of the disease is chronic diffuse body pain. Patients often have additional symptoms of fatigue, headaches, mood disorders, sleep disturbance, and bowel disorders. Patients show evidence of impairment of the hypothalamic-pituitary-adrenal axis. An increased level of excitatory neurotransmitters (including substance P) and reduction of other biogenic amines suggest that some symptoms of fibromyalgia are related to chronic central sensitization (Mease 2005). A large number of medications have been tried to alleviate the pain of fibromyalgia. Pregabalin, duloxetine, milnacipran, and amitriptyline are currently the first-line drugs for treatment of fibromyalgia, but their effect is modest (Häuser et al. 2014). Table 8.2 shows the recently revised diagnostic criteria of fibromyalgia according to the guidelines of the American College of Rheumatology (Wolfe et al. 2010).

Botulinum Toxin Treatment of Fibromyalgia

The published literature on the efficacy of BoNTs in fibromyalgia is very limited. Only two letters to the editor have specifically addressed this issue. Paulson and Gill (1996) compared the effects of onaA (100 units) with that of lidocaine (0.5 %) in ten patients with fibromyalgia. They employed a baseline fibromyalgia questionnaire to

Table 8.2 Revised diagnostic guideline criteria

Fibromyalgia diagnostic criteria			
Criteria			
A patient satisfies diagnostic criteria for fibromyalgia if the following three conditions are met:			
1. Widespread pain index (WPI) >7 and symptom severity (SS) scale score >5 or WPI 3–6 and SS scale score >9			
2. Symptoms have been present at a similar level for at least 3 months			
3. The patient does not have a disorder that would otherwise explain the pain			
Ascertainment			
1. WPI: note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19			
Shoulder girdle, left	Hip (buttock, trochanter), left	Jaw, left	Upper back
Shoulder girdle, right	Hip (buttock, trochanter), right	Jaw, right	Lower back
Upper arm, left	Upper leg, left	Chest	Neck
Upper arm, right	Upper leg, right	Abdomen	
Lower arm, left	Lower leg, left		
Lower arm, right	Lower leg, right		
2. SS scale			
Score: Fatigue			
Waking unrefreshed			
Cognitive symptoms			
For the each of the three symptoms above, indicate the level of severity over the past week using the following scale:			
0 = no problem			
1 = slight or mild problems, generally mild or intermittent			
2 = moderate, considerable problems, often present and/or at a moderate level			
3 = severe: pervasive, continuous, life-disturbing problems			
Considering somatic symptoms in general, indicate whether the patient has:[a]			
0 = no symptoms			
1 = few symptoms			
2 = a moderate number of symptoms			
3 = a great deal of symptoms			
The SS scale score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12			

From Wolfe et al. (2010) © 2010 by the American College of Rheumatology. With permission from John Wiley and Sons

[a]Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms

measure pain, disability, medication intake, and routine daily activities. Patients first received lidocaine followed by injection with BoNT. None of the patients who received BoNT injections into trigger points showed any improvement. In another small open observation (Asherson and Pascoe 2001), 16 patients who met the clinical criteria of fibromyalgia were injected with onaA (100 units) into multiple trigger points. Five patients had one injection, seven had two, while the remaining four patients had three and four injections. Authors reported significant improvement of pain in all patients. Pain relief lasted for 16 weeks after each injection. The method of assessing pain improvement and the exact dose per trigger point were not mentioned in the communication, however.

Comment

The role of BoNT treatment in fibromyalgia has not been assessed by controlled studies. Given the diffuse and sometimes poorly localized nature of the pain, along with the complexity of symptomatology of fibromyalgia, it is unlikely that BoNT treatment would be effective in this disorder.

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Chapter 9
Pelvic and Urogenital Pain

Abstract High-quality data regarding the efficacy of botulinum neurotoxins (BoNTs) in pelvic and urogenital pain disorders is limited. In female pelvic pain, one double, placebo-controlled study (class II) has shown significant improvement of pelvic pain after injection of onabotulinumtoxinA (onaA) into pelvic floor muscles (level C evidence, possibly effective). In male pelvic pain, related to prostatitis, a small study of 13 patients demonstrated modest improvement compared to placebo (level C evidence, possibly effective). For pain associated with interstitial cystitis (bladder pain syndrome), one small double-blind study showed no difference between 50 units of onaA and placebo (one class II study, possibly ineffective for that dose), whereas a comparator blinded study found 100 and 200 units of onaA injections were statistically more effective than the conventional treatment with hydrodistention alone (one class II, possibly effective for that dose in a comparator study). All four open long-term studies with BoNT-As in bladder pain syndrome also have suggested initial efficacy and better efficacy with repeat injections. In vulvodynia and vestibulodynia, one double-blind study of 60 patients has shown no efficacy with a dose of 20 units, whereas two open studies with comparable numbers suggest efficacy with 100 units of onaA. More controlled and blinded data are needed to discern the effectiveness of BoNT injections in bladder pain syndrome and vulvodynia, preferably with larger doses, comparable to those which suggested efficacy in the open trials.

Keywords Pelvic pain • Interstitial cystitis • Bladder pain syndrome • Vulvodynia • Vestibulodynia • Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA • AbobotulinumtoxinA • IncobotulinumtoxinA

Pelvic Pain

Introduction

Chronic pelvic pain (CPP) is a disabling disorder which is more common among women.

The American College of Gynecology defines chronic pelvic pain as noncyclic pain of more than 6 months duration that localizes to the pelvis, anterior abdominal wall at or below the umbilicus, the lumbosacral region, or the buttocks and is of

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sufficient severity to cause functional disability or require medical care (ACOG practice bulletin 2004).

In a prospective study of 5,253 women between ages 18 and 50, 14.7 % met the criteria of chronic (>6 months) pelvic pain and 45 % reported reduced work productivity. The cost to US economy for this age group is estimated as $881.5 million per year (Mathias et al. 1996). Among men, chronic pelvic pain is the cause of two million clinic visits per year and an annual economic burden of $86 million in the USA (Duloy et al. 2007). In many affected patients (female or male), CPP is manifested in the form of myofascial pain with trigger points in the muscles of the pelvic floor causing local and referred pain. In some patients, pain is a reflection of a serious pathology involving adjacent genitourinary structures. A careful examination of pelvic floor muscles and investigation (including advanced imaging, if necessary) of genitourinary pathology are necessary in order to avoid misdiagnosis.

Anatomy of the Pelvic Floor

The pelvic floor encompasses three layers of muscles. The most superficial layer consists of the bulbocavernosus, ischiocavernosus, and superficial transverse perineal muscles and external anal sphincter. The puborectalis muscle is between the superficial and deep muscles. The deepest layer or pelvic diaphragm consists of the pubococcygeus and iliococcygeus (together they form the levator ani), coccygeus, and ischiococcygeus muscles (Raizada and Mittal 2008) (Fig. 9.1). The piriformis and obturator internus are also deep muscles. The superficial layers are innervated by the pudendal nerve, while the deepest layer is innervated by S3, S4, and S5 sacral nerve roots.

The referred pain from these muscles' trigger points can be felt in the distribution and territory of the pudendal nerve. The pain emanating from the superficial muscle layer (bulbocavernosus and ischiocavernosus) is referred to the perineum and adjacent urogenital structures. Pain of the external anal sphincter may be referred to the posterior pelvic floor. The pain in the levator ani and coccygeus muscles would radiate to the vagina or sacrococcygeal area. The obturator internus generates referred pain to the anococcygeal region.

Pathophysiology and Treatment

A number of therapeutic strategies are employed in the management of pelvic pain. Pelvic floor physical therapy can be helpful and provides some pain relief to 63 % of the patients (Bedaiwy et al. 2013). Pharmacological therapy often encompasses a multimodal approach tailored to the needs of the individual patient: antispasmodic/anticholinergic drugs and analgesic agents (including nonsteroidal anti-inflammatory drugs) and, in some cases, antibiotics. Neuromodulation techniques (transperineal electromagnetic stimulation, pudendal nerve stimulation, sacral nerve root

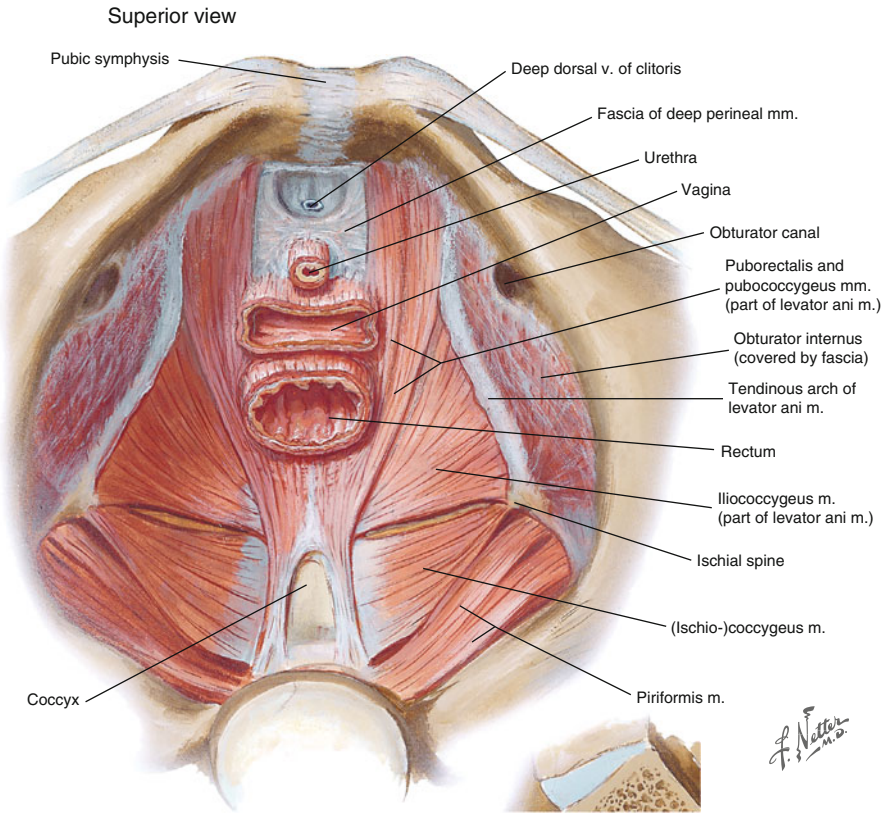

Fig. 9.1 Anatomy of the female pelvic floor (From Frank Netter collection. Netter illustration used with permission of Elsevier, Inc. All rights reserved www.netterimages.com)

stimulation) have been tried with some success in small open-label studies. Surgical approach is a last resort and is reserved for selective patients.

Carinci et al. (2013) recently reviewed the use of alternative and complementary therapies (acupuncture, pollen extract, mind and body practices) in chronic pelvic pain. The potential contribution of these modalities is discussed below.

Acupuncture

Two blinded studies have reported on the efficacy of acupuncture in pelvic pain. Both studies were conducted in male patients with pelvic pain related to chronic prostatitis. In one study (Lee et al. 2008), patients who underwent 20 sessions of acupuncture over 10 weeks demonstrated significant reduction in pelvic pain compared to the group who had sham acupuncture (six-point decrease in NIH-CPSI score at week 10, $p=0.02$, week 24, $p=0.04$). In another study (Lee and Lee 2009), the effect of electrical acupuncture (EA) with advice and exercise was compared to

sham EA with exercise or with exercise only (three arms), in 63 subjects. After 12 biweekly sessions, symptoms, mostly pain related, improved (six points in NIH-CPSI) in the group with electrical acupuncture ($p=0.001$). No blinded data in a female population with pelvic pain is available.

Pollen Extract

Pollen extracts containing amino acids, carbohydrates, lipids, vitamins, and minerals have been shown to relax sphincters of the bladder and urethra and have anti-inflammatory effect. A double-blind, placebo-controlled study of 60 patients with CPP (Elist 2006) revealed lower pain scores and less voiding symptoms in subjects who took pollen extract ($p=0.05$) at 6 months. In another controlled and blinded study (Wegenlehner et al. 2009) of 139 patients, subjects who took pollen extract demonstrated significantly ($p=0.008$) lower pain score (subset of NIH-PSI) and showed improved quality of life at 12 weeks ($p=0.002$).

Minimal data are available on *mind and body practice* which includes massage, spinal manipulation, deep-breathing exercises, guided imagery, hypnotherapy, progressive relaxation, qigong, and tai chi. These practices are based on using the mind to improve physical function. Although some small positive observations are reported in respect to improvement of pelvic pain, to date, no blinded observations are available.

Botulinum Toxin Treatment of Chronic Pelvic Pain

Botulinum neurotoxins (BoNTs) can improve pain via a number of different mechanisms. In addition to blocking the release of acetylcholine that could lead to relaxation of pelvic floor muscles, selective inhibition of pain mediators can decrease peripheral and central sensitization and alleviate pain (Chap. 2). Two prospective, placebo-controlled, double-blind studies have investigated the efficacy of BoNTs in chronic pelvic pain.

Abbott et al. (2006) studied 60 patients (30 toxin, 30 placebo) with CPP, 55 % of whom had endometriosis and a majority had had surgery to remove foci of endometriosis. Patients' major symptoms were non-menstrual pelvic pain, menstruation-related pelvic pain, dyspareunia, and dysmenorrhea. Patients were injected under conscious sedation either with 1 cc of study drug (80 units of onabotulinumtoxinA) or comparable volume of saline into two sites bilaterally within each of the puborectalis and pubococcygeus muscles (Fig. 9.1). Participants completed the VAS questionnaires for pain, bowel, and bladder and had examinations to assess pelvic floor tenderness and vaginal manometry measurements at 2, 4, 8, 12, 16, 20, and 26 weeks after injection. There was significant change from baseline in the botulinum toxin type A group for non-menstrual pelvic pain (VAS score 51 versus 22; chi2 = 16.98, $p=.009$) but not in the placebo group. Both onaA and

placebo subjects showed marked improvement of dyspareunia compared to baseline; this improvement was more prominent for the onaA ($p = 0.009$ versus 0.04) group. Both onaA and saline injections decreased the pelvic floor manometric pressure significantly.

The same group of investigators (Nesbitt-Hawes et al. 2013) studied the effect of a single injection of 100 units of onabotulinumtoxinA into the pelvic floor with multiple injections over time (2 or more) in 26 and 11 female patients with pelvic pain. The technique of injection was similar to that of their previous report (Abbott et al. 2006). Second injections were done no sooner than 26 weeks. Both single and repeat injections reduced non-menstrual pelvic pain (VAS value of 51 down to 23, $p = 0.04$) and vaginal pressure (40 versus 34 cmH_2O $p = 0.2$) and dyspareunia (VAS value of 54 down to 30 for single versus 51 down to 23 for multiple injections, $p = 0.001$).

In another double-blind, placebo-controlled study, Gottsch et al. (2011a) compared the effect of onabotulinumtoxinA (100 units) with saline in 13 male subjects with moderate to severe pelvic pain with chronic prostatitis. Injections were made into proximal and mid-bulbospongiosus muscle posterior to the perineal body. The response rate for onaA subjects was 30 % compared to 13 % in the saline group ($p = 0.002$). The pain component of the chronic prostatic symptom index (PCSI) improved significantly in the onaA subjects compared to the placebo group (0.05).

Comment

The placebo-controlled literature on use of BoNTs in chronic pelvic pain (CPP) is limited. The study of Abbott et al. (2006), a class II study, provides level C evidence (one class II, possibly effective) for the efficacy of onaA in female pelvic pain (AAN guidelines—Appendices 3.1 and 3.2). For male CPP, reports are encouraging, but the evidence is still limited to retrospective and one small prospective, double-blind study with modest results (Gottsch et al. 2011a). The optimal technique and dosage remain an evolving issue. For female pelvic pain, the technique and dose of Abbott et al. (2006) is the only one supported by a controlled study. It is crucial that only individuals with significant knowledge of pelvic anatomy perform the injections since improper injections can result in significant and unacceptable impairment of bladder and anal functions. Other techniques to improve pelvic pain with BoNT are being explored. One such technique involves BoNT block of ganglion impar that marks the termination of paravertebral sympathetic chain at the sacrococcygeal junction. Blockage of this ganglion with 100 units of onaA (mixed with 5 % anesthetic) is reported to ease pelvic pain for 6 months (Lim et al. 2010). Further confirmation of this approach is needed via blinded studies. The current data suggest that in recalcitrant chronic pelvic pain, BoNT treatment can be a useful addition to physical therapy and pharmacological treatment.

Painful Bladder Disorders

A number of bladder disorders have pain as a part of their symptomatology. These include bladder pain syndrome (BPS)/interstitial cystitis and to a much lesser extent detrusor muscle overactivity and detrusor sphincter dyssynergia. Since pain is the major symptom of BPS/interstitial cystitis, recent literature has focused on a potential role for BoNTs in relief of pain associated with this syndrome.

Bladder pain syndrome, caused by interstitial cystitis, is defined as a clinical condition characterized by suprapubic pain (due to bladder filling), diurnal and nocturnal frequency, and urgency in the absence of urinary tract infection or organic urological disease (Van de Merweet et al. 2008). Cystoscopic evaluation may show presence of glomerulations, petechiae, and sometimes mucosal ulceration.

The treatment is often difficult and generally unrewarding. In a recent communication, Cardella et al. (2014) reviewed pharmacological treatments currently used for interstitial cystitis. Amitriptyline, gabapentin, duloxetine, and venlafaxine were described as the most commonly used analgesic drugs for this condition with nonsteroidal anti-inflammatory agents (NSAIDs) and opioids as second line of treatment. The authors emphasized that, currently, there is no evidence from controlled studies that any of these drugs work. Hydroxyzine is used in cases where allergy seems to be a major contributing factor as it inhibits connective tissue mast cell infiltration.

Intravesical drug delivery approach for treatment of IC has gained popularity in recent years. These include introduction of locally active anesthetics (which have both anti-inflammatory and anti-mast cell effect), hydraulic acid and chondroitin sulfate (to promote regeneration of damaged GAC layer in BPS), and pentosan polysulfate (currently approved for oral use by FDA in interstitial cystitis). Pentosan polysulfate is believed to repair the GAG layer and has an anti-inflammatory effect and degranulates mast cells. These drugs, however, have not shown long-term positive effects. As another approach, bladder hydrodistention is currently used with limited success.

Botulinum Treatment of BPS/Interstitial Cystitis

A growing body of information has developed over the past 10 years (particularly past five) regarding the role of BoNT treatment in BPS (Smith et al. 2004; Kuo 2005; Giannantoni et al. 2006, 2010a, b; Ramsay et al. 2007; Kuo and Chancellor 2009; Pinto et al. 2013; Chung et al. 2012; Gottsch et al. 2011b; Shie et al. 2013; Lee and Kuo 2013). Russell et al. (2013) recently published a review on this subject and detailed the data in a comprehensive table. A total of 16 manuscripts had been published on this subject. Two were double blind and placebo controlled, four had long-term (beyond 2 years) follow-up with repeat injections, and ten were shorter retrospective studies. With the exception of one double-blind study that used only 50 units of onaA, all other studies used 100 units or more (100–300 units). In most studies, injections were into

the posterolateral wall of the bladder. The two blinded trials will be discussed first in some detail, followed by a brief account of the other studies.

In a double-blind, parallel design study, Kuo (2013) compared the efficacy of onabotulinumtoxinA in two groups receiving 100 and 200 units plus cystoscopic hydrodistention (HD) 2 weeks later and a third group treated with HD only. All 67 patients of the study had failed to respond to the conventional treatment for BPS. Injections were made into the urothelium of the posterior and lateral bladder walls at 40 points. In the 200 units group, each injection was 5 units, whereas the subjects of the 100 units group received 2.5 units per injection site.

The primary treatment outcome was change on global response assessment (GRA), a 7-point response from markedly worse to markedly better acknowledged by the patient and assessed at 3 months postinjection. A number of other scales including VAS for pain were also employed. At 3 months, 80 and 72 % of the patients in the 200 unit and 100 unit onaA groups, respectively, had significant improvement expressed in GRA compared to 48 % in the placebo group (0.032). The VAS pain scores decreased to 39, 55, and 18 % for 100 and 200 unit onaA and HD groups, respectively ($p=0.007$). The bladder capacity also increased significantly in the onaA groups: 26 % in the 100 unit group and 63 % in the 200 unit group compared to 4 % in the HD group. In the succeeding open arm of the study, GRA score was 71, 55, and 30 % at 6, 12, and 24 months but still significantly better than HD only ($p=0.002$).

Gottsch et al. (2011a) compared the effects of onabotulinumtoxinA in 20 women with placebo (saline) in a prospective and double-blind study. In the onaA group (nine patients), 50 units of toxin was diluted in 2 cc saline and injected periurethrally. Assessments included female modification of prostatitis symptom index (PSI). Symptom improvement by visual analog scale (VAS), AUA symptom index, and graded pain scale performed at baseline, 1, 2 (by mail), and 3 months during visit and examination. Although both the onaA and saline groups showed modest improvement of CPSI scores (more for saline 3.9 versus 1.9 for onaA), no statistically significant difference was found between the onaA and saline group as to CPSI score at 3 months ($p=0$ .97). All other indices also showed no difference between groups. The authors concluded that periurethral injection of BoNT in female patients with BPS does not improve pain and other symptoms.

Over the past 12 months, four investigations (Shie et al. 2013; Pinto et al. 2013; Lee and Kuo 2013; Kuo 2013) addressed the issue of repeated intravesical injections of botulinum neurotoxins for alleviation of pain in BPS/interstitial cystitis in open-label studies. All four found that initial injections effectively relieved symptoms in BPS (including pain), and three out of four reported repeat injections as being more effective. One group found better results in non-ulcerative interstitial cystitis (Lee et al. 2013).

The rest of the literature consists of ten retrospective reports with short-term follow-ups. All reports suggest efficacy based on improvement of pain, measured by VAS scale (response ranged from 30 to 90 %). Side effects consisted of dysuria, problem with bladder emptying, and urinary tract infection and were more common in patients who received 200 or more units of onaA.

The Proposed Mechanisms of BoNT Action in Bladder Pain

Local release of pain mediators by pathologic factors could lead to sensitization of nerve endings and dorsal root ganglia (peripheral sensitization) (Aokie and Francis 2011). The subsequent enhanced volume of afferent nociceptive volleys leads to central sensitization and chronic pain (Chap. 2). Several studies have demonstrated that administration of BoNTs into the bladder before bladder exposure to noxious stimuli can reduce the release of pain mediators and lower the magnitude of secondary central nervous system changes.

Lucioni et al. (2008) acutely injured the bladder explants by bathing them in HCl. The explants demonstrated marked release of calcitonin gene-related peptide (CGRP) and substance P (SP) compared to controls (1,235 and 1,655 pg/g, respectively, and controls 183 and 449 pg/g, respectively; $p < 0.001$). This increased release of pain mediators was partly inhibited by prior incubation of the explants in a medium that included ten units of onabotulinumtoxinA (870 and 1,033 pg/g ($p < 0.05$ and <0.01)). They found that cyclophosphamide (CYP)-induced chronic inflammation of the bladder significantly increased the release of SP compared to controls (1,060 and 605 pg/g, respectively; $p < 0.005$). Again, exposure to onaA partly inhibited the release of SP after CYP-induced cystitis (709 pg/g, $p < 0.05$).

In another study (Vermulakonda et al. 2005), administration of intraperitoneal cyclophosphamide increased the expression of c-Fos in the L6/S1 segments of the rat's spinal cord (78 and 107 %). This phenomenon was subdued by intravesical instillation of 20 units of onaA prior to cyclophosphamide treatment that resulted in lowering of the c-Fos level to 50–52 %. In animals pretreated with onaA, the intervals between bladder contractions increased by tenfold.

Smith et al. (2005) found that application of cyclophosphamide to the bladder urothelium increased ATP release from the inflamed urothelium by 94 % of animals. Intravesical infusion of onaA prior to cyclophosphamide therapy reduced the ATP release by 69 %. Collectively, these observations support the analgesic effects of BoNT-A in animal models of bladder injury-induced pain. Recently, Collins et al. (2013) have shown that onabotulinum Toxin-A inhibits ATP release from the urothelium.

Overactive Bladder and Detrusor Sphincter Dyssynergia

Overactive detrusor sphincter (overactive bladder) is a common cause of urinary urgency, frequency, and intermittent incontinence. Detrusor sphincter dyssynergia, a common disorder in multiple sclerosis, also produces urinary flow problems. A number of double-blind, placebo-controlled studies have shown efficacy of intravesical injection of onabotulinumtoxinA in reducing urinary urgency and increasing bladder capacity in both neurogenic (spinal cord injury, multiple sclerosis) and idiopathic detrusor overactivity (Gallien et al. 2005; Flynn et al. 2009; Dmochowski et al. 2010; Rovner et al. 2011; Dowson et al. 2011; Tincello et al. 2012). These studies led to the FDA approval of intravesical BoNT treatment for bladder overactivity. In neither of the two conditions, however, pain is a major issue; no controlled information in this regard is available.

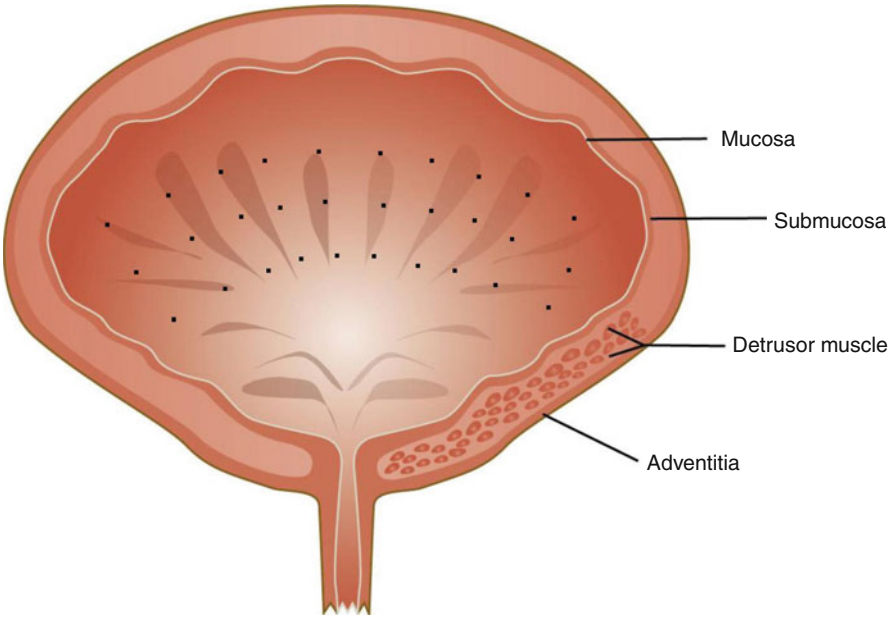

Fig. 9.2 The technique commonly employed for bladder injections with BoNTs (Modified from Karsenty et al. (2014) with permission © 2014 John Wiley and Sons Inc)

Comment

In the bladder pain syndrome/interstitial cystitis (BPS), all 14 open studies (four long term with repeated injections) and a blinded comparator study using injections into the bladder wall have shown significant pain reduction after BoNT administration. The smaller blinded study that used periurethral injections with a lower dose of 50 units failed to improve pain. Larger blinded studies are needed using bladder wall injection technique with doses higher than 50 units, which have suggested efficacy in the comparator blinded study and the open studies of BPS. Nonetheless, there is a concern with using doses of 200 units and higher due to few reports of persistent urinary retention. Most studies have used multiple injections into the posterolateral wall of the bladder sparing the bladder trigone (Karsenty et al. 2014) (Fig. 9.2). Trigone injection is less commonly employed (Pinto et al. 2010).

Vulvodynia

Vulvodynia is defined as chronic discomfort and pain in the vulva without objective findings or specific signs of a neurological disorder (Moyal-Barraco and Lynch 2004). The pain is usually burning in character and is often provoked by stimulation (sexual activity, tampon contact, etc.). A careful clinical examination and thorough

search for pelvic or urogenital pathology is in order before diagnosing a patient with essential (general) vulvodynia. Treatment of vulvodynia includes analgesic medications (gabapentin, tricyclic antidepressants), pelvic floor physiotherapy, biofeedback exercises, 5 % lidocaine ointment, and acupuncture; all produce only partial relief (Lotery et al. 2004). Results are often disappointing, and recalcitrant cases are disabling and emotionally drain the patient.

Earlier observations of Gunter et al. (2004) on a single case and Yoon et al. (2007) on seven patients with vulvodynia noted marked reduction of pain after injection of onaA into the vestibule, levator ani, and perineal body. Contrary to these positive observations, Petersen et al. (2009) found no difference between onaA and placebo in respect to pain relief (measured by VAS over 6 months) in a double-blind, placebo-controlled study of 60 subjects with vestibulovulvodynia. OnaA (20 units in 0.5 cc saline) or saline (0.5 cc) was injected into the bulbospongiosus muscle. Both the placebo and onaA group, however, showed marked decrease of VAS scores compared to baseline ($p<0.001$). The placebo group also showed marked decrease in sexual stress in 6 months ($p=0.04$).

Two subsequent reports have suggested efficacy of onaA in reducing pain of vulvodynia. Pelletier et al. (2011) injected 100 units of onaA into the vulvar vestibule (50 units on each side) of 20 affected patients. At 3 months postinjection, both pain (measured by VAS) and quality of life improved significantly compared to baseline values. The mean VAS score decreased from 8.37 to 1.22 ($p<0.001$) for 20 patients. The quality and frequency of sexual activity during the first 6 months after injection also improved ($p<0.001$). In another retrospective study, the authors (Jeon et al. 2013) described the efficacy of onaA compared to gabapentin in 73 patients with vulvodynia. The onaA dose utilized varied from 40 to 100 units (most patients received >70 units). The mean pretreatment VAS score was 8.6 (range, 6–10) for the gabapentin treatment group and 8.1 (range, 5–10) for the botulinum toxin A treatment group. Posttreatment VAS scores were significantly reduced for each group (VAS was reduced to 3.2 from 8.6 in the gabapentin group and to 2.5 from 8.1 in the botulinum toxin A group, $p<0.001$). The authors commented that lack of response in the controlled study of Petersen et al. (2009) could have been due to the low dose of BoNT (20 units of onaA) used in that study. Different techniques of injection have been employed in the BoNT studies of vulvodynia. The technique employed by Goldstein et al. (2011) is illustrated in Fig. 9.3.

Comment

Controlled and blinded information regarding the treatment of vulvodynia and vestibulodynia face similar criticisms as those conducted in interstitial cystitis. A number of open studies with larger doses of onaA (40–100 units) suggest efficacy, whereas the sole blinded study that used much lower dose (20 units) did not find any difference between the onaA and placebo group. However, in this study, onaA effectively reduced the subjects' pain compared to baseline similar to the placebo. Hence,

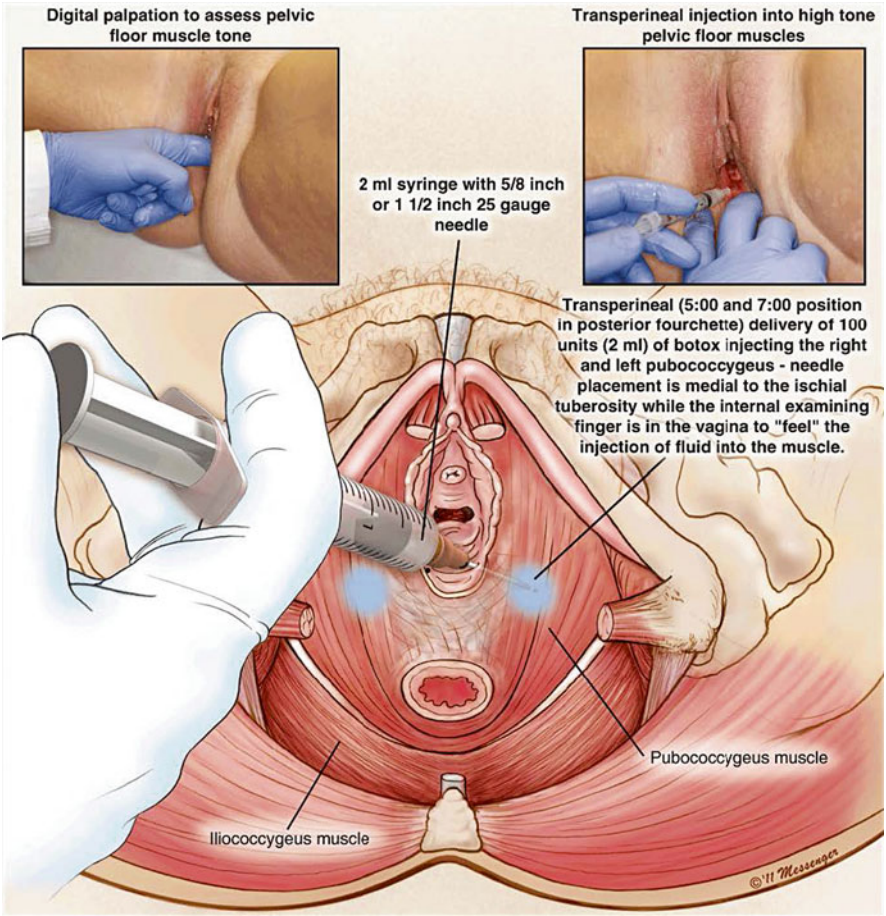

Fig. 9.3 Sites of BoNT injection for vulvodynia (From Goldstein et al. (2011). Reprinted with permission from *Journal of Sex Medicine* © 2011 John Wiley and Sons Inc)

findings of this study may merely show a population with high placebo effect and not necessarily the lack of efficacy for onaA. Considering these issues, elucidation of the true efficacy of BoNT treatment in vulvodynia requires conducting larger studies with higher doses of BoNT, hopefully with less placebo effect.

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Chapter 10
Botulinum Toxin Treatment of Chronic Facial Pain: Trigeminal Neuralgia, Temporomandibular Disorders, and Dental-Related Pain

Abstract Chronic facial pain is physically and emotionally disabling. Trigeminal neuralgia, pain associated with temporomandibular disorders, and dental-related pain are some of the most common forms of chronic facial pain. Despite the advances in pharmacological therapy of these disorders, many patients with these ailments remain unsatisfied with the level of pain relief. This chapter begins with a review of clinical features, pathophysiology, and conventional treatment of these three forms of chronic facial pain. The literature in the efficacy of botulinum neurotoxins (BoNTs) in trigeminal neuralgia, pain related to temporomandibular disorders, and dental disorders is reviewed. Case reports from the author's experience are provided in selected patients. A comment page, at the end of each section, critically reviews the technical and dosage issues and provides recommendations for the design of future studies.

Currently, a significant level of efficacy for local use of botulinum toxins can be ascribed only for trigeminal neuralgia (one class I study, level B, probably effective). In temporomandibular pain, data generated from retrospective studies and observation of experienced clinicians suggesting efficacy are encouraging, but solid blinded and controlled studies are lacking and very much needed. In chronic neuropathic pain following dental procedures, the positive data on the local use of BoNTs is limited to few anecdotal observations.

Keywords Facial pain • Trigeminal neuralgia • Temporomandibular disorder • Temporomandibular joint • Dental pain • Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA • AbobotulinumtoxinA

Introduction

Management of facial pain is a major challenge in clinical medicine. Most facial pains reflect a form of neuropathic pain. The role of botulinum toxins in neuropathic pain (including trigeminal neuralgia) is of considerable interest (Brown et al. 2014). Facial pain is treated separately in this chapter since the pathophysiology of pain in a vast majority of cases pertains to the dysfunction of a single cranial nerve.

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Trigeminal Neuralgia

Trigeminal neuralgia is one of the most painful of human afflictions. Its incidence in the USA is estimated at 4/100,000 individuals (Katusic et al. 1990). Women are more frequently affected. The peak age of onset is between 50 and 70 years (Yoshimasu et al. 1972).

The pain is severe and often described as jabbing, stabbing, and shock-like. It involves one side of the face and may affect any branch of the trigeminal nerve, but the ophthalmic and maxillary branches are more commonly affected. The pain usually lasts for seconds, but durations of up to 2 min are also observed. Bouts of pain may occur multiple times a day and disable the patient. Facial movements, eating, speaking, chewing, and shaving often exacerbate the pain. Many patients have local trigger points in the face that upon touching provoke severe pain. In the chronic state, a high proportion of the patients live in constant fear and anticipation of upcoming bouts of pain. Table 10.1 summarizes the clinical features of TN and provides a list of differential diagnoses.

Pharmacological approaches to therapy include antiepileptic drugs such as carbamazepine, oxcarbazepine, and gabapentin that specifically block pain mediators and GABAergic medications such as baclofen (30–60 mg) which enhances inhibitory mechanisms (Fromm et al. 1981). In one blinded study, combination of carbamazepine and baclofen proved more effective than either of the two alone (Fromm et al. 1984). Unfortunately, with passage of time, patients will require more analgesics and higher doses of medications to control pain with the risk of developing more side effects (particularly among elderly). Narcotic analgesics are not usually helpful.

In many cases, trigeminal neuralgia is caused by an anomalous artery or vein impinging against the trigeminal nerve at or close to its exit point from the brain stem. This compression causes focal demyelination in the nerve which, over time, leads to generation of ectopic discharges. Hence, in recalcitrant cases, surgical intervention may prove helpful. The anomalous vessel can be surgically lifted from the nerve during decompression surgery (Brown 2014). Gamma Knife surgery is also effective; the frequency of this approach is increasing (Baschnagel et al. 2014). Both approaches are not devoid of side effects which may be substantial and include permanent ataxia, brain stem damage, and cranial nerve palsies. It is currently believed that at least half of the patients with TN are not satisfied with their medical management. Therefore, a pharmacological agent with low incidence of side effects would be welcome in the management of TN.

Anatomy and Physiology of Trigeminal Sensory System

Sensations from the face, gums, inner part of the cheeks, and teeth are conveyed to the central nervous system via three branches of the trigeminal nerve, namely, the ophthalmic, maxillary, and mandibular. The ophthalmic branch innervates the skin

Table 10.1 Diagnostic criteria of trigeminal neuralgia (TN) and how these compare with other entities in the differential diagnoses

Symptom	TN	Pulpitis	TMD	Neuropathic trigeminal pain	SUNA/SUNCT	Paroxysmal hemicrania
Character	Shooting, stabbing, sharp, electric	Sharp, aching, throbbing	Dull, aching, nagging, sharp at times	Aching, throbbing	Burning, stabbing, sharp	Throbbing, boring, stabbing
Site/radiation	Trigeminal distribution only, intraoral and extraoral, affects V(a) rarely	Around a tooth, intraoral	Preauricular, radiates down the mandible, temple area, may be postauricular or neck	Around tooth or area of trauma/dental surgery or facial trauma	Periorbital but can affect maxillary division	Orbit, temple
Severity	Moderate to severe	Mild to moderate	Mild to severe	Moderate	Severe	Severe
Duration	1e60 s refractory period	Rapid but no refractory period	Not refractory, lasts for hours, mainly continuous, can be episodic	Continuous soon after injury	Episodic 5e240 s	Episodic 2e30 min
Periodicity	Rapid onset and termination, complete periods of remission weeks to months	Unlikely to be more than 6 months	Tends to build up slowly and diminish slowly, lasts for years	Continuous	Numerous, can be periods of complete remission	1e40 a day, can be periods of complete remission
Provoking factors	Light touch, non-nociceptive	Hot/cold applied to teeth	Clenching teeth, prolonged chewing, yawning	Light touch	Light touch	Nil
Relieving factors	Keeping still, drugs	Avoid eating on that side	Rest, decrease mouth opening	Avoid touch	Nil	Indometacin
Associated factors	Local anesthetic placed in trigger area relieves pain	Decayed tooth, exposed dentine	Muscle pain in other parts of the body, limited opening	History of dental treatment or trauma in the area	Often restless	May have migrainous features

From Zakrzweska and Mc Millan (2011), reprinted with permission
SUNA short unilateral neuralgiform pain with autonomic symptoms, *SUNCT* short unilateral neuralgiform pain with conjunctival tearing, *TMD* temporomandibular disorder

of the forehead and top of the head and provides corneal sensation. The ophthalmic sensory branch to the cornea is the afferent arm of the corneal reflex, one of the most informative reflexes used in clinical medicine. The ophthalmic branch enters the cranium through the superior orbital fissure, travels with the maxillary branch in the cavernous sinus, and then along with the maxillary and mandibular branches converges into the trigeminal ganglion (Gasserian ganglion), located in the middle fossa.

The maxillary branch of the trigeminal nerve innervates the middle part of the face, cheek, upper teeth, and mucosa of the nasal cavity, soft and hard palates, and the pharynx. Innervation of the nasal mucosa is the basis for sternutatory reflex (unilateral grimacing after gently putting a Q-tip inside one nostril) that tests the integrity of the maxillary branch of the trigeminal nerve. The maxillary nerve leaves the face through the inferior orbital fissure and enters the skull via the foramen rotundum.

The sensory part of the mandibular nerve (third division of trigeminal nerve) carries information from the skin of the lower face, side of the face and head, lower teeth, anterior two thirds of the tongue, and mucosa of the mouth and cheeks. The mandibular nerve enters the skull via the foramen ovale and ends in the inferior part of the trigeminal ganglion.

Many major pain mediators, specific pain receptors, and pain-activating voltage-gated sodium channel are highly expressed in the neurons of trigeminal ganglia and trigeminal nerve endings. Cultured trigeminal neurons, within days, release large amounts of calcitonin gene-related peptide (CGRP), a major inflammatory pain mediator (Durham et al. 2004). Transient receptor potential vanilloid 1 (TRPV1), a cation channel, is recognized as a major contributor to nociception since its activation releases CGRP. TRPV1 is highly expressed in a large number (≥90 %) of trigeminal neurons (Meng et al. 2009). More recently, the role of endothelins (A and B) has been investigated as pro-nociceptives in the trigeminal system (Chichorro et al. 2010).

Botulinum Toxin Treatment of Trigeminal Neuralgia

Since 2002, a total of eight studies have reported on the efficacy of BoNT treatment in trigeminal neuralgia (Borodic and Acquadro 2002; Turk et al. 2005; Bohluli et al. 2011; Piovesan et al. 2005; Zuniga et al. 2008; Wu et al. 2012; Shehata et al. 2013; Wang et al. 2014). One study was prospective and double blind (class I) (Wu et al. 2012). Of the remaining seven, one was single blind and prospective (Shehata et al. 2013), while the six were retrospective. All used type A toxin and reported various degrees of pain relief with no serious side effects. In the retrospective studies, some did not mention the exact type of A toxin or the number of injections. The two blinded studies are described in some detail here.

Wu et al. (2012) enrolled 42 patients with trigeminal neuralgia in a 13-week, randomized, parallel design, double-blind, placebo-controlled study. Forty patients, 21 in the BoNT and 19 in the saline (placebo) group, completed the study. Botulinum toxin A (Chinese toxin from Lanzhou Institute) was diluted in 1 cc of normal saline and injected, using a 16 mm-long needle, either between the epidermis and dermis

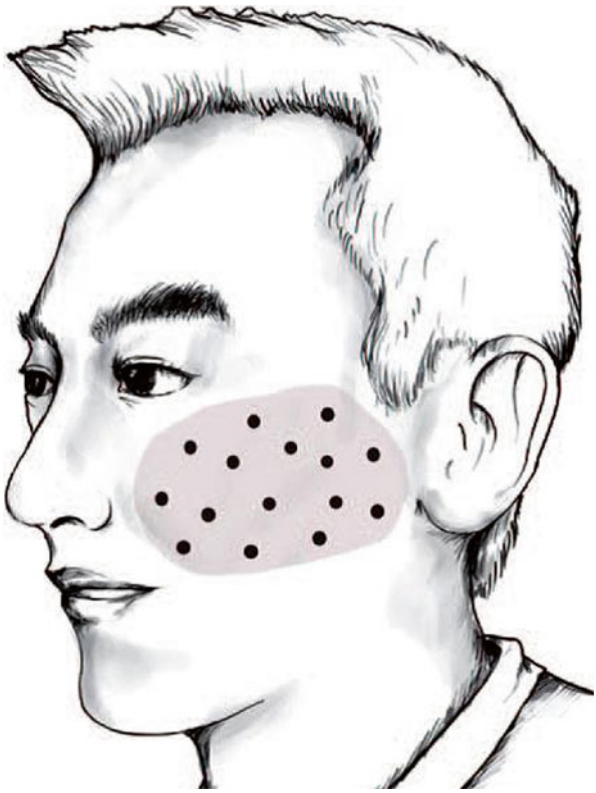

Fig. 10.1 The area of facial pain (highlighted in *gray*) in trigeminal neuralgia and the sites of injections (From Wu et al. (2012), © 2012 SAGE Publications reprinted with permission from SAGE)

or submucosally in the areas affected by pain (Fig. 10.1). Subjects in the BoNT group received 25–75 units, and a comparable volume was administered to the subjects in the saline group. Patients remained on the same dose of their medications (carbamazepine, gabapentin, and pregabalin) during the study.

The primary outcome was a significant change in pain frequency and intensity (VAS) compared to placebo. Secondary outcomes were patient global impression of change (PGIC) and proportion of responders defined as 50 % or more compared to baseline. Both primary outcomes and all the secondary outcomes improved significantly in the BoNT group compared to the placebo ($p<0.001$). Side effects were noted in the subjects who received BoNT; seven developed mild facial asymmetry which disappeared after 7 weeks, and three developed local facial swelling which subsided in a week.

In the single blind study of Shehata et al. (2013), 20 subjects with TN were randomized into BoNT and placebo groups. In the BoNT group, the subjects received subcutaneous injections of 40–60 units of onabotulinumtoxinA into 8–12 points (five units per point) in the face. Primary outcome was a decrease in pain intensity at 12 weeks measured by VAS compared to the placebo. At 12 weeks, the onaA group demonstrated a reduction of 6.5 points in the VAS compared to three points in the placebo group ($p=0.0001$). As a secondary outcome, quality of life also improved significantly, and more patients in the BoNT were able to reduce the number of their pain medications.

Case Report 10-1

A 41-year-old woman was referred to the Yale Botulinum Neurotoxin Treatment Clinic for consideration of BoNT therapy for a disabling trigeminal neuralgia. She began to have severe left-sided face pain and headaches following a car accident 20 years earlier. The pain was dull and deep at first but gradually transformed into bouts of sharp and jabbing pain lasting 15–20 s. Many factors provoked pain especially exposure to cold environment. She reported several trigger points close to the nose and corner of the mouth, making application of the makeup difficult. In "bad days," pain affected the region around the left eye and made it "twitch."

The patient had tried multiple medications for the pain including beta-blockers, antiepileptic drugs, calcium channel blockers, nonsteroidal anti-inflammatory drugs, oxycodone, and acupuncture. She had had three surgical procedures in the past: decompression surgery via retro-mastoid craniotomy for relieving pressure upon the trigeminal nerve, exploration for possible CP angle pathology (second surgery), and cortical stimulation for pain relief. None of the three procedures relieved her pain. Patient described constant daily background facial pain with superimposed bouts of sharp pain. Past medical, family, and social history disclosed no issues of concern.

On examination, several trigger points were identified on the left side of the face close to the nose and corner of the mouth. A total of 30 units of onaA was injected subcutaneously in 20 sites (1.5 units per site) into the V2 distribution. In addition, another 10 units (4 points) was injected into the left frontalis (2.5 units, 4 sites) and 5 units into the anterior temporal region (2.5 units, 2 points) (Fig. 10.2).

After 2 weeks, patient reported marked reduction in severity of pain (from level 9 in VAS to 2) and in the frequency of sharp pains (90 % less). This response lasted for 5 months at which time the severity of pain returned and required another injection that produced a similar effect. No side effects were reported. Patient described her experience as very satisfactory in patient global impression of change.

The Mechanism of Action of BoNT-A in Trigeminal Neuralgia (TN)

The data from cell culture and animal studies explains some of the mechanisms through which administration of BoNTs relieves pain in trigeminal neuralgia. Addition of onaA to the cultured trigeminal neurons results in marked reduction of CGRP release from stimulated trigeminal neurons (Durham et al. 2004). In acute infraorbital nerve injury that causes significant local allodynia in the rat, subcutaneous injection of onaA improved allodynia and reduced release of pain mediators from disconnected trigeminal neurons (Kitamuaraet al. 2009).

Addition of A/E chimera of botulinum toxin (which specifically targets sensory neurons) to the trigeminal cell culture inhibits the release of CGRP secondary to activation of TRPV1 (Meng et al. 2009). Furthermore, subcutaneous injection of 0.25 and

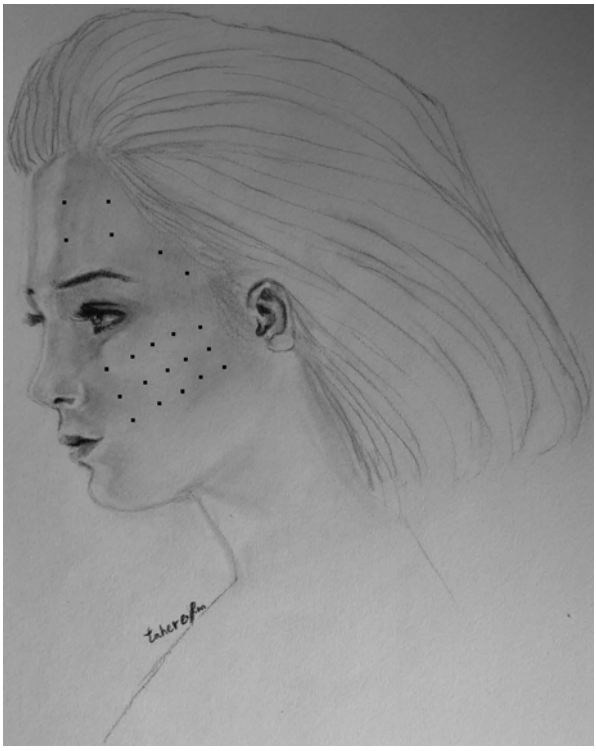

Fig. 10.2 Case report 10-1, trigeminal neuralgia. The dose is two units per site for injections in the V2 distribution and 2.5 units per site in V1 and other sites (Created by Tahereh Mousavi; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

0.5 ng/kg of botulinum toxin A (onaA) into the rat's face markedly reduces the expression of TRPV1 in the trigeminal neurons within 2 days (Shimizu et al. 2012).

Matak et al. (2011) maintain the view that the analgesic effect of the BoNT-A in experimental trigeminal neuralgia of rats (formalin injection into the whiskers) results in a large part from a direct central effect of the toxin. In this model, after BoNT-A administration, the authors have detected presence of truncated SNAP25 in the sensory trigeminal nucleus in the medulla. The analgesic effect of the toxin was blocked by injection of colchicine into the trigeminal ganglia which blocks and prevents the toxin from reaching the CNS.

Comment

The efficacy of botulinum toxin treatment for trigeminal neuralgia is supported by a single controlled, double-blinded study (Wu et al. 2012). Using the criteria of the Assessment Subcommittee of the American Academy of Neurology (Appendices 3.1 and 3.2), this study qualifies as a class I study. The level of evidence for one class I study is defined as level B; BoNT-A is probably effective in trigeminal neuralgia. In a more recent study (Zhang et al. 2014), have shown that a dose of 25 units is as effective as 75 units in trigeminal neuralgia (using Wu's method and toxin).

Much remains to be established regarding the correct type of toxin, technique, dose, and number of injections. A dose of 30–40 units, injected into 15–20 sites, per side seems reasonable, but focal injections with a large dose such as 100 units in zygoma in two sites (Turk et al. 2005) probably run the risk of unacceptable facial weakness. The type of toxin reported in the blinded study of Wu et al. (2012) is the Chinese toxin that is unfamiliar to most researchers and clinicians in the West. How the units of this toxin translate to the more commonly used type A toxins (ona-, abo-, and inco-BoNT-As) or the B toxins is still a matter of debate. In our clinic, we have been successful in using 30–40 units of onaA (per side) in a half dozen of patients with trigeminal neuralgia.

Despite limitations, the current data in botulinum toxin treatment of TN is welcoming news since even with new analgesics (gabapentin and pregabalin), at least half of the patients with TN remain unsatisfied with their pain management. The persistent pain is often severe and the cause of significant emotional and psychosocial distress. Botulinum toxins, when effective, usually provide prolonged relief (3 months or longer) and in general are safe and well tolerated. The study of Wu et al. (2012) and the positive data derived from it has opened the door for refinement of the technique and better definition of optimum dosage through future controlled and blinded studies.

Temporomandibular Disorders (TMDs)

Temporomandibular joint disorders are a group of conditions related to pathological processes which affect the jaw and muscles of mastication (Song et al. 2007). Temporomandibular disorders may be myogenic or arthrogenic depending on the source of pathology. The former arises from myofascial involvement of the masseter, lateral pterygoid, and temporal muscles, while the latter originates from pathology of the temporomandibular joint. The prevalence of TMD in general population is hard to define due to overlap of clinical symptomatology with other facial pain disorders. Manfredini et al. (2011) reported the following prevalences in TMD based on the underlying pathology: disc disease 25 %, myofascial masseter pain 12.9 %, and inflammatory pain of the temporomandibular joint 8.9 %. The underlying pathology is difficult to discern with certainty in a majority of patients.

Pain is a major symptom of TMDs. It can be localized to the temporomandibular joint with local tenderness at palpation, or it may be felt over the masseters as a myofascial pain syndrome. Some patient presents with limitation of jaw opening often associated with disturbing jaw pain. In case of a dislocated joint, the patient often experiences a clicking sound at the region of the joint upon jaw movements. Associated headache is not uncommon and could take the form of tension or migraine headaches. Schiffman et al. (2012) indicated a sensitivity of 89 % with specificity of 87 % ($p<0.001$) for the following two criteria in TMD headache: (1) temple area headache that changes with jaw movement and (2) provocation of that headache by temporalis muscle palpation or jaw movement. Limitation of jaw

opening can be confused with dystonia of jaw opening—a form of focal dystonia which also may cause pain. Additional forms of facial pain in OMDs also occur which at times take the form of sharp and fleeting pains and can be confused with trigeminal neuralgia. The differential diagnosis also includes other common conditions such as pain of sinusitis or root and muscle pain related to cervical osteoarthritis. The condition is often difficult to diagnose due to the overlap of symptomatology with the aforementioned facial and neck pain disorders. Graff-Radford and Bassiur (2014) suggest that clinicians should highly consider the diagnosis of TMD if at least three of the following four features exist: (1) pain in the preauricular and temporal region brought on by functions such as chewing; (2) pain on palpation over the TMJ; (3) joint noise such as clicking, popping, or crepitus; and (4) limited range of motion of the TMJ.

Treatment

The first line of treatment includes noninvasive measures such as massage, warm compresses, and physical therapy. Physical therapy encompasses posture training exercises, joint mobilization, orthotic devices, and splint therapy. Other modes of treatment such as electrotherapy, ultrasound, laser therapy, and acupuncture have also been employed, but their efficacy is in question (Graff-Radford and Bassiur 2014). Pharmacological agents such as nonsteroidal anti-inflammatory drugs, muscle relaxants, tricyclic antidepressants, and antiepileptic analgesics (gabapentin, pregabalin) may provide partial relief. Opioid analgesics are used for recalcitrant pain, but significant relief occurs only in half of the patients with non-cancer-related pain (Zenz et al. 1992). Surgical intervention is considered the last resort and, depending on the pathology of TMD, consists of disc repositioning, repair of disc perforation, disc recontouring, lysis of adhesions, and discectomy (Vallerand and Hall 1991).

Botulinum Toxin Treatment of TMDs

In 1997, Daelen et al. and Moore and Wood independently reported that botulinum toxin A may prevent TM joint dislocation and relieve TMJ pain in patients with TMD due to masseter and lateral pterygoid spasticity. The former authors described a 56-year-old man with multiple sclerosis and frequent dislocation of TM joint due to spasticity in whom administration of onaA into the masseter and lateral pterygoid muscles resulted in correction of dislocation and pain relief. The positive results lasted for 4 months and were reproducible with repeat injections. The patient reported by Moore and Wood (1997) received 75 units of onaA into each lateral pterygoid muscle and had similar results lasting for 10 months.

For the past 15 years, a number of retrospective studies have supported these observations (Freund and Schwartz 2003, Von Linden 2001). Similar favorable opinion regarding treatment of TMD with BoNTs has been reported by clinicians with considerable expertise in the use of BoNTs in head and neck pain disorders (Blitzer et al. 1989).

Two blinded, placebo-controlled studies, however, provided contradictory results. In one study (Kurtuglu et al. 2008), 24 patients with TMD with symptoms referable to the masseters and temporalis muscles were randomized to BoNT-A and saline groups. BoNT-A was injected under electromyographic guidance into the masseter and temporalis muscles. Patients were evaluated with a biobehavioral questionnaire that included assessment of pain and psychosocial status at baseline, 14, and 28 days after injection. Patients in the toxin group demonstrated improvement of pain and psychosocial status compared to placebo both at 14 and 28 days.

Ernberg et al. (2011) conducted a double-blind, crossover, multicenter study on 21 patients who met the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMDs) (Dworkin and Le Resche 1992). The group was heterogeneous, but most patients had myofascial pain in the masseter region. A total of 50 units of BoNT-A was injected into the masseter muscles. Subjects were tested with a variety of scales for pain, quality of life, and psychosocial effects. Regarding pain, a 30 % decrease in VAS was considered significant since this degree of pain reduction has been shown to correspond to "much improved" reported by patients in the patient global impression of change (PGIC); 50 % reduction would correspond to "very much improved" (Farrar et al. 2001). Weekly change in VAS (30 % or more) was considered as the primary outcome of the study. Both onaA and placebo improved pain by 30 % or more, but the difference between the two groups was not significant. The authors mentioned several shortcomings of the study which include small number of patients and injections limited to the masseter muscles.

Comment

Botulinum toxin treatment of temporomandibular disorders is complicated due to the variability of symptomatology which may require different injection schemes and dosage per given patient.

Recently, Blitzer's group in New York reported (Song et al. 2007) a success rate of 60 % with onaA in relieving pain of over 200 patients with TMDs. They used a dilution of 50 units/cc and injected 50 units into each masseter muscle. Masseter was injected in five points and temporalis in four points at each side. At Yale, we have had a similar experience (success rate of 50 %) in a smaller number of patients with the same dose/masseter while using a dilution of 100 units/cc. The temporalis and pterygoid muscles are also often injected.

The negative double-blind study of Ernberg et al. (2011), as the authors pointed out, had shortcomings. The injections were limited to the masseter muscles, and the injected dose was small, 25 units per masseter versus 50–100 units/masseter used by others (Song et al. 2007, Von Linden 2001). Finally, in this study, both the BoNT and placebo groups showed the targeted primary outcome—VAS improvement of 30 % or more—a finding that may merely represent a large placebo effect and would not necessarily negate the efficacy of the toxin. Another issue of concern in this study is the higher incidence of weakness in the placebo group compared to the onaA group.

We conclude that a technique that combines onaA injection of the masseter and temporalis muscles (and sometimes also the lateral pterygoid) has shown efficacy against the pain of TMD in the practice of experienced clinicians and in the open studies. Since no class II studies exists in this area (Erenberg's double-blind study is probably class III), we consider the evidence for efficacy of BoNT in TMD at this time as at U level, i.e., inconclusive (Appendices 3.1 and 3.2, AAN's subcommittee guidelines). Future, larger blinded studies are needed, which should preferably employ the technique and doses which are reported effective in open observations.

Case Report 10-2

A 29-year-old female visited the Yale Botulinum Toxin Treatment Clinic for evaluation of jaw stiffness, tenderness over the right masseter and temporomandibular joint, and right-sided headaches. She noted the onset of her symptoms about 8 years ago. The symptoms gradually increased in severity. The headaches, in particular, became disabling occurring almost daily with marked exacerbations several times per week. During swallowing and chewing, she often heard a clicking sound bilaterally. Treatment with a variety of analgesic medications including tricyclic antidepressants, nonsteroidal anti-inflammatory agents, and antiepileptic drugs failed to relieve the pain. Her past and family history was noncontributory. She did not smoke or drink alcohol and did not use illicit drugs.

The general medical examination was normal. Opening and closing of the jaw caused discomfort. The regions of the right masseter and temporalis muscles were tender to touch. Neurological examination including assessment of cognition, cranial nerves, motor and sensory systems, cerebellar testing, speech, gait and stance, and reflexes was normal. A detailed ear-nose and throat evaluation showed no abnormality. Imaging studies of the brain and TM joints were normal.

onaA was injected bilaterally into the masseter and temporalis muscles (Fig. 10.3). The dose per masseter was 40 units (divided into two 20 unit injections at two sites), while the dose per temporalis muscle was 20 units per side (2 injections, each 10 units). A week after the injection, the patient reported marked reduction of jaw stiffness, masseter pain, and headaches reflecting a 90 %

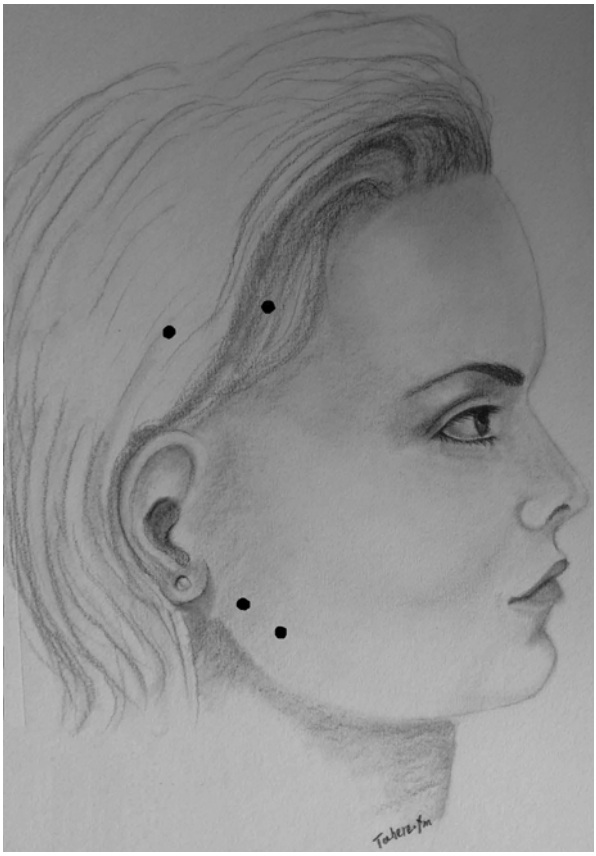

Fig. 10.3 Case report 10-2, temporomandibular joint disorder. Sites of injections: two injections 20 units each into the masseter and two injections 10 units each into the temporalis muscle on each side. Patient keeps the teeth clenched during the injections (Created by Tahereh Mousavi; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

improvement. In patient global impression of change, her impression was "very much improved." The improvement lasted for 3 months. Repeat injections over a year of follow-up (every 4 months) had the same effect.

Pain Related to Dental Procedures

A variety of dental procedures may damage the branches of trigeminal nerve and cause chronic pain in the oral cavity. Tinastepe and Oral (2013) have recently reviewed the issue of neuropathic pain after dental procedures. Extraction of the third molar tooth can damage the inferior alveolar nerve (IAN), lingual nerve, or buccal nerve due to proximity of the tooth's root to the mandibular canal. Permanent deficits and symptoms including pain have been reported in 2 % of the patients after this procedure (Renton et al. 2005).

In dental implantation, permanent symptoms due to IAN damage occur in 1–8 % of patients due to bone removal and detachment of the mucoperiosteal flap (Ellies and Hawker 1993). The incidence of chronic pain per se is not known, however (Gregg 2000). Persistent pain has been reported in 3–13 % of the patients after root canal treatment of molar teeth (Knowles et al. 2003; Pogrel 2007), and phantom tooth pain occurs in 2–3 % of the patients with orthodontic procedures on these teeth (Reinhilde et al. 1998; Campbell et al. 1990). Procedure -related dental pain is generally treated with conventional analgesic drugs such as tricyclic antidepressants, nonsteroidal anti-inflammatory agents, and antiepileptic drugs with efficacy in neuropathic pain (gabapentin and pregabalin).

Botulinum Toxin Treatment of Chronic Pain After Dental Procedures

No randomized clinical trials (RCTs) are available pertaining to neuropathic pain secondary to dental procedures. The patient presented below is from the author's positive experience in a patient with chronic, severe, refractory pain after molar extraction.

Case Report 10-3

A 60-year-old gentleman, successful physicist, developed marked allodynia of the gum and bouts of severe, jabbing pain in the gum close to the site of extraction radiating to the upper lip on the left side, following extraction of the molar teeth on that side 3 years ago. His past medical history was negative. The bouts of sharp pain occurred several times daily and were rated 9 or 10 on VAS. The area of pain was sensitive, interfering with brushing of the teeth. Many different analgesic medications failed to control the pain; his current medication was gabapentin (600 mg four times daily).

On examination, areas of exquisite painful hypersensitivity to touch (allodynia) were noted over the gum at and slightly anterior to the site of extraction as well as over the upper lip on that side (Fig. 10.4). Injection of 10 units of onabotulinumtoxinA into the allodynic area of the gum, 2–3 mm below the surface (2.5 units at 4 sites), resulted in marked reduction of allodynia and cessation of the episodic pain after 1 week. The pain returned to the same level after 6 months. A repeat injection had the same effect. The patient rated his impression of change in PGIC as "very much improved."

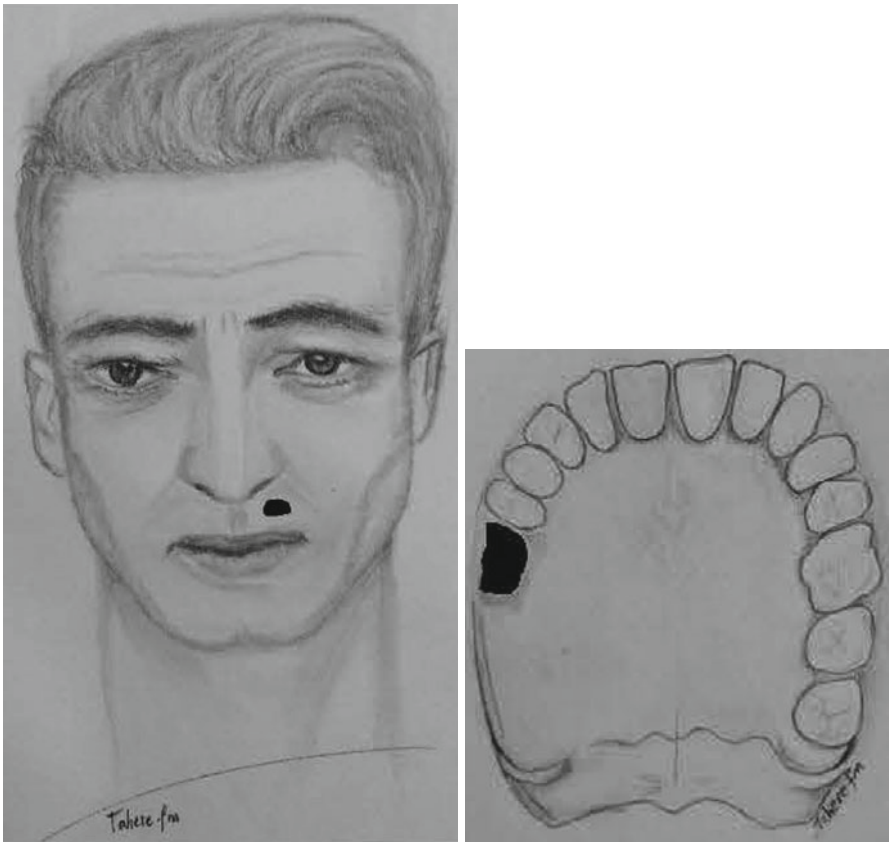

Fig. 10.4 Case report 10-3. The sites of pain on the gum around the extracted teeth and the upper lip are marked with dark ink. onaA was injected into the marked area of the gum (four 2.5 units, total 10 units) (Created by Damoun Safarpour; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

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Chapter 11
Botulinum Neurotoxins for Relief of Pain Associated with Spasticity

Abstract Spasticity is a common and disabling complication of stroke, multiple sclerosis, brain and spinal cord injury, and cerebral palsy. Pharmacological treatment, although effective, is confounded by undesirable side effects and short duration of response. Botulinum neurotoxins (BoNTs) have been approved by FDA for treatment of spasticity. The role of BoNT therapy in spasticity-related pain is less established. In this chapter, the literature from double-blind, placebo-controlled studies on this subject is reviewed.

Nine double-blinded, placebo-controlled studies included assessment of pain in the investigation of BoNT efficacy in upper limb spasticity. Four studies that used validated pain scales (visual analog scale, VAS) reported efficacy for abobotulinumtoxinA (aboA) in spasticity-related pain (level A, effective). For lower limb spasticity-related pain, the data is limited to three controlled studies. One study demonstrated efficacy for onaA using a validated pain scale (level B, probably effective) and another for aboA using a scale of 0–5 for assessment of pain. In cerebral palsy (CP), one blinded study reported significant relief of spasticity-related pain after administration of onabotulinumtoxinA (up to 12 units/kg) in children (level B, probably effective, one class I study). A number of open studies have also suggested efficacy for other types of BoNTs in children suffering from CP. Overall, this encouraging literature shows an increasing role for BoNTs in treatment of spasticity-related pain.

Keywords Spasticity • Pain • Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA • AbobotulinumtoxinA • IncobotulinumtoxinA • RimabotulinumtoxinB • Cerebral palsy

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Introduction

Spasticity is a clinical condition caused by damage to the central nervous system (brain or spinal cord) and characterized by a velocity-dependent increase in stretch reflex (muscle tone), in the absence of volitional activity (Lance 1980). Many affected patients also demonstrate pathological reflexes and signs (Babinski reflex, Wartenberg's sign) denoting CNS damage. Spasticity occurs in 38 % of patients with stroke (Watkins et al. 2002), half of the patients with brain injury (Wedekind and Lippert-Grüner 2005), and one third of the patients with spinal cord injury (Noreau et al. 2000). Rizzo et al. (2004) found mild to severe spasticity (19 % mild, 17 % moderate, 13 % severe) in 49 % of 513 patients surveyed from North American registry for multiple sclerosis. In one third of the group, impairment of quality of life could be attributed to spasticity. Lower limb spasticity has been reported in one third of adults after stroke, half to two thirds of patients with multiple sclerosis, and three quarters of children with cerebral palsy (Martin et al. 2014).

Increased tone and stiffness of the muscles in spasticity limits and slows limb movements and, in the lower limbs, also impairs ambulation. Progressive spasticity leads to muscle shortening and contractures with further limitation of movements. Treatment is aimed at reducing muscle tone, preventing complications, and alleviating pain. The incidence of pain in spasticity has not been adequately investigated. In some patients, spasticity-related pain (SRP) is quite severe and more disabling than the spasticity itself.

Pathophysiology of Spasticity and Spasticity-Related Pain (SRP)

The pathophysiology of spasticity has been reviewed recently in a comprehensive two-part article by Gracies (2005a, b). In brief, damage to the central nervous system leads to acute and chronic changes. The acute effects include paresis and short-term immobilization, whereas chronic effects include plastic rearrangements in the CNS as the result of either CNS injury and/or chronic disuse (Fig. 11.1). These changes influence the innervation of the muscles and the reflex arch leading to spasticity, spastic dystonia, and spastic co-contractions. The end result is muscle shortening and contracture caused by chronic spasticity and muscle disuse.

The exact mechanisms through which a state of muscle hyperactivity and spasticity develops after CNS injury are still unclear. As emphasized by Gracies (2005b), extensive sprouting and new synapse formation may play an important role in inducing overactive stretch reflex since the new connections are often hyperexcitable and may act differently from those lost secondary to CNS damage (Gioux and Petit 1993). There is some evidence for both decreased reciprocal I a inhibition (which inhibits alpha motor neurons via a disynaptic interneuron) and decreased I b, nonreciprocal inhibition (which via activity of Golgi tendons limits limb

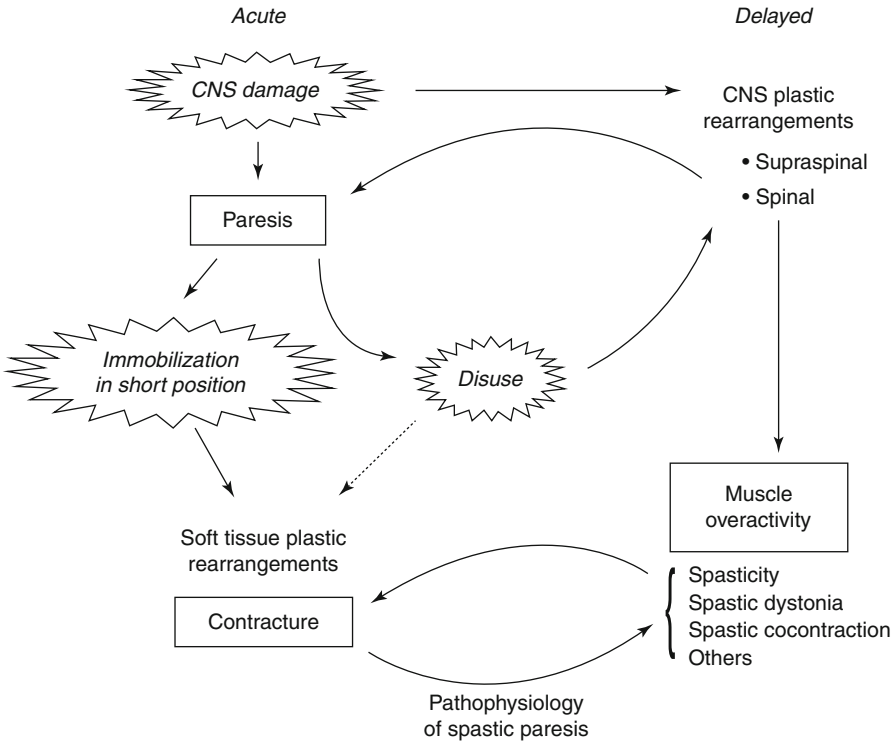

Fig. 11.1 Mechanisms of motor impairment after disruption of the central execution of motor command, paresis, soft tissue contracture, and muscle overactivity (From Gracies 2005 © 2005 Wiley Periodicals Inc, reprinted with permission from John Wiley and Sons)

extension), suggesting contributions from these mechanisms to the increased stretch reflexes in spasticity (Crone et al. 2003). Furthermore, muscle immobility (as seen in spastic paresis) increases the discharge of muscle spindles (Williams 1980) which via the gamma system can lead to increased stretch reflexes and increased muscle tone. Finally, electrophysiological studies of patients with spastic hemiplegia indicate hyperexcitability of small group II afferents (originating from spindle's secondary endings) which in a normal state inhibit motor neurons via spinal interneurons (Marque et al. 2001). The function of these type II afferents is modulated and inhibited by descending rubro- and vestibulospinal pathways that often get damaged in CNS injuries.

On the other hand, Renshaw cell inhibition (RCI) and direct alpha motor neuron hyperexcitability do not seem to play a major role in spasticity. In fact, in human, RCI has been shown to increase after CNS damage and in the presence of spasticity (Katz and Pierrot-Deseilligny 1982).

Spasticity may cause pain through a variety of mechanisms. Some spasticity-related pain (SRP) occurs in the form of muscle spasms caused by increased muscle

tone and enhanced reflex activity. The pain could arise from the affected joints that are limited in movement by the attached stiff, spastic muscles. The frequent pain from spastic muscles and painful joints can also set in motion spinal and supraspinal circuits which cause central sensitization leading to pain chronicity (Chap. 2). In small children, adductor spasticity could lead to hip subluxation and pain.

Treatment of Spasticity

Treatment of spasticity is heavily weighed on pharmacological agents which can cause muscle relaxation. The commonly used drugs for treatment of spasticity include GABAergic agents such as baclofen and benzodiazepines. Tizanidine, an alpha adrenergic drug and a potent muscle relaxant, is also widely used. Unfortunately, severe spasticity often requires larger doses of these medications that are beset by emergence of undesirable side effects (sedation, hypotension). Severe and advanced cases of spasticity (especially in the lower limb) may require baclofen pump placement. Although treatment of spasticity may alleviate the associated pain, in most cases, addition of analgesic drugs is required. The commonly used pharmacological agents include tricyclic antidepressants, nonsteroidal anti-inflammatory agents, and, in severe cases, opioid analgesics.

Botulinum Toxin Studies in Spasticity That Have Included Assessment of Pain

This section covers the blinded studies that assessed pain in adults' upper and lower limb spasticity and in spasticity-related pain of children with cerebral palsy.

Upper Limb Spasticity-Related Pain in Adults

A total of nine blinded and controlled studies included pain assessment among the assessed variables evaluated in the investigation and reported in the results. All nine studies found BoNTs (A and B) to be effective against upper limb spasticity (Brown et al. 2014) which led to the FDA approval of onaA for treatment of upper limb spasticity.

Bakheit et al. (2001), in a blinded, controlled study of 59 patients, first reported on evaluation of BoNT efficacy against pain associated with spasticity. The pain was assessed on a 0–3 scale (no pain to severe pain). AbobotulinumtoxinA, 1,000 units, was injected into different arm and forearm muscles. The authors noted no improvement of pain after aboA administration. In 2004, Childers et al. and Brashear et al. also found no pain improvement in their studies of 91 and 15 patients, respectively. The former authors used three different doses of onaA (90, 180, and 360 units),

while the later employed two doses of rimaB (5,000 and 1,000 units). Childers et al. (2004) assessed pain through a 0–4 scale with four being severe pain, whereas the exact method of pain assessment was not defined in Brashear et al.'s study (2004). In agreement with the above studies, another more recent study which assessed the efficacy of aboA (1,000 units) in 55 patients with spasticity also failed to note any significant improvement in pain after administration of the BoNT into the muscles of the upper extremity (Lam et al. 2012). Since the study was conducted in noncommunicative patients, the evaluation of pain was conducted via an observational 0–5 scale (PAINAD).

In contrast to the aforementioned studies, five other blinded studies of BoNTs and spasticity, four using aboA and one rimaB, reported significant improvement of pain after administration of BoNTs into the upper limb muscles. Four of five of these studies used the validated and widely used visual analog scale (VAS).

Suputtitada and Suwanwela (2005), in a study of 50 patients, reported significant improvement of pain after administration of aboA (three doses: 375, 500, and 1,000 units) injected into spastic upper limb muscles. The positive result of this study was supported by another blinded study (Marco et al. 2007) of aboA in spasticity that used 500 units. The assessment tool for pain was VAS in both studies.

Another two blinded studies of BoNT treatment in spasticity that assessed pain via VAS also reported significant pain relief. Shaw et al. (2011) enrolled 333 patients with spasticity in a prospective, placebo-controlled, blinded study. Patients received either placebo, 100, or 200 units of aboA in the spastic upper limb. Reinjections were performed at 3, 6, and 9 months. A significant improvement of pain was noted at 12 months but not at 1 and 3 months. In another blinded study of 163 patients (Rosales et al. 2012), administration of 500 units of aboA into the arm and forearm muscles caused significant pain relief at 4 and 24 months. Marciniak et al. (2012) assessed pain through the short-form McGill Pain Questionnaire in 37 patients with post-stroke shoulder spasticity who participated in a double-blind trial investigating the efficacy of onaA (140–200 units) in spasticity. At 4 weeks, pain was significantly reduced ($P<0.05$) compared to baseline, but the placebo group also demonstrated the same degree of pain reduction.

A recent double-blind study (Gracies et al. 2014) that used rimaB toxin (5,000 and 10,000 units) in elbow flexors also demonstrated significant reduction of pain at 1 month following toxin injection ($P=0.017$). The main features of the nine double-blinded BoNT spasticity studies that have reported on the results of pain assessment are presented in Table 11.1.

Comment

At first glance, the results of BoNT treatment in spasticity-related pain from the nine blinded studies mentioned above may appear controversial or contradictory (four against and five in favor). A more careful evaluation of these studies, however, provides useful explanations for the apparent contradictory results. All four studies

Table 11.1 Blinded, botulinum toxin treatment trials of upper limb spasticity which included assessment of pain

Study	# of pts	Class	Toxin	Dose (U)	Pain scale	Result compared to baseline	Comment
Shaw et al. (2011)	333	I	AboA	100/200	Mean VAS	No significant change at 1 and 3 month. At 12 months, $P=0.002$	Delayed pain relief
Suputtitada and Suwanwela (2005)	50	I	AboA	375/500/1,000	Pain scale?	Improved	
Marco et al. (2007)	31	I	AboA	500	Mean VAS	Pain reduction noted on weeks 1, 2, 3, 4, 5, 6 months ($P=0.001$)	
Rosales et al. (2012)	163	I	AboA	500	Mean VAS	Significant pain reduction weeks 4 and 24	
Childers et al. (2004)	91	I	OnaA	90/180	5-point scale	No significant change	Unvalidated scale?
				360			Low baseline pain
Brashear et al. (2004)	15	I	RimaB	5,000 and 10,000	Pain scale?	No significant change	
Bakheit et al. (2001)	59	I	AboA	1,000	0–3 pain scale	No significant change	Unvalidated scale?
Lam et al. (2012)	55	I	AboA	1,000	Observational scale 0–5	No significant change	Unvalidated scale?

that used an established and validated pain assessment tool (in this case VAS) reported efficacy against pain. Using the assessment criteria of the American Academy of Neurology (Appendices 3.1 and 3.2), the level of evidence for efficacy for aboA in spasticity-related pain of the upper limb (using VAS for pain assessment) is A (established efficacy based on two or more class I studies). The delayed efficacy (at 12 months, probably after third injection) in the study of Shaw et al. (2011) is most probably related to the small dose of aboA used by the investigators (100 and 200 units versus 500 and 1,000 units used by others). Such cumulative, late effect after repeat injections has been reported in other pain indications after BoNT treatment especially with onaA administration in chronic migraine (Aurora et al. 2014). The efficacy of aboA in relieving spasticity-related pain is supported by a recent large prospective, open-label European study (Jost et al. 2014) of 408 patients in which 58.9 % of the patients reported pain relief. Evaluation of the efficacy of the other forms of botulinum neurotoxin in spasticity-related pain deserves further investigation via placebo-controlled studies.

Case Report

A 65-year-old gentleman had suffered an acute cerebral infarct and a left hemiparesis 3 years earlier. The left-sided weakness gradually improved with physical therapy and regular exercise. He visited Yale Botulinum Toxin Treatment Clinic for evaluation and management of spasm and pain in the left pectoralis major and left trapezius muscle. The pain was constant for the past 6 months but also occurred in the form of intermittent spasms and interfered with his sleep.

On examination, the left shoulder was elevated, and the left trapezius muscle demonstrated increased tone. The left pectoralis major muscle was also spastic which, at rest, caused over-adduction of the left arm. Under electromyographic guidance, 120 units of onabotulinumtoxinA was injected into the trapezius and pectoralis muscles (each muscle received 20 units in three sites for a total of 60 units) (Figs. 11.2 and 11.3). After 1 week, the patient reported cessation of spasms and marked improvement of daily discomfort. Repeat injections every 3 months remained effective 4 years postinjection of therapy and are ongoing.

Lower Limb Spasticity-Related Pain of Adults

Three double-blind, placebo-controlled studies have reported on the effects of BoNTs on lower limb spasticity-related pain.

Hyman et al. (2000) studied 74 patients with lower limb spasticity stratified into four groups: placebo group and three groups receiving aboA with doses of 500, 1,000, and 1,500 units, respectively. The frequency of muscle spasms was assessed among other assessments. The authors reported that the frequency of muscle spasms improved in all groups, but the difference between the groups was not significant.

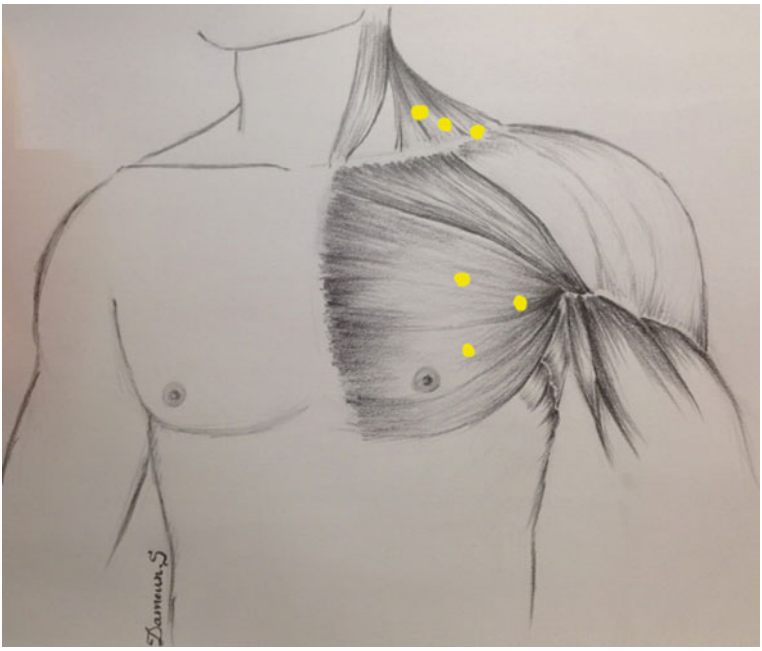

Fig. 11.2 Location of botulinum toxin injections in case 11-1, with left trapezius and left pectoralis major spasticity and pain after stroke. In each muscle, 20 units of onaA is injected in three sites (60 units/muscle) (Created by Damoun Safarpour; published with kind permission of © Bahman Jabbari 2014. All Rights Reserved)

Another group of investigators (Pittock et al. 2003) used the same study design assessing the efficacy of aboA in calf spasticity after stroke. The study encompassed a much larger group of patients (234 from 19 centers), stratified into four groups of placebo and aboA toxin (500, 1,000, and 1,500 units). Injections were made at 4 points into the gastrocnemius muscle. The authors used a 0–3 scale for severity of pain. No pain relief was seen in the placebo group. All three aboA groups reported significant pain relief which was more notable at 8 weeks with 1,000 units ($P=0.0019$) and 1,500 units ($P=0.0066$) but also at 4 weeks ($P=0.0044$ and $P=0.0040$, respectively) and 12 weeks ($P=0.0128$ and $P=0.0488$, respectively). A lower level of pain relief was noted at 8 weeks in the group receiving 500 units ($P=0.0222$).

Dunne et al. (2012) investigated the efficacy of onabotulinumtoxinA in 85 patients (multicenter study) with painful plantar flexor/inverter spasticity after stroke. The frequency of painful spasms was assessed before and after treatment. Three study groups were designed to receive saline, 100, and 200 units of onabotulinumtoxinA. The onabotulinumtoxinA-injected subjects showed significant reduction of spasm frequency (22/54 versus 4/29, $P=0.01$), pain reduction (8/54 versus 1/29, $P=0.02$), and active dorsiflexion (8/54 versus 1/29 $P=0.03$).

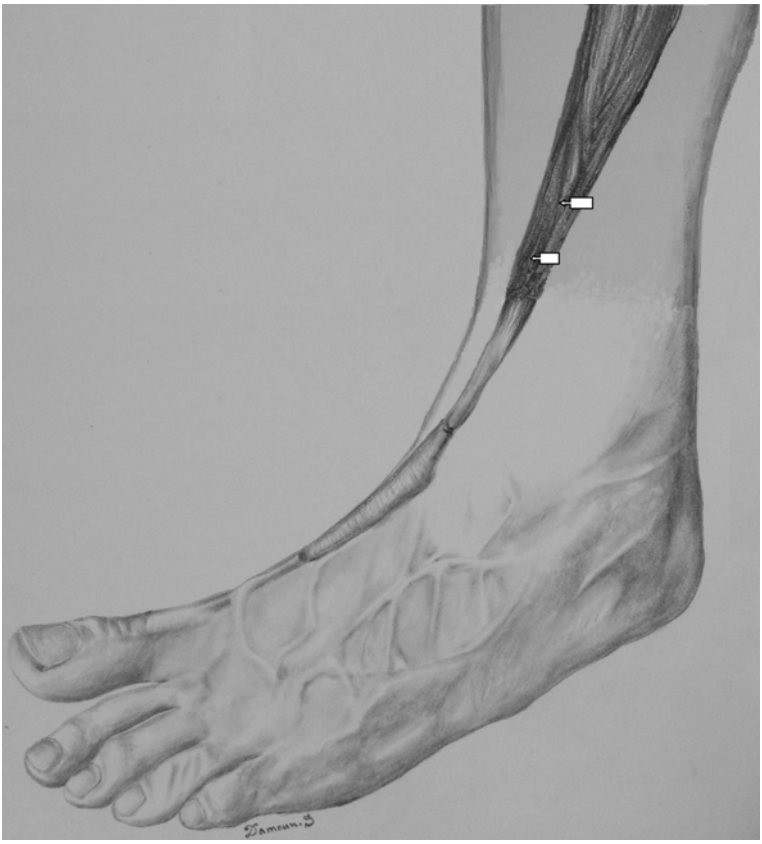

Fig. 11.3 Location of botulinum toxin injection into the extensor hallucis muscle of a patient with multiple sclerosis for relief of spastic, extended, painful big toe. A total of 100 units was injected into two sites (50 units/site) (Created by Damoun Safarpour; published with kind permission of © Bahman Jabbari 2014. All Rights Reserved)

Recently, in a prospective, open-label study (Santamato et al. 2013) of 71 patients with lower limb spasticity using incobotulinumtoxinA (N201), the authors reported significant reduction of spasm frequency at 30 and 90 days. The total dose administered to each patient per session was 180 units. The notable features of BoNT studies in spasticity-related pain of the lower limbs are shown in Table 11.2.

Comment

Information regarding the effects of BoNT therapy on lower extremity spasticity-related pain in adults is limited. Level B efficacy (probably effective) can be ascribed to both aboA (one class I study, Pittock et al. 2003) and rimaA (one class

Table 11.2 Blinded, botulinum toxin treatment trials in lower limb spasticity which included assessment of pain

Study	# of pts	Class	Toxin	Dose (U)	Pain scale	Result compared to baseline	Comment
Hyman et al. (2000)	74	I	AboA	500/1,000, 1,500	Frequency of spasms	Frequency improved in all groups. No difference between groups	No values provided large placebo effect
Pittock et al. (2003)	233	I	AboA	500/1,000	0–3 scale	Significant improvement at 4, 8, 12 weeks ($P<0.005$) in 1,000 and 1,500 unit group—in 500 unit group week 4 ($P<0.005$)	
Dunne et al. (2012)	85	I	OnaA	100/200	VAS and spasm frequency	VAS: improved ($P=0.02$), spasm frequency improved ($P=0.01$)	

I study, Dunne et al. 2012) based on the subcommittee guidelines of AAN (Appendices 3.1 and 3.2). The study of Hyman et al. (2000) is hard to interpret due to the paucity of information. The fact that both the placebo and toxin improved pain significantly may imply a large placebo effect and does not necessarily negate the efficacy of the toxin.

Effects of BoNT Treatment on Spasticity-Related Pain in Children with Cerebral Palsy

Performance of double-blind studies for assessing the efficacy of BoNTs on spasticity or spasticity-related pain in children with cerebral palsy is difficult due to procedural and ethical issues. The issue of treatment of pain with BoNTs in children with CP pertains both to treatment of existing spasticity-related pain and to preventing spasticity-related complications which can cause future pain and problems (e.g., hip subluxation in small children).

One double-blind, placebo-controlled study and a number of open-label (prospective and retrospective) studies have evaluated the effect of BoNT treatment on spasticity-related pain of children with cerebral palsy. These studies uniformly report improvement of spasticity-related pain in children with cerebral palsy. The double-blind study is described in some detail below followed by a brief description of the two open studies.

Copeland et al. (2014) studied 41 nonambulatory children with advanced spasticity and cerebral palsy. The study was prospective and double blind. The mean age of the children was 7.1 years. Twenty-three received BoNT-A and 18 received a sham procedure. The efficacy of injections was assessed during a 12-month follow-up period by physicians using a Modified Ashworth Scale, joint range of motion, Physician Rating Scale, Gillette Functional Assessment Questionnaire, and Gross Motor Function Measure-66 and by patients/parents using visual analog scale and the Pediatric Pain Profile (PPP). OnabotulinumtoxinA was injected into spastic muscles using a maximum dose of 12 units/kg or a total dose of 400 units per session. Following administration of onaA, in addition to improvement of the aforementioned parameters, the children who received BoNT injections (and parents) reported significant reduction of pain compared to baseline at 4 and 16 weeks (P values <0.05 and <0.01, respectively). In the sham procedure group, no significant response was observed.

In a study of 26 children with CP, spasticity, and hip pain (Lundy et al. 2009), investigators injected either onaA (nine children) or aboA (17 children) into the adductor magnus, hamstring, and iliopsoas muscles. The dose per session was up to 12 units/kg for onaA and up to 30 units/kg for aboA. The pain was measured by Pediatric Pain Profile. Injection of both neurotoxins resulted in marked reduction of pain at 3 months ($P=0.001$).

A multicenter, prospective, observational study from France (Chaleat-Valayer et al. 2011) reported on the treatment of 286 children suffering from CP with botulinum toxin A, followed for 12 months. Administration of botulinum toxin A improved range of motion, movement capacity, gait, and spasticity-related pain.

Rivard et al. (2009) asked the parents of 34 children with CP (mean age 9) and spasticity-related pain about the intensity and frequency of pain after BoNT-A injection into spastic muscle. The parents reported cessation of pain at week 4 in 62 % of the children.

In very young children, cerebral palsy with bilateral proximal lower limb spasticity often causes hip dislocation resulting in significant pain, impaired ambulation, and disability. In a study of 98 children, Pascale-Leone from La Paz Hospital in Madrid (2003) found continuous worsening of lateral hip migration in 86 % and full subluxation in 11.4 %. Administration of BoNT into the hip adductor and iliopsoas muscles stopped the progression in 74 % of the children via reduced spasticity and reverted the condition in another 14 %. The author advocates early and aggressive treatment, every 3–4 months, to prevent this complication.

In collaboration with our pediatric neurologist, Marc Difazio M.D, we treated and followed over 200 children with cerebral palsy with onabotulinumtoxinA at Walter Reed Army Medical Center, Washington DC. Some of the children were followed up to 8 years. The maximum dose used per session was 12 units/kg. Injections (upper or lower limb) were very effective in reducing spasticity, improving quality of life (sleep, hygiene, mood, irritability), and reducing pain. In general, parents were very satisfied with the results. No serious side effects were noted during the 8-year follow-up. My continued experience with treatment of child spasticity with onabotulinumtoxinA at Yale (past 10 years) agrees with my practice in the Washington area. The results are very much appreciated by the parents.

The Mechanism of Action of BoNTs in Spasticity-Related Pain (SRP)

The mode of action of BoNTs in SRP most probably involves both muscular and neural mechanisms. On the muscular side, BoNTs block the release of acetylcholine from presynaptic vesicles causing muscle relaxation that in turn can reduce the frequency of painful spasms. Furthermore, relaxation of muscles leads to better joint motility and prevents secondary pain and discomfort related to awkward joint-muscle interactions. In children, focused relaxation of hip adductors can prevent subluxation and related discomfort. On the neural side, some of the pain in advanced spasticity and contracture may originate from peripheral nerve fibers in the affected contracted tissue. Numerous animal studies have shown that BoNTs inhibit the release of pain mediators (glutamate, substance P, and calcitonin gene-related peptide) from peripheral nerve endings and dorsal root ganglia (Chap. 2).

Also, it is now increasingly recognized that peripheral injection of BoNTs (intramuscular or subcutaneous) has a direct central effect via retrograde transport and transcytosis (Mazzocchio and Caleo 2014). In support of the central effect of the toxin, Bach-Rojecky et al. (2010) have shown bilateral improvement of leg hyperalgesia after unilateral injection of onabotulinumtoxinA into the affected area on one side. Furthermore, following injection of the toxin into the rat's eye, truncated SNAP25 was detected in the midbrain tectum terminals despite the Wallerian degeneration of the axon that transports the toxin (Restani et al. 2012).

Such central effects can invariably impact the function of spinal circuits, interneurons, and spinal sensory neurons, all of which play an important role in spasticity and spasticity-related pain.

Conclusion

Blinded and placebo-controlled studies of adult spasticity have illustrated the efficacy of abobotulinumtoxinA in the management of upper limb spasticity-related pain. In lower limb spasticity-related pain, however, data is still limited though it strongly suggests efficacy. Studies in children with cerebral palsy suggest efficacy of different types of BoNTs in reducing spasticity-related pain. BoNT injection into spastic hip adductor muscles of children with CP may be helpful in preventing the painful and serious complication of hip subluxation.

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Chapter 12
Treatment of Dystonic Pain with Botulinum Neurotoxins

Abstract Focal dystonia is a common neurological disorder which is often painful. This chapter reviews clinical features of three common and painful focal dystonias, namely, cervical dystonia, focal dystonia associated with neurodegenerative disorders, and post-traumatic dystonia. The literature on the efficacy of botulinum toxins for these three forms of dystonic pain is reviewed. Fourteen blinded and placebo-controlled clinical trials assessed pain at baseline and after BoNT treatment of cervical dystonia. All 14 reported efficacy against pain. CD-related pain responded also to all three types of A neurotoxins as well as the type B neurotoxin. Small retrospective studies and clinical observations demonstrate that currently available neurotoxins (A or B) improve pain of Parkinson-related dystonias (toe flexion and foot inversion) as well as painful post-traumatic dystonias. Blinded studies for these indications are not available. Case reports and short videotape clips from author's experience are provided to demonstrate patients' histories and the technique of BoNT administration.

Keywords Cervical dystonia • Dystonic pain • Parkinson's disease • Atypical Parkinson disorders • Post-traumatic dystonia • Pain • Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA (onaA) • AbobotulinumtoxinA (aboA) • IncobotulinumtoxinA (incoA) • RimabotulinumtoxinB (rimaB)

Introduction

Dystonia is a movement disorder characterized by sustained twisting and turning and abnormal postures. The recent classification defines two diagnostic axis, clinical and etiological (Albanese et al. 2013). Classification in the clinical axis is based on the age at onset, temporal pattern of dystonia, body distribution (focal, hemidystonia, segmental, multifocal, and generalized), and coexistence of other movement disorders and other neurological or systemic manifestations. The etiological axis

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encompasses idiopathic, inherited, and acquired dystonias. Focal dystonias can be idiopathic, inherited, or acquired and in any of these settings can be painful.

In this chapter, three common and often painful focal dystonias will be discussed: cervical dystonia, focal dystonia in neurodegenerative disorders (Parkinson's disease and atypical Parkinson disorders), and post-traumatic/postsurgical limb dystonia.

Cervical Dystonia

Cervical dystonia (CD) is the most common form of idiopathic focal dystonia with an incidence of 1.07 per 100,000 person-years (Steeves et al. 2012) and a prevalence rate of 8.9/100,000 (Nutt et al. 1988). It is a late onset dystonia which typically affects head and shoulder muscles. Dystonic head jerks (usually in the direction of limited head movements) and limitations of neck movement are the hallmarks of the disorder. Patients commonly complain about neck and shoulder pain which for many is the most disturbing symptom. Based on the pattern and posture of the head deviation, cervical dystonia is classified as torticollis (head rotation), laterocollis (head tilt), retrocollis (head bent back), and anterocollis (head bent forward). Patients may have more than one type of cervical dystonia. The most common combination is torticollis and laterocollis.

In 1991, two retrospective studies from Baylor Medical College in Houston (Jankovic et al. 1991) and Columbia University in New York (Chan et al. 1991) defined characteristic of CD in a sizeable number of patients (in 300 and 266 patients, respectively). The basic data regarding CD was fairly similar between the two institutions regarding mean age at onset (41.9 vs. 41 years), female preponderance (1.9:1 vs. 1.5:1), and occurrence of pain (67 % vs. 75 %). In the Baylor series, pain was the presenting symptom in 17 % of the patients.

Progress in genetic testing has identified several genes in the familial forms of cervical dystonia starting with DYT6 a form of cervicocranial dystonia with the onset in young age and tendency to generalization. More recently, whole-exome sequencing has identified several genetic abnormalities in families with adult onset cervical dystonia (Skogseid 2014). GNAL gene which encodes for G protein (important in dopamine signaling) is the latest of these discoveries (Fuchs et al. 2013).

Very recently, the result of a large multicenter, prospective study on clinical features of pain in CD (CD-Probe study) has been published (Charles et al. 2014). The study was conducted at 88 centers in the USA and included 1,037 participants. The study compared the demographic and clinical profiles of CD patients with no/mild pain and those with moderate/severe pain. It assessed the impact of pain and the motor component of CD on quality of life and compared the initial onabotulinum toxin treatment paradigm between groups. The most common types of CD were torticollis (47.6 %) and laterocollis (38.8 %) with retrocollis and anterocollis considerably less common than the first two (5.3 and 5.7 %, respectively).

Pain was assessed through several questionnaires:

1. Pain numeric rating scale (PNRS) range 0–10. Based on this questionnaire, the level of pain was defined as mild (<4), moderate (4–6), and severe (7–10).
2. Via CD impact profile-58 which has eight subsets; one of eight pertains to pain.
3. Pain subset (0–20) of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).

Through these scales, a number of other parameters were also assessed: severity of torticollis, disability, head and neck symptoms, pain and discomfort, upper limb activities, walking, sleep, annoyance, mood, psychosocial functioning (each ranging from 0 to 100), work productivity, and type of CD (anterocollis, laterocollis, retrocollis, or torticollis).

The results showed that 88.9 % of the patients reported pain related to CD at baseline and 70.7 % rated their CD-related pain as moderate or severe at baseline (PNRS score 4–10). Comparing the group with moderate to severe pain (4–10 on the scale of 0–10) with the no or mild pain (0–3) group, patients with moderate to severe pain were significantly younger ($P<0.0001$). Gender, race, and ethnicity were not different between the two groups. A higher percentage of patients among moderate to severe pain group was disabled (14.7 % vs. 4.9 %) ($P<0.0001$), and those in the moderate to severe pain group were twice more likely to have stopped work because of CD ($P<0.019$). Moderate/severe pain was a significant predictor that employment status would be affected by CD ($P=0.0001$). When the impact of pain on different subsets of CDIP-58 questionnaire was studied, pain had a larger impact than motor findings on mood, annoyance, sleep, head and neck, and upper limb activities, while pain and motor component had an equal impact on walking and psychosocial functioning.

Treatment

Anticholinergic and GABAergic drugs (benzodiazepines and baclofen) are both effective in reducing the symptoms of cervical dystonia including the pain. In the former category, trihexyphenidyl (6–30 mg/day) and benztropine (1–3 mg day) are the two most commonly used drugs. Baclofen (30–60 mg day) and diazepam (10–30 mg/day) also improve symptoms of CD. Clonazepam 2.5–1 mg three times daily is also helpful especially when CD is associated with cervical myoclonus. All aforementioned drugs need to be started at low dose and gradually built up over several weeks. Elderly patients have poor tolerance for anticholinergic medications, and many such patients also find baclofen hard to tolerate. Patients who fail pharmacological treatment may benefit from selective cervical rhizotomy (cutting the cervical nerve roots) under careful electrophysiological guidance. The procedure should be performed in specialized centers. In recent years, deep brain stimulation has been employed for the treatment of recalcitrant cases of cervical dystonia. Although the number of treated patients is still small, pallidal stimulation seems to be effective as a secondary therapeutic option for severe CD (Walsh et al. 2013).

Introduction of BoNTs for the treatment of cervical dystonia has revolutionized the management of this disorder. All types of BoNTs (ona, abo, inco, and rima, types A and B) have been proven effective with a rate of efficacy of over 80 % and safety profile unmatched by any other therapeutic modality. Treatment improves all major symptoms of CD and prevents development of contractures and radiculopathy (Jankovic 2004). More favorable results have been reported in one study in which BoNT therapy was combined with physical therapy (Tassorelli et al. 2006). In a recent systematic review and meta-analysis (Marsh et al. 2014) which assessed 18 studies and over 1,900 patients, the mean duration of onaA effect was 93.2 and 95.2 days for fixed and random effect models, respectively. Doses of over 180 units of onaA for the treatment of cervical dystonia produced longer-lasting effects (107–109 days vs. 86–88 days for doses of <180 units).

One of the most important early observations in treatment of CD with botulinum neurotoxins (in this case onaA) was the recognition that neck pain relief in CD often occurred before improvement of posture and limitation of head movement (Jankovic and Schwartz 1990). This important early observation suggested an analgesic effect for botulinum toxins in human, independent from its other effects which proved to be correct in the following years.

Effects of BoNTs on Pain Associated with Cervical Dystonia

Among the double-blind studies which have reported on the efficacy of BoNTs in cervical dystonia, 14 included assessment of pain.

In the pioneering study of Tsui et al. (1986), 14 of 16 patients with CD reported significant reduction of neck pain after administration of onabotulinumtoxinA into the neck and shoulder muscles (0.002). In a larger study of 55 patients, Greene et al. (1990) also reported significant pain relief of their subjects 6 weeks after administration of onaA for CD. In another study of 23 patients, 19 of whom complained of pain, Lorentz et al. (1991) reported pain relief in 12 of 19 patients who were injected by onaA, but only in 1 of 19 subjects injected by saline ($P = 0.002$). Lew et al. (1997) conducted an efficacy and safety study on 122 patients with CD evaluating the effects of 2,500, 5,000, and 1,000 units of rimaB against placebo (saline). Pain was assessed through the pain subset of TWSTRS and the visual analog scale (VAS). At 4 weeks, all three doses had produced significant pain relief compared to the placebo ($P < 0.05$). This relief was more pronounced for the largest dose used in the study (<0.004). Poewe et al. (1998), in a study of 31 patients with neck pain and CD, also found a clear difference in pain improvement in favor of aboA (compared to placebo) at 4 weeks. The difference between the three dose groups of toxin (250, 500, and 1,000 units), however, was not significant.

In 1999, two studies assessed the efficacy of rimabotulinumtoxinB (rimaB) in cervical dystonia and associated pain. In one study (Brashear et al.), the investigators compared the efficacy of 5,000 and 10,000 units of rimaB with placebo in 109 patients using visual analog scales. Compared to placebo, at 4 weeks, significant

reduction of pain was noted in both toxin groups compared to placebo; 5,000 unit group ($P=0.001$) and 10,000 unit group ($P=0.0002$). Overall, the TWSTRS scores also improved more in the 10,000 unit group. In the same year, Brin et al. (1999) published the results of another investigation on efficacy of rimaB versus placebo in 77 patients with CD. Administration of 10,000 units of rimaB improved neck pain significantly at 4 weeks ($P<0.001$). Wissel et al. (2001) studied 68 patients with CD (with minimum Tsui score of 9) comparing the effect of aboA (500 units) with placebo (saline). Patients were assessed at weeks 4, 8, and 12 with Tsui scale rating the severity of CD and pain. At week 4, 49 patients in aboA group were pain-free versus 33 patients in the saline group ($P=0.02$). In the following open phase of the study, the aboA group demonstrated significant pain relief ($P=0.011$). Truong et al. (2005) investigated the efficacy and safety of abobotulinumtoxinA (aboA) (500 units) in 80 patients with CD. Participants were followed up for 4–20 weeks, until they needed further treatment. The efficacy was assessed with TWSTRS at baseline and weeks 2, 4, 8, 12, 16, and 20 after treatment. Pain was evaluated via pain subset of TWSTRS on VAS scale of 0–100 mm. At 4 weeks, the reduction in VAS score was 13.4 for aboA group and 1.9 for the placebo group ($P=0.02$). This significant degree of pain reduction was also noted at week 8.

In the past 3 years, four multicenter studies in a sizeable number of patients with CD-related pain and botulinum toxin therapy have been published (Truong et al. 2010; Comella et al. 2011; Charles et al. 2012; Fernandez et al. 2013). Truong et al. (2010) reported on the results of a multicenter study of 116 patients (61 placebos) with CD after administration of 500 units of abobotulinumtoxinA (aboA) into the neck and shoulder muscles. Four weeks after administration of aboA, the VAS score was reduced 3.7 for the onaA group and 1.4 for the placebo group, respectively. Comella et al. (2011) reported on the efficacy of two doses of incobotulinumtoxinA (incoA), 120 and 240 units on 233 patients with cervical dystonia. Both doses were equally effective in improving all subsets of the TWSTRS including pain. The pain subset of TWSTRS (0–20) was markedly improved ($P<0.0001$) at 4, 8, and 12 weeks. In another study (Charles et al. 2012), the efficacy of onabotulinumtoxinA (mean dose 241 unit) versus placebo was assessed in 170 patient with cervical dystonia (88 onaA, 82 placebo) using dystonia severity scale and physicians global assessment scale at baseline and 6 weeks after injection. Evaluation of pain subset showed significant improvement ($P<0.05$) at 2, 4, and 6 weeks posttreatment in the toxin group versus placebo. In a multicenter double-blind, placebo-controlled study, Fernandez et al. (2013) studied the effect of two doses (120 and 240 units) of incobotulinumtoxinA in 233 patients with CD. Pain was assessed through TWSTRS pain subset. At 4 weeks postinjection, patients in both 120 and 240 groups demonstrated significant reduction of neck pain ($P<0.0001$). There was no significant difference in pain response between the two prescribed doses of the neurotoxin. In contrast, Kaji et al. (2013), using the TWSTRS pain subset, found doses of 2,500 and 5,000 units of rimabotulinumtoxinA (rimaA) ineffective in alleviating the pain of cervical dystonia at 4 weeks following toxin administration. The 10,000 unit dose, however, improved the pain significantly ($P<0.05$).

Comparator Studies

Same Toxin, Different Doses

Laubis-Herrmann et al. (2002) studied the effect of high-dose (500 units) and low-dose (130 units) aboA administration for pain relief in CD. Subjects who received high dose (assessed by pain subset of TWSTRS at 6 weeks postinjection) reported pain relief ($P<0.03$), while those on the low dose only showed a trend toward improvement ($P<0.06$). However, in most other measures of the TWSTRS, the response did not differ between the two groups.

Different Toxins

Ranoux et al. (2002) compared the efficacy of onaA and two different doses of aboA (3:1 ratio to onaA and 4:1 ratio to onaA) in a blinded study of 54 patients with CD. Function was assessed through Tsui scale (0–25) and pain through the pain subset of TWSTRS. All three toxin preparations relieved pain. Both aboA preparations were more effective than onaA in respect to pain relief (0.04 and 0.02 for 3:1 and 4:1, respectively). There was a difference between the toxins in respect to side effects. OnaA produced considerably less dysphagia than either of the two preparations of aboA (3 % vs. 15 % and 17 %).

Another comparator study (Comella et al. 2005) compared the efficacy of onaA with rimaB using TWSTRS in 139 CD patients (previously treated with onaA). Efficacy against symptoms of CD was evaluated at 4 weeks (pain was assessed via the pain subset of TWSTRS). Administration of both toxins relieved the neck pain significantly ($P<0.001$). The drop in the pain score was 3.2 for onaA and 4 for rimaB, respectively (not a significant difference).

Pappert et al. (2008), in a non-inferiority study, compared efficacy, safety, and duration of onaA (150 units) and rimaB (10,000 units) in 111 toxin-naïve cervical dystonia (CD) subjects. Fifty-six of 111 subjects received placebo. Pain was assessed through the pain subset of TWSTRS along with other assessments at baseline and at 4 weeks following treatment. Both toxins were found to be equally effective in improving symptoms of CD ($P=0.001$) and pain. One patient in the rimaB group developed moderate dysphagia which improved spontaneously.

Another study (Quagliato et al. 2010) comparing 300 units of onabotulinumtoxinA with 300 units of Prosigne (Chinese toxin from Lanzhou Institute) found both equally effective in relieving pain at 4 and 16 weeks (using form SF36, pain subset). The study had 12 patients in each group (toxin and placebo). The authors suggested equal units for onaA and Prosigne.

Brans et al. (1996) compared the efficacy of abobotulinumtoxinA with trihexyphenidyl in 66 patients with cervical. In the aboA group, subjects received two injections of the neurotoxin at week 0 and week 8 (mean dose 292 units and 262 units for weeks 0 and 8, respectively). The dose in the trihexyphenidyl group was up to 24 mg/day. Pain assessment (pain subset of TWSTRS) was performed at week 12 (4 weeks after the second injection). Although more patients in the aboA group

demonstrated pain relief compared to the trihexyphenidyl group, the difference was not statistically significant.

Comment

Pain is a major and disabling symptom of cervical dystonia. The above-cited double-blind, placebo-controlled studies of BoNTs in CD strongly support the efficacy of all four FDA-approved BoNTs in relieving CD-related pain. The level of efficacy of the neurotoxins for this form of pain is A (established efficacy) based on AAN guidelines Appendices 3.1 and 3.2 (more than one class I study). Several studies with rimaB (Lew et al. 1997; Brashear et al. 1999; Kanji et al. 2013) and one study with onaA (Laubis-Herrmann et al. 2002) have suggested that employment of larger dose of the toxin improves its efficacy. In a recent review Lew et al. (2010) point out that Rima-B seems to be more helpful in relieving pain of cervical dystonia than other BoNTs. More studies are needed to verify these important observations. The clinicians, however, need to weigh the risk of complications versus the achievement of better response when considering the use of larger doses of BoNTs.

As to the type of the neurotoxin, although some comparative studies have found one toxin superior to the other for pain relief in CD (e.g., aboA was reported to be superior to onaA in the study of Ranoux et al. 2002), blinded, comparative studies in a larger number of patients are necessary in order to confirm such claims. The same applies to the report of higher incidence of side effects with aboA compared to onaA in treatment of CD (Ranoux et al. 2002).

The comparative study of trihexyphenidyl (THP) with abobotulinumtoxinA in CD suggested that aboA is more efficient than THP in improving the main CD symptoms, but there was no difference between the two in case of pain relief. This result was probably due to the employment of a low dose of aboA (less than 500 units) in this study.

Botulinum Toxin Treatment of Painful Dystonia in Neurodegenerative Disorders

Neurodegenerative disorders such as Parkinson's disease (PD) and atypical Parkinson's disorders (corticobasal degeneration, multiple system atrophy, progressive supranuclear palsy) are often associated with focal dystonia (Armstrong 2014, Singer and Papapetropoulos 2006). Dystonia can be intermittent and take the form of dystonic spasms (involuntary toe flexion or foot inversion in PD) or manifest as persistent and progressive—the pattern most often seen in corticobasal degeneration but also sometimes in PD. Both forms can be painful and disabling (Wasner and Deuschl 2012; Ha and Jankovic 2012). Focal dystonia in PD may be the result of PD itself or can be levodopa induced. Focal dystonia often develops during the course of PD but may precede classical PD symptoms by months or years (LeWitt et al. 1986).

The foot is most commonly involved. In a study of 40 patients with pain in PD, Tinazzi et al. (2006) identified 19 cases of dystonic pain. Of these 19, 17 patients manifested dystonic foot pain, and 2 had painful cervical dystonia. Dystonic pain was significantly associated with more advanced stage of PD and with motor complications of Parkinson's disease ($P=0.001$).

Several authors have reported successful treatment of painful hand and foot dystonia in PD with botulinum toxins (Pacchetti et al. 1995; Duarte et al. 1995; Jankovic and Tintner 2001; Cordivari et al. 2001; Sheffield and Jankovic 2007). No blinded and controlled studies are available, however.

Müller et al. (2002) reported on the treatment of ten patients with focal upper limb dystonia in atypical Parkinson's disorders. In two patients with corticobasal degeneration (CBD), administration of abobotulinumtoxinA into upper limb muscles (proximal and distal) improved dystonia and alleviated pain (method of pain assessment was not described). In another study (Cordivari et al. 2001), administration of onaA into the hand and forearm muscles improved dystonia and dystonic pain in three patients with CBD.

In my own experience, EMG-guided botulinum toxin treatment is highly effective for the treatment of pain in dystonic toe flexion and foot inversion in patients with Parkinson's disease. The results are less gratifying in dystonic pain of atypical Parkinson's disorders (CBD, PSP, MSA), but some patients find the treatment worthwhile and continue with the treatment.

The following case reports demonstrate EMG-guided, BoNT treatment of two of our patients. One patient had painful toe flexion dystonia due to Parkinson's disease, and the other presented with painful foot inversion dystonia due to probable corticobasal degeneration.

Case 12-1

A 70-year-old female was referred to the Yale Movement Disorder Clinic for management of the symptoms of Parkinson's disease. She had carried the diagnosis of Parkinson's disease for 2 years. Her main complaints included "stiffness of the muscles bilaterally," slowness of movements, postural instability, and intermittent painful toe flexion "spasms" (several times daily). The timing of the painful foot dystonia showed no relationship to medication dosage. Her medications included carbidopa/levodopa 25/100 three times daily and pramipexole (0.5 mg three times per day). Further increase of medications caused unacceptable dyskinesias.

On neurological examination, the main findings were confined to the motor system. She demonstrated bilateral moderate rigidity and hypokinesia (left more than right) and mild left-hand tremor. She had a slow and wide-based gait with slow turns. There were bilateral choreo-dystonic dyskinesias—more on the left side. During the 45 min duration of her visit, she experienced a painful episode of involuntary plantar foot flexion with flexion of all toes lasting several minutes. She measured the pain as 7 out of 10 in VAS.

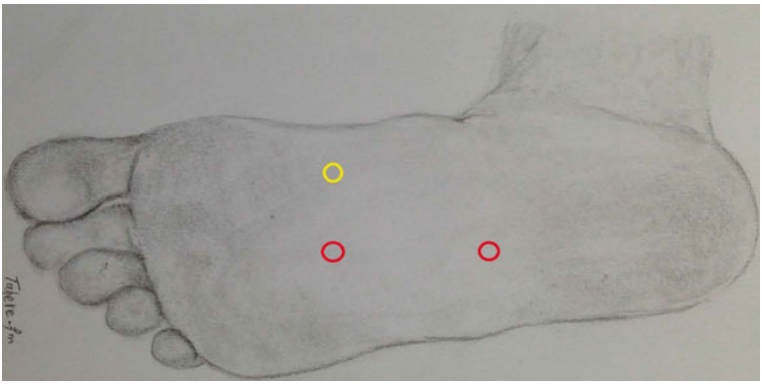

Fig. 12.1 Case 12-1: painful toe flexion dystonia in Parkinson's disease. Two injections of onaA, 50 units each, are introduced into the flexor digitorum brevis (*red dots*) and one injection of 30 units into the flexor hallucis (*yellow dot*) (Created by Tahereh Mousavi; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

Injection of onabotulinumtoxinA, 100 units into the flexor digitorum brevis (two sites) and 30 units into flexor hallucis (one site) (Fig. 12.1, Video 12.1), under EMG guidance resulted in marked reduction (less than one episode per month) of the dystonic foot pain. Patient rated her response in PGIC as "much improved" and continued with BoNT treatment every 3 months (follow-up 2 years). No side effects were noted. Deep brain stimulation of the right subthalamic nucleus, 18 months after initiation of BoNT treatment, stopped the left-sided levodopa-induced dyskinesias and improved her left side hypokinesia and rigidity, but did not influence the episodic toe flexion dystonias.

Case 2

A 72-year-old woman complained of involuntary movements of her left leg which had begun insidiously a year earlier. The movements had gradually increased in intensity, and the involved limb showed some "stiffness." A magnetic resonance imaging of the head showed microvascular changes compatible with age, but no other abnormality. A dopamine transporter imaging (DAT) showed decreased level of dopamine bilaterally in the putamen. She was treated by a local neurologist with carbidopa/levodopa 100 mg four times daily. Since treatment failed to improve the symptoms, the patient asked for a second opinion and visited the Yale Movement Disorder Clinic approximately 1 year after the onset of her symptoms.

The patient had enjoyed good health throughout her life. She had a fall a few weeks before the onset of left leg movements during which she had landed on her left thigh. There was no family history of any neurological disorders. Her general medical examination was normal. Neurological examination showed involuntary

continuous, semi-rhythmic and rhythmic movements of the left lower leg which were more prominent during action and when the limb was held against gravity. She also had non-velocity dependent, diffusely increased muscle tone in her left lower limb. There was no weakness and no pathological reflexes. A retrial of levodopa 250 mg, four times daily, failed to improve the symptoms. Cervical, thoracic, and lumbar MRIs were normal. A paraneoplastic panel showed no abnormality, and cerebrospinal fluid examination was normal.

Over the next 2 years, patient's symptoms gradually worsened. Muscle rigidity affected the upper extremity as well, and she developed mild resting tremor in the left upper limb. The left lower limb became very rigid with progressive painful inversion dystonia of the left foot. She often did not know the position of the left limbs (upper or lower). The movements at times were irregular and at times semi-rhythmic, and the left foot assumed a dystonic inversion. She could no longer walk without assistance. Aggressive physical therapy offered modest help. EMG-guided injection of onabotulinumtoxinA improved dystonia and rigidity of the left side and relieved the foot pain (Video 12.2). The following muscles were injected in the left leg: tibialis posterior (100 units), soleus (80 units, two sites), gastrocnemius (80 units, two sites), and hamstring (120 units, two sites). Patient's rating of global impression of change (PGIC) in response to onaA treatment for pain was "much improved," and she continued with treatment every 3–4 months (2 years follow-up). She now carries the diagnosis of probable CBD based on the unilateral progressive nature of the disease, significant limb dystonia, limb apraxia, alien limb syndrome, and myoclonus.

Post-traumatic Dystonia

Post-traumatic, focal limb dystonia is often painful. It can result from a physical injury to the limb (often hand or foot) or from postsurgical trauma (e.g., carpal tunnel syndrome). The prevalence of post-traumatic dystonia is unknown. A retrospective review of 36 patients with foot dystonia, seen at Mayo Clinic, between years 1996 and 2006 included ten patients in whom the foot dystonia was post-traumatic. In some of these patients, the treatment with botulinum toxin improved dystonia and reduced pain (McKeon et al. 2008).

I have seen several patients with post-traumatic dystonia (mostly affecting the upper limb) with severe pain in the affected muscles. Injections were done through EMG guidance, via a recording hollow needle. The EMG unit was a compact, handheld unit with audio but no screen (Clavis from Dantac). Patients were pleased with the outcome and rated their impression of change (patient global impression of change—PGIC) in respect to pain as "improved" or "much improved." One such patient is reported below.

Case 12-3

A 36-year-old female suffered from a right forearm injury after falling from a ladder. During the acute phase, the arm and hand were edematous and had multiple bruises. She was left with mild diffuse weakness of that hand and intermittent paresthesias in median and ulnar distribution. A few months after the trauma, she began to experience episodes of involuntary rapid finger flexion in the right hand associated with right wrist flexion with concurrent sharp pains in the right wrist and forearm. The episodes occurred two to three times per day, lasted for several minutes (up to 15 min), and afterward left a deep diffuse pain in the forearm which lasted for hours. She described the intensity of her pain as excruciating.

Injection of onabotulinumtoxinA under EMG guidance into the forearm muscles resulted in marked reduction in frequency and intensity of pain (frequency down to 1 per month and intensity down from 10 to 4 when pain did occur). The following muscles were injected with onaA every 3 months over 4 years of follow-up: flexor carpi ulnaris (60 units), flexor carpi radialis (40 units), flexor digitorum superficialis (20 units, two points), flexor digitorum profundus (20 units, two points), and lumbricals (15 units, three points).

Comment

Open-label studies and clinical observations strongly suggest efficacy of EMG-guided, botulinum toxin injections in painful focal dystonia especially toe flexion and foot inversion dystonia of patients with PD. In atypical Parkinson's disorders, BoNT treatment can also improve dystonic pain and dystonic posture. The clinical observations on post-traumatic dystonias are also encouraging and suggest an important role for botulinum toxin treatment for relieving pain.

Careful, double-blind and placebo-controlled studies could provide significant support for these positive observations.

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Chapter 13
Botulinum Toxin Therapy for Prevention of Postsurgical Pain

Abstract Postsurgical pain is a common disorder which results from spasm of muscles or sphincters and peripheral nerves after surgery. Persistent postsurgical pain results in application of polypharmacy and may lead to lengthy hospitalization.

This chapter reviews the data in intraoperative, intramuscular, or intrasphincteric use of botulinum neurotoxins (BoNTs) for relief of postsurgical pain. As examples, five areas of postsurgical pain are chosen in which blinded or prospective, open-label studies are available. These consist of pain syndromes after mastectomy, hemorrhoidectomy, adductor release surgery in cerebral palsy, hernia repair, and cholecystectomy. The collective results of these reports are encouraging. They not only suggest the efficacy of botulinum neurotoxins (mainly onabotulinumtoxinA) for prevention of postsurgical pain but also suggest that treatment with BoNTs in these syndromes may have predictive value regarding the efficacy of certain surgical procedures which are currently employed to relieve such pains.

Keywords Pain • Mastectomy • Hemorrhoidectomy • Adductor release surgery • Hernia repair • Cholecystectomy • Botulinum neurotoxin • Botulinum toxin • OnabotulinumtoxinA • onaA • AbobotulinumtoxinA • aboA

Introduction

Following a number of surgical procedures, the muscles affected by surgery may contract and cause local muscle spasms and pain. In 20–40 % of the patients, pain can be severe, responds poorly to analgesic medications, and impairs the quality of life (Gerbershagen et al. 2013). A growing body of the literature strongly suggests that injection of BoNT into the involved muscles before the intended surgical procedure can reduce and sometimes prevent the postsurgical pain. Alleviation and prevention of postsurgical pain are obviously of significant importance to the patient.

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Postmastectomy, Reconstruction, and Breast Expansion Pain

Following mastectomy, breast reconstruction, and expansion, many patients experience postoperative pain. It is now recognized that postmastectomy/breast expansion pain results mainly from the spasm of the pectoralis muscle. These painful spasms can occur acutely but, in some cases, continue for months and years after surgery. The pain has been attributed to muscle hypoxia, leading to muscle fiber degeneration and fibrosis (Gur et al. 1998). In some patients, spasms of pectoralis muscle may be quite severe and debilitating (Senior 2000; Wong 2000). In order to avoid such pain, continuous infusion of lidocaine through a catheter has been proposed and employed in a large number of patients (Pacik et al. 2003). Though effective, the procedure is cumbersome and carries the risk of infection. Persistent pain after reconstructive surgery may require special procedures such as bilateral pectoral neurectomies (Mast 1999; Hoffman and Elliot 1987).

Winocour et al. (2014) reviewed the literature in the use of botulinum toxins for prevention or treatment of postmastectomy pain. They cited a total of eight studies in which injection of the neurotoxin was used for pain prevention. Most studies were considered weak with a rating of <5 in Newcastle–Ottawa Scale (NCOS 0–8). Only the study of Layeeque et al. (2004) was given a rating of 7 (on NCOS scale), for having a good design despite being a non-blinded study. The utilized dose of the toxin was comparable between different studies (100 units for onaA), and the investigators found injection of BoNTs intraoperatively helpful in preventing postmastectomy pain.

Layeeque et al. (2004) conducted a prospective, randomized study in 48 patients who were undergoing mastectomy followed by placement of expander. Twenty-two patients received onabotulinumtoxinA (onaA), and 26 did not. The groups were comparable in terms of age, tumor size, and expander size. In the onaA group, 100 units of toxin was diluted with 40–60 cc of saline and injected at four sites into the pectoralis muscle before surgery (Fig. 13.1). Pain was evaluated through visual analog scale (0–10). The group that received onaA experienced less pain shortly after surgery and during expansion procedures ($p < 0.0001$ and $p < 0.009$). A number of other parameters also improved including shorter hospital stay and the dose of morphine required during hospital stay for pain control (Table 13.1). No side effects were reported.

Contrary to the above reports, a recent, double-blind, placebo-controlled study on 23 patients (class II) reported failure of BoNT to prevent this kind of pain (Lo and Aycock 2013), however. All patients had bilateral mastectomy. Investigators injected 100 units of BoNT in 1 side and saline in the other side into the pectoralis muscles. No difference between the pain scores was found between the toxin group and the placebo group.

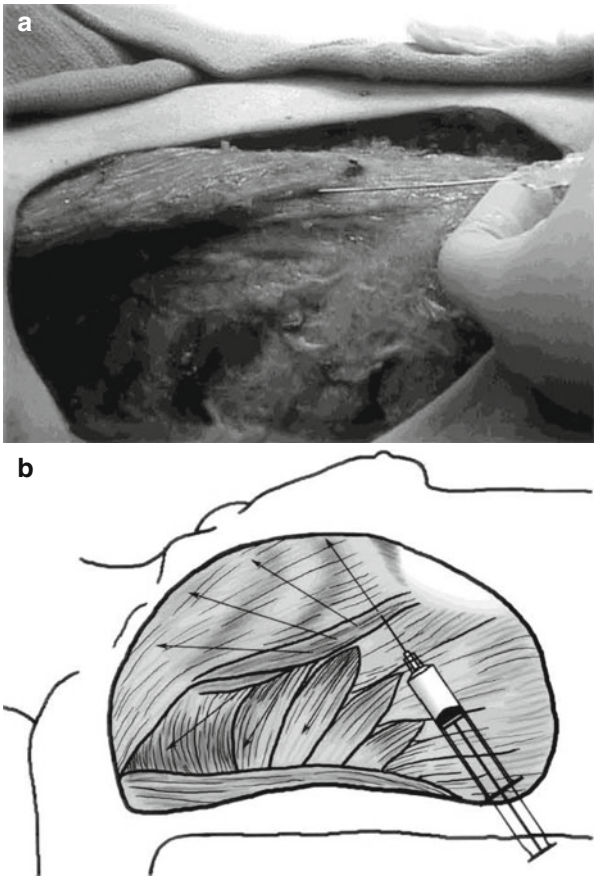

Fig. 13.1 Technique of injection into pectoralis muscles (From Layeeque et al. (2004). With permission from Wolters Kluwer Health)

Table 13.1 Comparison of variables between BoNT group and Standard group

Characteristics	BT group, $n=22$ (46 %)	Standard group, $n=26$ (54 %)	p value
Immediate postoperative pain	3.09 ± 0.92	6.80 ± 1.98	<0.0001
Length of hospital stay, h	26 ± 8	37 ± 19	0.015
Dose of morphine used during first 24 h, mg	3.27 ± 3.18	17.15 ± 10.40	<0.0001
Pain during initial expansion	1.95 ± 1.88	5.61 ± 2.77	1.6×10^{-6}
Pain during final expansion	1.04 ± 1.65	2.76 ± 1.99	0.009
Number of expansion sessions	5.72 ± 1.48	7.27 ± 3.07	0.0260
Time between mastectomy and permanent implant insertion, mo	6.57 ± 3.59	5.76 ± 2.54	0.448

From Layeeque et al. (2004)

Comment

A number of small, open retrospective studies and one well-designed prospective study which included a control group strongly suggest the efficacy of BoNTs in preventing postmastectomy/expander placement pain. The results of a recently published blinded study, however, stand at odds with the encouraging data presented from open-label trials. The reason for this discrepancy is not clear. The difference between techniques and small size of the recent blinded study may be a contributing factor. Larger, controlled studies are needed to define the role of intraoperative pectoralis muscle injection with BoNTs in prevention of pain that develops postmastectomy, insertion of expanders, and reconstructive procedures.

Post-hemorrhoidectomy Pain

Hemorrhoid is one of the most common forms of human ailments with a prevalence of 4–36 % (Altomare and Giannini 2013). Men and women are equally affected. The prevalence increases with age from the beginning of adulthood until the seventh decade and declines thereafter. More individuals are affected in the higher socioeconomic groups and among the Caucasians and Jews (Loder et al. 1994). Hemorrhoidectomy ranks among the most common procedures in the USA and Europe with an annual rate of 60 and 46 per 100,000 of individuals reported in the USA and France, respectively (Johanson and Sonnenberg 1991; Tiret et al. 1988).

Postsurgical pain after hemorrhoidectomy is common and can be severe and exhausting. The pain can occur at rest or during defecation and is generally attributed to spasm of the internal anal sphincter.

Treatment of Post-hemorrhoidectomy Pain

The first line of treatment is proper diet and pharmacological therapy which includes the use of acetaminophen, nonsteroidal anti-inflammatory analgesic drugs, muscle relaxants, and opioids. In recent years, blinded and placebo-controlled studies have shown partial efficacy of two forms of topical ointments. Glyceryl trinitrate ointment (0.2 %) is now commonly used for treatment of post-hemorrhoidectomy pain based on controlled investigations (Elton et al. 2001; Hwang et al. 2003; Tan et al. 2006). In one study (Khan et al. 2014), a combination of glyceryl trinitrate ointment with lignocaine (lidocaine 2 % and GTN 0.2 %) has been found better than either treatment alone. Calcium channel blocker (CCB) ointments also have shown efficacy against post-hemorrhoidectomy pain in two blinded placebo-controlled studies (Amoli et al. 2011; Perrotti et al. 2010). In both studies (one using diltiazem and the other nifedipine), the pain was considerably less at 7 days postsurgery in patients taking CCB compared to the placebo group ($p < 0.05$).

In case of persistent pain, other measures may be employed which have shown some efficacy in blinded studies. These consist of local anesthetic infiltration (Ho et al. 2000), anesthetic regional blockage (Luck and Hewett 2000), transdermal fentanyl (Kilbride et al. 1994), and diathermy excision (Andrews et al. 1993). More details on various approaches to manage post-hemorrhoidectomy pain can be found in a recent review by Siddiqui et al. (2011).

Botulinum Toxin Treatment of Post-hemorrhoidectomy Pain

The controlled studies on this subject include three blinded studies with a placebo arm and one randomized, prospective comparator study.

Blinded, Placebo-Controlled Studies

Davies et al. (2003) conducted a double-blind, placebo-controlled study in 50 consecutive patients who were undergoing Milligan–Morgan hemorrhoidectomy. OnabotulinumtoxinA or saline was injected at two points (0.2 cc site) into the posterior midline of the internal anal sphincter via a 27 gauge needle. In case of onaA, the preparation was 50 units in 1 cc of saline; hence, 0.4 cc of the solution contained 20 units of the toxin. At the end of the procedure, both groups were injected with 20 ml of bupivacaine (0.25 %) into the perianal skin. Patients were also prescribed a 7-day supply of co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg, four times per day orally) and instructed to use this as required. Pain was assessed by visual analog scale (0–10) at baseline and then daily via a questionnaire for the 7 days following the procedure. The mean pain score at postoperative days 6 and 7 was significantly less in the patients who had onaA injections ($p<0.05$). No side effects were reported.

In another blinded and placebo-controlled study of 30 patients, the effect of BoNT-A versus saline was investigated in peri- and post-hemorrhoidectomy symptoms including pain (Patti et al. 2005). Patients had grades III and IV hemorrhoids. In the toxin group, the solution was prepared by adding 2 cc saline to the onaA vial of 100 units (50 units/cc). Then 0.4 cc (20 units) was injected into the anterior midline of the anal sphincter at two points. The control group received the same volume of saline. Patients were assessed at baseline and followed for 30 days.

The postoperative pain measured by VAS was significantly less in the onaA group compared to the placebo during the first 7 days ($p=0.001$). Subsequently, patients in the placebo group used a larger number of analgesic tablets compared to the onaA (22.3 ± 5.1 vs. 14.8 ± 6.2; $p<0.05$). In the placebo group, the manometric anorectal resting pressure (MRP) was significantly raised ($p<0.05$) on the fifth postoperative day, whereas it was significantly reduced ($p<0.01$) in the onaA group. The length of wound healing was 23.8 ± 4.1 days in the onaA group compared to 31.3 ± 5.5 days in the placebo group ($p<0.05$). The same investigators

(Patti et al. 2008) found very similar positive findings in another double-blind study which assessed efficacy of intra-sphincter injection of onaA in relieving the pain of inoperable, thrombosed hemorrhoids. The type of toxin, dose, and technique of injection were identical to their postsurgical study.

In contrast to the two abovementioned studies in post-hemorrhoidectomy pain, a third placebo-controlled study of 32 patients with grades III and IV hemorrhoids found no improvement of postoperative pain and no change in RMP after injection of BoNT-A into the intersphincteric space (Singh et al. 2009). The BoNT group, however, demonstrated significantly lower squeeze resting pressure ($p < 0.05$) compared to the placebo. The authors used 150 units of abobotulinumtoxinA diluted in 0.5 cc of saline in this study. Pain and MRP were assessed over 14 days (13 and 13 patients in each group).

Prospective, Randomized Comparator Studies

Patti et al. (2006) evaluated the efficacy of onabotulinumtoxinA versus topical glyceryl trinitrate (GT) ointment in 30 patients with grades III and IV hemorrhoids undergoing hemorrhoidectomy. In the toxin group, each patient received a total of 20 units (2 injections, each 10 units) into anterior midline of anal sphincter. The dilution was 50 units/cc, hence 20 units/0.4 cc. The other group used the topical GT (300 mg) three times daily for 30 days. The postsurgical pain (assessed by VAS), the duration of wound healing, and anorectal manometry were evaluated before and after hemorrhoidectomy. The onaA group demonstrated significant pain relief at rest, but not during defecation ($p = 0.01$, observed up to 7 days). Patients in the GT group used a larger number of analgesic tablets compared with the onaA group (20.4 T 6.1 vs. 16.8 T 5.3; $p < 0.05$). The maximum resting pressure (MRP) was also decreased in the toxin group at both day 5 and 40 ($p < 0.0001$) postoperatively. The wound healing duration was shorter in the onaA group, but the difference did not reach statistical significance. The authors concluded that a single injection of BoNT-A improved pain and reduced anorectal pressure significantly more than 1 month of GT treatment.

Comment

The literature on the efficacy of onabotulinumtoxinA in reducing post-hemorrhoidectomy pain contains three double-blind, placebo-controlled, class II studies two of which demonstrated preventive value of BoNT injections in reducing postoperative pain. Furthermore, one class II comparator study also reports the efficacy of onaA against this form of pain. The negative report on efficacy of abobotulinumtoxinA for this indication is confusing since both ona and abo toxins are type A toxins, and the employed dose of aboA (150 units) did not seem to be insufficient. One reason for this discrepant result may be the difference between the employed techniques. Another reason may be a large placebo effect since a close look at their

data shows that the mean of maximum pain score improved notably for both the toxin and the placebo around days 10–12 (6.5–3.5 in VAS for the toxin). When the number of studied patients is small and both drug and placebo show notable improvements of a measured outcome, the results do not necessarily negate the efficacy of the drug. Using the guidelines provided by the Assessment Subcommittee of the American Academy of Neurology (Appendices 3.1 and 3.2), the level of evidence for the use of onaA in this form of pain is B (probably effective based on two class II studies).

More blinded studies are necessary to discern the efficacy of BoNT injections for this important form of postsurgical pain.

Prevention and Reduction of Post-hernia Repair Pain

Incisional hernia repair (IHR) is often associated with severe postoperative pain which could affect quality of life, the length of hospital stay, and, ultimately, return to full activity at work. In one study, the average VAS pain score for the first 14 days after hernia repair was 6.1, and in some patients, the severe pain lasted well beyond 14 days (Eriksen et al. 2009).

Zendejas et al. (2013) hypothesized that injection of botulinum neurotoxins into the abdominal muscles before surgery can improve hernia repair and reduce postsurgical care through muscle relaxation. The authors compared postoperative pain, opioid requirement, and procedure complications with controls in 88 patients (22 toxin, 66 controls) who underwent incisional hernia repair. Pain was assessed by the visual analog scale (0–10). Patients and controls were matched for age, body mass index, and the type of repair. OnabotulinumtoxinA (onaA) was injected into the transverse abdominis and internal and external oblique muscles under ultrasonic guidance during conscious sedation. The total dose was 300 units diluted in large amount of saline (150 cc).

Patients who were injected with onaA reported less pain in hospital day (HD) 2 (5.2 ± 1.5 vs. 6.8 ± 2) and HD4 (3.6 ± 1.2 vs. 5.2 ± 1.9): all $p < 0.007$. Also, the group that received onaA injection required significantly less opioid analgesia (mean ± SD morphine equivalents) when compared to controls on hospital days (HD) 2 and 5, HD2 48 ± 27 versus 87 ± 41 and HD5 17 ± 16 versus 48 ± 45. There was no difference in postoperative complications (surgical site, 9 % vs. 14 %), opioid-related adverse events (%5 vs. 5 %), hospital stay (4 ± 3 vs. 3 ± 2 days), or hernia recurrence at 18 months mean follow-up (9 % vs. 9 %).

Reduction of Severe Pain After Adductor Release Surgery

Adductor release surgery is an established procedure which can prevent hip dislocation in children with adductor spasticity and cerebral palsy (CP) (Mallet et al. 2014). The procedure is effective, but, in many children, postoperative spasm of adductor muscles develops after surgery causing severe pain.

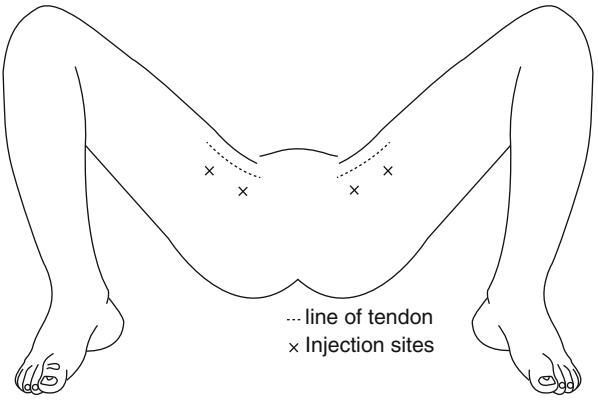

Fig. 13.2 Technique of onabotulinumtoxinA injection into the adductors before adductor release surgery (From Barwood et al. (2000). With permission © 2000 John Wiley and Sons)

Barwood et al. (2000) conducted a prospective, randomized, double-blind study in 16 children with CP and spasticity who were undergoing adductor release procedure. The children were diplegic or quadriplegic with a mean age of 4.7 years. The surgery was performed in order to prevent hip subluxation. The authors used onabotulinumtoxinA (onaA), Allergan Inc., prepared as 10 units/0.1 cc (100 unit vial diluted with 1 cc saline). Each adductor muscle was injected at two sites (two units/kg per site) for a total dose of eight units/kg, 5–10 days before surgery (Fig. 13.2).

The patients in the onaA group did considerably better in respect to postoperative care, reduction of analgesic requirement, and shortening the length of hospital stay. The mean pain score in the onaA group showed a reduction of 74 % ($p<0.003$), and patients' analgesic requirement dropped approximately 50 % ($p<0.005$). The onaA group also had significantly shorter length of hospital stay with 33 % reduction in length of stay ($p<0.003$).

Botulinum Toxin Injection of Sphincter of Oddi for Postcholecystectomy Pain

After cholecystectomy, increased pressure in the biliary duct leads to postcholecystectomy biliary pain in a sizeable number of patients. Increased pressure in the duct also carries 3–31 % danger of pancreatitis (Sherman and Lehman 2001; Murray 2005). Persistent pain associated with increased pressure in the biliary duct after cholecystectomy is often treated with Oddi sphincterotomy (Geenen et al. 1989).

One prospective open-label study and one retrospective chart audit study have reported significant improvement of postcholecystectomy pain after administration of onabotulinumtoxinA into the sphincter of Oddi. Furthermore, both studies claim a predictive value for botulinum toxin therapy since patients who responded well to BoNT therapy were more likely to respond well to endoscopic sphincterotomy.

Wehrmann et al. (1998) enrolled 22 patients with a history of cholecystectomy and postcholecystectomy pain and monometrically confirmed sphincter of Oddi dysfunction (SOD) in a 3-year prospective study. All patients received injections of onabotulinumtoxinA into the ampulla of Vater, a total of 100 units at 1 site. After onaA treatment, manometric pressure returned to normal in all patients. Twelve of 22 patients (55 %) became pain-free. Pain returned in 6 months, however. Subsequent endoscopic sphincterectomy relieved pain in 11 of 12 patients (91 %) who had responded to onaA, but in only 2 of 10 patients (20 %) who had not responded to onaA ($p < 0.01$). The authors concluded that not only onabotulinumtoxinA relieves post-cholectomy pain in a sizeable number of patients, it also can predict who will later respond to endoscopic sphincterectomy. One patient in this study developed mild pancreatitis.

The conclusion of the aforementioned study is supported by another recent retrospective chart audit of 64 patients with postcholecystectomy pain (four episodes or more per month) who received onaA injection (100 units) into the sphincter of Oddi for pain relief (Murray and Kong 2010). Of the 64 patients, 46 (72 %) had experienced at least 4 pain-free weeks after onaA treatment, and 44 of 46 (96 %) had experience pain relief following endoscopic sphincterectomy. Every patient with Oddi hypertension defined by manometry who also had at least 4 weeks of pain relief following onaA injection experienced pain relief following endoscopic sphincterotomy. No patient had any side effect after BoNT injection. The investigators came to the same conclusion that injection of onaA into the sphincter of Oddi improves postcholecystectomy pain and has predictive value as to the outcome of subsequent endoscopic sphincterectomy.

Comment

The data from non-blinded studies on alleviating effect of onabotulinumtoxinA in post-hernia and postcholecystectomy pain are encouraging considering the fact that both conditions may lead to chronic pain and disability. The predictive value of onaA response in postcholecystectomy pain regarding response to subsequent endoscopic sphincterectomy is also very important since a variable efficacy ranging from 37 to 85 % has been reported for this procedure (Sherman and Lehman 2001). Blinded and placebo-controlled studies are necessary to support these important observations.

Conclusion

The area of postsurgical pain and its management are challenging issues for clinicians and surgeons. Preventive use of botulinum neurotoxin treatment is a novel approach which, if proven efficacious in additional studies, could lead to

postsurgical pain relief in a large number of patients. In the future, refinement of technique of injection and selection of optimum dosage will help achieve better results and optimize preventive botulinum toxin therapy in this important area of pain management.

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Chapter 14
Botulinum Toxins for Treatment of Pain in Orthopedic Disorders

Abstract Chronic pain is a major issue in many orthopedic disorders. With the discovery of analgesic effects of botulinum neurotoxins (BoNTs), there is an emerging interest in exploring the potential role for BoNTs in relieving orthopedic pain.

In this chapter, the data on BoNT therapy in four orthopedic disorders for which placebo-controlled studies are available are presented. These disorders consist of chronic lateral epicondylitis, painful local arthritis, refractory pain after total knee arthroplasty, and anterior knee pain related to vastus lateralis imbalance. Using the recommendations of the Assessment Subcommittee of the American Academy of Neurology, an evidence-based level of efficacy is defined for each condition.

The level of evidence for chronic lateral epicondylitis is B (probably effective) based on one class I and two class II studies. It is level C (possibly effective) for both refractory pain after total knee arthroplasty and local painful arthritis and anterior knee pain related to vastus lateralis imbalance (each with one class II study). While these positive data are encouraging, better designed, high-quality, and controlled studies (class I and II) are needed for optimal definition of the analgesic role of botulinum neurotoxins in orthopedic disorders.

Keywords Lateral epicondylitis • Tennis elbow • Anterior knee pain • Patellofemoral syndrome • Osteoarthritis • Arthritis • Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA • AbobotulinumtoxinA • IncobotulinumtoxinA • RimabotulinumtoxinB

Introduction

Over the past 15 years, a variety of communications have drawn attention to the usefulness of botulinum neurotoxin (BoNT) therapy in orthopedic conditions with refractory pain. In this chapter, we will discuss four such disorders in which blinded, placebo-controlled studies and case series have suggested the efficacy of BoNTs. These consist of chronic lateral epicondylitis, refractory pain after total knee arthroplasty (TKA), chronic joint pain related to arthritis, and anterior knee pain with vastus lateralis imbalance.

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Chronic Lateral Epicondylitis

Lateral epicondylitis (LE) is a clinical condition characterized by pain in the elbow related to overuse of the joint commonly noted among athletes (tennis elbow) or heavy workers (Ahmad et al. 2013). Currently, it is believed that degeneration of the extensor tendons is responsible for the clinical symptoms (Nishl and Ashman 2003), although the role of inflammation is still debated despite paucity of pathological evidence. The concept of tendinopathy and tendon degeneration is supported by ultrasound examination of the affected joints (Connel et al. 2001). Lateral epicondylitis is a common disorder with a prevalence of 4–7/1,000 patients per year (Hamilton 1986; Verhaar 1994). In clinical practice, patients with acute LE recover within 12 months (83 % in one observation—Smidt et al. 2002). The small percentage that evolves into the chronic form (CLE) is often resistant to pharmacotherapy. Treatment of CLE includes avoiding exposure of the affected elbow to heavy load, bracing, physical therapy, pharmacotherapy, and surgery. Pharmacotherapy encompasses commonly used analgesic medications: cyclooxygenase inhibitors, nonsteroidal anti-inflammatory drugs, GABAergic analgesics (gabapentin and pregabalin), and, in more severe cases, opioid analgesics. Injection therapy introduces steroid and no-steroid drugs into the painful region. Krogh et al. (2013) recently reviewed the world literature on injection therapy for CLE. Of the 141 clinical trials (RTC), 17 studies were chosen for final meta-analysis: 10 corticosteroids, 4 botulinum toxins, 3 autologous blood, 2 PRP, and 1 each for hyaluronic acid, prolotherapy, polidocanol, and glycosaminoglycan polysulfate. Although most of these studies strongly suggested efficacy, the authors concluded that presence of high state of bias rendered interpretation of the data difficult in most of the studies; a number of factors such as assessor or patient blinding, allocation concealment, selection or attrition reporting, and company's interest were the areas of concern.

Botulinum Neurotoxin Studies in CLE

Of the five reported RTCs in CLE, four were blinded and placebo controlled and one was a blinded but a comparator study.

Placebo-Controlled Studies

Wong et al. (2005) evaluated the efficacy of abobotulinumtoxinA (aboA) in 60 subjects (49 women) with CLE in a double-blind, placebo-controlled study. The primary outcome was reduction of pain in VAS (0–100 mm) at weeks 4 and 12. Handgrip strength was the secondary outcome. The toxin group received 60 units of aboA diluted in 1 cc of normal saline. The injections (saline or toxin) were administered "deeply into the subcutaneous tissue and muscle," 1 cm from the lateral epicondyle, and were aimed toward the tender spot.

Table 14.1 Comparison of clinical pain scores between groups

Visit	Score[a]		
	Botulinum	Placebo	*p* value[b]
Injection	8.43 ± 0.24 (68)	8.55 ± 0.21 (62)	0.920
Week 2	5.24 ± 0.38 (68)	6.85 ± 0.35 (61)	0.003
Week 6	4.53 ± 0.37 (68)	5.69 ± 0.37 (61)	0.020
Week 12	3.76 ± 0.36 (68)	5.02 ± 0.41 (61)	0.023
Week 18	2.88 ± 0.35 (68)	4.29 ± 0.41 (57)	0.009

From Placzek et al. (2007). Printed with permission from the *Journal of Bone and Joint Surgery*

[a]The values are given as the mean clinical pain score and the standard error of the mean with the number of patients in parentheses

[b]The level of significance of the difference between the botulinum and placebo groups as assessed with the Mann–Whitney *U* test

The mean VAS scores for the botulinum group at baseline and at 4 weeks were 65.5 and 25.3 mm, respectively. For the placebo group, the VAS scores were 66.2 and 50.5 mm at the same time points, denoting a significant improvement in favor of the toxin ($p < 0.001$). At week 12, the mean VAS scores were 23.5 mm for the botulinum group and 43.5 mm for the placebo group, again supporting an analgesic effect for aboA ($p = 0.006$). The grip strength decreased slightly in both groups, but the difference between the two groups was not statistically significant. At 4 weeks, four patients on aboA experienced paralysis of finger extension.

In another blinded and controlled study, Hayton et al. (2005) compared the effect of abobotulinumtoxinA (50 units) with saline in 40 patients with CLE who had failed to respond to steroid therapy. The injections were intramuscular and performed 5 cm distal to the maximum point of tenderness at the lateral epicondyle, in line with the middle of the wrist. Investigators assessed pain with the visual analog scale, the quality of life with short-form SF12, and handgrip with Jamar dynamometer before injection and 3 months after injection. They found no difference between the toxin and the placebo with the aforementioned assessments at 3 months.

Placzek et al. (2007) conducted a multicenter, double-blinded, placebo-controlled RTC in 130 patients with CLE. The toxin group received 60 units of abobotulinumtoxinA diluted in 0.6 cc of saline (0.9 %). The control group received the same volume of saline. The solution (toxin or saline) was injected 3–4 cm distal to the tender epicondyle and at two locations reflecting different depths after partial withdrawal of the needle following injection of one half of the solution. The level of pain was assessed by VAS at baseline (before injection) and at 2, 6, 12, and 18 weeks. Patients' and physician's satisfaction were measured on a score of 0 (substantially worse) to 4 (substantially better) at the same time points. The strength of finger extension was also measured by a vigorimeter in all patients. Injection of aboA resulted in significant improvement of pain at all weeks after injection (2, 6, 12, and 18—$p < 0.05$) (Table 14.1).

Espandar et al. (2010) conducted a randomized placebo-controlled study of 48 patients with chronic refractory lateral epicondylitis. The patients in the toxin group received 60 units of abobotulinumtoxinA, and the control group received the same

volume of normal saline. The site of injection was chosen based on prior studies on cadavers (Liu et al. 1997), 33 % of the arm length below the lateral epicondyle. In most individuals, the posterior interosseous nerve innervates the extensor carpi ulnaris and extensor digitorum at this point. The primary outcome was intensity of pain at rest measured by VAS (0–100 mm) at 4, 8, and 16 weeks after injection. Secondary outcomes included intensity of pain during maximum pinch, maximum handgrip, and grip strength. The aboA group showed significant reduction of pain at rest compared to the placebo group at 4 weeks (14.1 mm), at 8 weeks (11.5 mm), and at 16 weeks (12.6 mm) ($p=0.01$). Among the secondary outcomes, the intensity of pain during the maximum pinch was also decreased significantly in the aboA group compared to controls ($p=0.004$). All patients in the toxin group developed some weakness of finer extensors which resolved by week 8. In one patient, weakness of the third and fourth fingers which had developed at week 4 resolved by week 16.

Comparator Study

Lin et al. (2010) compared the effect of 50 units of onabotulinumtoxinA (onaA) with steroid injection (40 mg of triamcinolone acetonide) in a small double-blind study of 16 patients with CLE. The onaA and triamcinolone were injected into the extensor carpi radialis brevis near the common origin of the wrist and finger extensors of the affected elbow. The level of pain, handgrip, and quality of life were assessed with VAS, dynamometer, and the World Health Organization's brief questionnaire at baseline, 4, 8, and 12 weeks. Both onabotulinumtoxinA and triamcinolone improved pain at 4, 8, and 12 weeks. At 4 weeks, the analgesic effect of triamcinolone was greater than aboA (0.02), but as time went on, there was a trend for onaA to have more analgesic effect. The strength of handgrip was mildly diminished in the onaA group. No other side effects were noted. BoNT studies in CLE are summarized in Table 14.2.

Comment

In Table 14.2, the class and level of evidence for BoNT studies in CLE are defined according to the criteria of the Assessment Subcommittee of the American Academy of Neurology (Appendices 3.1 and 3.2). One class I (Paczek et al. 2007) and two class II (Wong et al. 2005; Epandar et al. 2007) studies, all using aboA have indicated efficacy, whereas one class III study (Hayton et al. 2005) using onaA refutes effectiveness of BoNT against pain of CLE. Based on this information, treatment of CLE with abobotulinumtoxinA meets at least level B evidence (probably effective). The problem with Hyton's study (2005) is its small number of patients and, more importantly, the use of only one efficacy assessment at 3 months. Experience from other indication of BoNT

Table 14.2 Blinded studies of BoNT-A in chronic lateral epicondylitis

Study	Class	# of pts	Type	Toxin	Dose (u)	PO at week(s)	SO	Results
Wong et al. (2005)	II	60	DBPC	AboA	60	VAS: 12	Handgrip	$p<0.001$ (VAS)
Hayton et al. (2005)	II	40	DBPC	AboA	50	VAS	SF12, handgrip	NS
Placzek et al. (2007)	I	130	DBPC	AboA	60	VAS: 2, 6, 12, 16	PPS	$p<0.05$—VAS all weeks, PPS $p<0.05$
Espandar et al. (2010)	II	48	DBPC	AboA	60	VAS: 4, 8, 16 MP, MG		$p=0.01$ (VAS) $p=0.04$ (MP)
Lin et al. (2010)	II	16	Comp	OnaA and triamcinolone	50	VAS: 4, 8, 12		$p=0.02$ (VAS) week 4 triamcinolone > onaA

Study class according to definition of the Assessment subcommittee of AAN (Appendices 3.1 and 3.2, Chap. 3, French and Gronseth 2008)
DBPC double blind, placebo controlled, *Aboa* abobotulinumtoxinA, *onaA* onabotulinumtoxinA, *PO* primary outcome, *SP* secondary outcome, *PPS* patient and physician satisfaction scale (0-4), *MP* maximum pinch, *MG* maximum grip, *ns* not significant

therapy tells us that the effect of BoNTs often disappears by 3 months. In the comparator study of Lin et al. (2010), the number of subjects (16) was also too small, and the results may be biased by a type II statistical error. Furthermore, the baseline data showed a low pain level (mean 44 mm) for the toxin group (versus 57.5 in the triamcinolone group) which might have influenced the results.

At the present time, a major issue with the positive results of the blinded studies in CLE is the development of enduring weakness of the finger extensors after BoNT injections. Larger blinded studies with different types of neurotoxins and with modified techniques are necessary to produce pain relief without enduring weakness of finger extensors.

Intra-articular (IA) Botulinum Neurotoxin Treatment for Total Knee Arthroplasty

Chronic, advanced osteoarthritis of the knee is a major source of chronic pain in adults with poor response to medications. Total knee arthroplasty (TKA) is often successful in providing pain relief and improving the quality of life (Nashi et al. 2014). It is a very common procedure in the USA with an annual volume of 500,000/year. A sixfold increase to 3.48 million/year is projected by 2030 (Singh et al. 2010).

Unfortunately, 25 % of the patients remain unsatisfied with the procedure (Anderson et al. 1996) and 7–44 % continue to have refractory pain after TKA (Baker et al. 2007: Wylde et al. 2011). There is evidence for active contribution of known pain transmitters to the mechanism of pain of TKA. The joint fluid of patients with chronic osteoarthritis who have undergone TKA has demonstrated elevated substance P level, a finding which is absent in normal joints (Prichett et al. 1997). Understandably, novel treatment strategies are welcome in this area of pain medicine since chronic pain of TKA is often refractory to pharmacotherapy.

Singh et al. (2010) investigated the efficacy of intra-articular injection of onabotulinumtoxinA in alleviating chronic TKA pain. A total of 54 patients were enrolled in their randomized, double-blind, placebo-controlled study. Mean age was 67 years, 84 % were men, and mean duration of TKA pain was 4.5 years. All subjects had moderate or severe pain (>6 on 0–10 VAS), and their pain duration exceeded 6 months. In the toxin group, the patients received intra-articular (IA) injections of onaA, 100 units diluted in 5 cc of 0.9 % saline without preservative. The control group received 0.5 cc of IA normal saline. The primary outcome in this study was the proportion of patients with a decrease of two points or more in numerical visual 0–10 scale (VAS) compared between the BoNT and placebo group at 2 months. VAS and McMaster "Osteoarthritis Index Physician Function" were evaluated at baseline and at 2, 3, and 4 months. The patient and physician global impression of change (PGIC) were also assessed at 2, 3, and 4 months.

A greater proportion of patients (71 %) in the onaA compared to the placebo group (35 %) experienced reduction in pain assessed by VAS at 2 months ($p=0.028$). The duration of meaningful pain relief was 39.6 days (SD 50.4) for the onaA group compared to 15.7 days (SD 22.6; $p=0.045$) for the placebo group. The following outcomes also demonstrated significant differences between the onaA and placebo group at all assessment times in favor of onaA: physician global assessment of change ($p=0.003$); Western Ontario McMaster Osteoarthritis Index physical function ($p=0.026$), stiffness ($p=0.004$), and total scores ($p=0.024$); and Short-Form 36 pain subscale score ($p=0.049$). No serious side effect related to treatment was noted in the BoNT group. The incidence of other side effects such as local pain after injection and subtle transient weakness around the joint was not statistically different between the two groups.

Comment

Postsurgical pain is a challenging issue in the field of pain medicine. Emerging literature strongly suggests utility of BoNT treatment in a variety of postsurgical pains including postmastectomy, hemorrhoidectomy, cholecystectomy, hernia repair, and post-adductor release surgery in children with cerebral palsy (see Chap. 13 of this book—BoNT treatment of postsurgical pain). The cause is probably multifactorial including local accumulation of pain transmitters, damage to terminal nerve endings, local inflammation, and yet other unknown factors.

The study of Singh et al. (2010) qualifies as a class II study, using the criteria and guidelines of the American Academy of Neurology's Subcommittee on Assessment

of the efficacy of randomized clinical trials (RCT) (Appendices 3.1 and 3.2 in this book). According to these guidelines, one class II study presents a C level of evidence (possibly effective). The positive result of this study should encourage initiation of more RCTs of high quality (classes I and II) in order to better define the role of botulinum neurotoxin treatment in refractory pain of TKA.

Intra-articular Use of Botulinum Neurotoxins for Treatment of Arthritic Pain

Arthritis is a huge health problem, with arthritis of the knee affecting approximately 46 million people in the USA. Recently, Cheng et al. (2012) reviewed the world literature on the efficacy of intra-articular (IA) introduction of different agents for the management of arthritic knee pain. Steroids and hyaluronate both showed efficacy, while the latter provided possibly a longer duration of pain relief. Triamcinolone hexacetonide acted better than triamcinolone acetonide and was recommended for IA use. Tropisetron and tanezumab were also effective and were given a 2B+ efficacy level. Various IA radioisotopes are also partially effective, but their long-term safety and efficacy remain to be established.

Mahowald et al. (2006) first reported on the long-term results of intra-articular injection of onabotulinumtoxinA for arthritis and arthritic pain in a small series of 15 patients (9, shoulder; 3, knee; 3, ankle). All patients had received previous intra-articular injection of steroids and/or viscosupplement agents with partial or inadequate relief. OnabotulinumtoxinA was injected into shoulder (100 units) and limb joints (25–50 units). Following IA injection of onaA, the mean maximum reduction in limb joint pain was 55 % ($p=0.02$) and 38 % ($p=0.044$) at 4 and 10 weeks, respectively. For shoulder pain, there was even a higher magnitude of pain reduction (72 %, $p=0.001$). The subjects also demonstrated improved range of motion, both for shoulder and for limb joints. No significant side effects were reported.

In a prospective, open-label study of five patients with post-hemiplegic shoulder pain, Castiglione et al. (2011) injected BoNT-A (onaA, two patients; incoA, two patients; aboA, one patient) into the glenohumeral painful joint (Fig. 14.1). The dose was 100 units for onaA and incoA and 500 units for aboA. Patients' level of pain was assessed by VAS at rest and during the passive arm abduction at 2 and 8 weeks. At both 2 and 8 weeks, all patients showed marked improvement of shoulder pain measured both at rest and at arm abduction ($p=0.001$, $p<0.001$). There was no difference in the level of pain relief at 2 and 8 weeks.

Comparator Study

Boon et al. (2010) compared the efficacy of low dose (100 units) and high dose (200 units) of onabotulinumtoxinA with 40 units of methylprednisolone acetate in 60 subjects with pain (minimum six level at VAS) and functional impairment due to

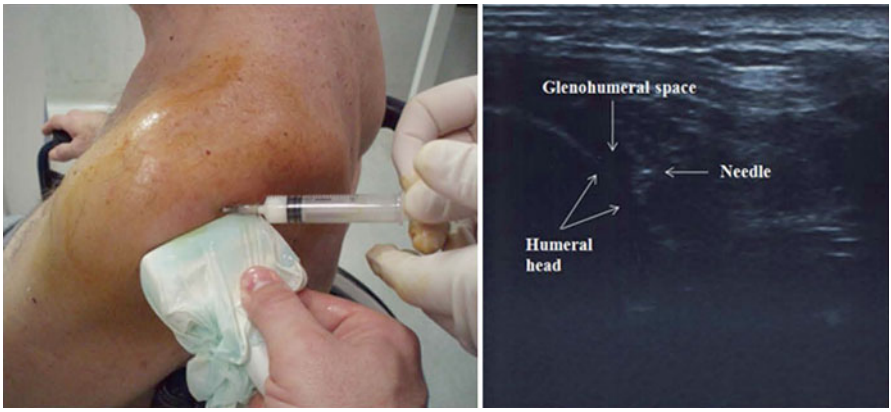

Fig. 14.1 Method of glenohumeral injection of BoNTs for hemiplegic refractory shoulder pain (From Castiglione et al. 2011. With permission from Elsevier)

osteoarthritis of the knee. Patients in the enrolled cohort had failed to respond to both conventional and physical therapy. The primary outcome was defined as reduction of pain in VAS at 8 weeks. Patients were reassessed at 26 weeks. The secondary outcomes included Short-Form 36 for quality of life, Western Ontario McMaster Arthritis Index (WOMAC), and patient global assessment (in a three-question format). All 60 patients completed the 8-week evaluation period, while 38 patients had another evaluation at 26 weeks. All three approaches were effective in reducing pain, but the reduction reached significance only for the low-dose onaA group at 8 weeks ($p = 0.01$). Also, all groups showed a statistically significant decrease in the subsets of pain and stiffness in WOMAC. Side effects were mild and included dry mouth, local swelling and pain at the site of injection, and balance problem. The latter two were more frequent in the high-dose onaA group, but the difference between groups did not reach statistical significance.

Sun et al. (2014) conducted a single blind (assessor), prospective study comparing the efficacy and safety of onaA with hyaluronate plus rehabilitation in 75 patients with symptomatic ankle osteoarthritis. Thirty-eight patients received a single injection of 100 units of onaA into the ankle joint, and 37 had a single injection of hyaluronate plus 12 sessions of physical therapy. The frequency of PT was three times per week for 4 weeks with each session lasting 30 min. The primary outcome was measured through the Ankle Osteoarthritis Scale (AOS) which includes pain and disability scale; each measured the intensity on the scale of 0–10. Among the secondary outcomes, the following scales pertained to pain assessment: visual analog scale (VAS) and global patient satisfaction. Pain-related outcomes were assessed at baseline (before injection) and at 2 weeks and 1, 3, and 6 months. The authors considered 30 % or more decline in the pain score as significant. The ankle joint was injected with 100 units of onabotulinumtoxinA. The needle was inserted 1 cm anterior to the distal medial malleolus and advanced posteriorly and slightly superiorly toward the middle of the ankle joint above the talus. If an effusion were present, it

was aspirated before injection. After treatment, subjects in both groups (onaA and hyaluronate) experienced marked reduction of pain measuring 50 % or more in the pain subset of AOS and in VAS score. In the toxin group, the mean baseline VAS value of 4 was reduced to 1.8 at 2 weeks with a further reduction to 1.7 at 3 months. There was, however, no significant difference between the two groups regarding pain relief. Both groups also showed substantial improvement in the disability scores. For some patients, these improvements lasted 6 months. The injections did not induce any significant side effects in either of the two groups.

Comment

One small blinded class II study (Mahowald et al. 2006), two blinded comparator studies, and a small open-label study have suggested the efficacy of intra-articular injection of onaA in arthritic joint pain. One comparator study (Boon et al.) had a high level of dropouts (30 %) and showed an unexplained better response to the low dose rather than the high dose of onaA. This study may be best defined as class III due to the high frequency of patient dropout. The other comparator study is single blinded. The level of evidence for efficacy of BoNTs in painful arthritis (AAN guidelines, (French and Gronseth 2008; Gronseth and French 2008) is, therefore, C (possibly effective) based on the availability of one class II study. Additional controlled studies are necessary to support these positive claims.

Anterior Knee Pain with Vastus Lateralis Imbalance

Anterior knee pain is a common and debilitating ailment with a proposed incidence of 22/1,000 individuals per year (Boling et al. 2010). Patellofemoral syndrome is one of the main causes of anterior knee pain. It is characterized by anterior knee pain, predominately in young females, in the absence of significant knee pathology (Petersen et al. 2014). Imbalance of the vastus lateralis muscle has been proposed as one of the causes of anterior knee pain and patellofemoral syndrome (Powers 2000). Considering this causative factor, Singer et al. (2010) conducted a double-blind, placebo-controlled study in 24 patients with anterior knee pain. AbobotulinumtoxinA or saline was injected randomly into the vastus lateralis muscle. The dose of aboA was 500 units diluted in 4 cc of saline. The control group received the same volume of saline without the aboA. Injections were performed under electromyographic guidance. The dose was administered into eight sites with 0.5 cc per site (Fig. 14.2). The primary outcomes included improvement in knee pain-related disability and activity-related knee pain (in VAS) at 3 months. The BoNT-A-injected group demonstrated a clinically significant reduction in mean pain scores for kneeling (−50.5, $p<0.001$), stair walking (−20.9, $p<0.006$), squatting (−30.8, $p<0.001$), and level walking (−20.3, $p<0.003$). Placebo subjects demonstrated a reduction for stair

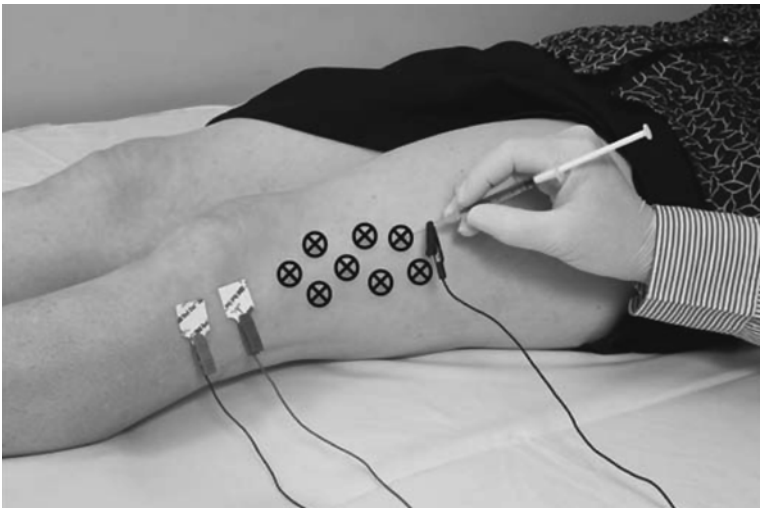

Fig. 14.2 Site of injections of abobotulinumtoxinA used for treatment of vastus lateralis imbalance (From Singer et al. 2010. With permission from BMJ Publishing Group Ltd.)

walking only (−20.4, not statistically significant $p = 0.097$). The authors concluded that onaA improves anterior knee pain caused by vastus lateralis imbalance. This single class II study defines a C level of evidence (possibly effective) for this indication (AAN assessment of evidence Appendices 3.1 and 3.2, French and Gronseth 2008; Gronseth and French 2008).

Conclusion

The encouraging results of RCTs with botulinum neurotoxin treatment in orthopedic disorders discussed in this chapter have opened the door for further controlled studies in this important area of pain medicine. Hopefully, with refinement of techniques and application of optimum dosage, this form of treatment could become a valuable option for management of refractory pain in orthopedic disorders.

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Chapter 15
Botulinum Toxins for the Treatment of Cancer-Related, Postradiation, Postsurgical, and End of Life Pain

Abstract Botulinum neurotoxins exert an analgesic effect through a variety of mechanisms including inhibition of acetylcholine release from neuromuscular junction and release of pain mediators from peripheral nerve endings, dorsal root ganglia, and at the spinal sensory neuron level. Four open-label prospective studies have demonstrated effectiveness of ona-, abo-, and incobotulinum toxins in relieving pain at the site of radiation or surgery for cancer. Furthermore, single-case observations with onabotulinumtoxinA have shown that local intramuscular injection of this toxin can alleviate chronic and disabling local pain in advanced cancer and improve the quality of the end of life state among patients with terminal cancer.

Keywords Cancer • Cancer pain • Botulinum toxin • Botulinum neurotoxin • OnabotulinumtoxinA (onaA) • AbobotulinumtoxinA (aboA) • IncobotulinumtoxinA (incoA) • Allodynia • Hyperalgesia

Introduction

Focal cancer therapy-related pain is induced by a variety of mechanisms. Approximately 25 % of the patients who undergo radiation or surgery for cancer develop pain at or close to the area of local radiation or surgery (Kanner and Foley 1981; Kehlet et al. 2006). List and Bilir (2004) attributed the postradiation pain observed in 15–30 % of patients with head and neck cancer to the development of fibrosis, scar, and keloid. Topical application of trolamine, calendula officinalis, hyaluronic acid, and lidocaine patch may provide transient relief (Fisher et al. 2000; Chargari et al. 2009; Kirova et al. 2011), but sustained relief is uncommon and was noted in only 25 % of patients who applied lidocaine patch to the allodynic region (Fleming and O'Connor 2009). Severe local pain after radiation and surgery may require potent systemic analgesic medications such as opioids which, although effective, often cause undesirable side effects. Among the multitude of side effects with these agents are nausea, somnolence, and constipation, each noted in more than 20 % of the patients (Cochrane review, Wiffen et al. 2014).

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Advanced cancer is associated with severe pain in 70–80 % of patients (Caraceni et al. 2012). The prevalence of severe pain in advanced cancer is similar to that of other chronic and advanced medical disorders (Harris 2014). For instance, the estimated prevalence of pain in chronic heart disease and chronic obstructive pulmonary disease has been reported as 44–77 % and 34–77 %, respectively (Solano et al. 2006; Borsook 2012). Palliative treatment of this form of pain is often difficult, and side effects of analgesic medications are poorly tolerated by debilitated patients.

This chapter will start with a discussion of therapy of postsurgical/postradiation pain in cancer patients, followed by application of botulinum neurotoxin (BoNT) therapy to chronic, severe end of life pain in cancer patients. To illustrate the intricacies of treatment with BoNTs in these settings, case reports are provided from the author's experience.

Botulinum Neurotoxin Therapy for Postsurgical/Postradiation Pain in Cancer Patients

The literature on this subject includes seven open-label (four prospective and three retrospective) studies (Table 15.1) as well as a few case reports (Fabregat et al. 2013). No blinded studies are available. The data collectively indicate that local injection of BoNTs into scarred/fibrotic or allodynic area significantly improves this form of pain in cancer patients.

Retrospective Studies

In the study of Van Daele et al. (2002), injection of onabotulinumtoxinA into the tight and painful sternocleidomastoid muscle relieved the pain and tightness in four of six patients. All patients had received radiotherapy for head and neck cancer. The injected dose was 20–25 units administered at 1 or 2 points into the sternocleidomastoid muscle.

Anecdotal case reports have also described marked reduction of postradiation pain after local BoNT-A injection. As an example, a 75-year-old gentleman with rectal cancer developed severe rectal pain and a large noncancerous rectal ulcer after local resection and radiation. Injection of onaA into the rectal wall at multiple sites reduced the pain dramatically and helped healing of the ulcer (De Micheli et al. 2003).

Stubblefield et al. (2008) also found BoNT-A injection helpful in relieving focal pain caused by radiation fibrosis. In this retrospective study of 23 patients, 30 % had painful trismus, and 43 % had trigeminal and cervical plexus neuralgia.

Voung et al. (2011) studied the effect of BoNT injection into the rectal wall immediately after high-dose-rate endorectal brachytherapy (HDREBT) in 15 patients with prostatic cancer. The patients who received 100 units of onaA into the rectal wall had a lower incidence of acute radiation prostatitis with significant reduction of bowel frequency and urgency ($P<0.05$) and lesser degrees of pain ($P=0.07$).

Table 15.1 Studies of BoNTs in post radiation/postsurgical pain of cancer patients

Study	Pts	Toxin type	Dose	Treatment	Location	PO	Results
Van Daele et al. (2002)	6 R	BoNT-A	20–25	Rad/chemo	Head and neck	Pain	Complete pain relief
							4 out of 6 patients
Wittekindt et al. (2006)	23 P	BoNT-A	60–120	Rad/surg	Head and neck	VAS at day 28	Only low dose was effective ($P<0.05$)!
			160–240				
Hartl et al. (2008)	19 P	onA/aboA	50/250	Chemo/rad	Head/neck	VAS and function, 4 weeks	VAS ($P=0.02$), function ($P=0.04$)
Stubblefield et al. (2008)	23 R	onaA	25–200	Rad/surg	Head/neck	Pain	Improved in 87 %
Mittal et al. (2012)	7 R	onaA	100	Rad/surg	Head/neck and breast	VAS, PGIC at week 4	VAS ($P<0.05$)
							PGIC: satisfactory
Bach et al. (2012)	9 P	aboA	100–400 (SCM)	Rad/surg	Head and neck	FDSNP at week 4	FDSNP ($P=0.01$)
			125–200 (PF)				Pain ($P=0.01$)
Rostami et al. (2014)	12 P	incoA	100 units	Rad/surg	Head and neck mastectomy	VAS at week 6	VAS, PGIC ($P<0.05$)

P prospective, *R* retrospective, *VAS* visual analog scale, *PGIP* patient global impression of pain, *FDSNP* functional disability scale for neck pain, *SCM* sternocleidomastoid, *PF* pectoralis flap

In another study (Bach et al. 2012) of nine patients with postsurgical contracture of sternocleidomastoid or pectoralis major muscle related to head and neck cancer, patients expressed pain relief after administration of aboA into sternocleidomastoid muscle (100–400 units) or the pectoralis muscle flap (125–200 units) with no side effects. Injections were administered at four to five locations into sternocleidomastoid muscle or into the pectoralis muscle flap.

Prospective Studies

Wittekindt et al. (2006) examined the efficacy of BoNT-A (type not specified) in 23 patients who reported neuropathic pain in the neck and shoulder following neck dissection for squamous cell carcinoma of upper "aerodigestive tract." BoNT-A was diluted by 1 or 2 cc preservative-free saline before administration. Patients were divided into low-dose (80–120 units) and high-dose (160–240 units) groups. Patients and physicians were blinded to the dose of injections. Injections were performed in 8–12 locations subcutaneously into targeted neck and shoulder regions. Patients' response to BoNT injection was measured by visual analog scale (VAS) at baseline prior to injections and at day 28 after injections. The mean baseline pain was 4.3 on VAS (0–10). The quality of life was evaluated by a questionnaire from the European Organization for Research and Treatment of Cancer (EORTC), specifically prepared for head and neck cancers, at the same time frames. At day 28, mean VAS score for the low-dose group changed from 4.3 to 3.6 ($P<0.05$), but the change for the high-dose group was not significant. Furthermore, the low-dose group also showed a trend for improvement of quality of life.

In another prospective study (Hartl et al. 2008), the efficacy of onabotulinumtoxinA (onaA) and abobotulinumtoxinA (aboA) was assessed in 19 patients with nasopharyngeal and oropharyngeal cancer who developed severe spasm of masseter muscles and trismus, on the average, 5.6 years after radiotherapy for cancer. Eleven patients had received chemotherapy in addition to radiation. The location of cancers was in the nasopharynx ($n=3$), oropharynx ($n=9$), oral cavity ($n=2$), oral cavity and nasopharynx ($n=1$), larynx ($n=3$), and parotid gland ($n=1$). Each masseter muscle was injected at two points, either with onaA (50 units) or aboA (250 units). At 4 weeks postinjection, pain, spasms, and functional score (measured in a 20 subset questionnaire) all improved significantly compared to baseline ($P=0.002$, $P=0.004$, $P=0.04$, respectively). No difference was noted between onaA and aboA.

Yale Ongoing Prospective Study

We are currently studying the effect of incobotulinumtoxinA (incoA) on moderate to severe focal pain (VAS >5) at the site of cancer resection or cancer radiation. Patients had had radiation and surgery for breast or head and neck cancer. Efficacy

of treatment is measured by VAS, patient global impression of change (PGIC), and Quality of Life Scale for pain at 4, 6, 8, 10, and 12 weeks postinjection. The primary outcome is two grades or more improvement in VAS with additional patient satisfaction expressed in PGIC at 4 weeks. The secondary outcome is improvement of quality of life at 6 weeks. A total of up to 100 units of incobotulinumtoxinA, diluted in 1 cc of saline, was injected into the area of local pain indicated by the patient. The injections were both subcutaneous and intramuscular. The target number of the study is 20 patients. The preliminary results (Rostami et al. 2014) of this open-label prospective study are presented below. To date, 12 patients were enrolled in the study, and 10 patients completed the assessments. Two patients died during the study from complications of cancer and were removed from the final analysis. Of the remaining ten who completed the study, eight patients demonstrated significant reduction of pain and improvement of both quality of life and patient impression of change 6 weeks postinjection. The mean VAS of 7.4 at baseline was lowered to 3.8 at week 6 ($P < 0.05$). These positive results agree with our previous retrospective report of seven cancer patients with local postradiation/postsurgical pain (Mittal et al. 2012). In these seven patients, intramuscular injection of 80–160 units of onabotulinumtoxinA (onaA) reduced the local pain at 4 weeks postinjection. Both types of BoNT-A (inco and ona) seemed to be equally effective against pain. None of the patients developed any side effects in either of the prospective or the retrospective study.

The following cases are presented from the authors experience with BoNT therapy for postradiation/postsurgical pain in cancer patients.

Case 1: Carcinoma of the Base of the Tongue Associated with Painful Upper Neck Spasms and Burning Pain Interfering with Speaking and Swallowing

A 47-year-old, right-handed gentleman was referred to the Yale Neurotoxin Treatment Clinic for evaluation of right upper neck pain and difficulty in swallowing and speaking of 5 years duration. Six years ago, he was found to have a tumor at the base of the tongue and cervical lymphadenopathy on the right side. He underwent resection of the tumor with removal of lymph nodes and neck muscles on the right side. The tumor was a squamous cell carcinoma. Shortly after resection, he received radiotherapy to the base of the tongue and right side of the neck. A few months later, he experienced tingling and pulling of the base of the tongue which gradually evolved into painful spasms and burning sensation below the angle of the right jaw interfering with speaking and eating. Treatment with a variety of analgesic drugs was only minimally helpful.

General medical and neurological examinations were normal except for loss of muscles on the right side of the neck and mild weakness of the tongue. A vertical surgical scar was visible on the right side of the neck extending from lower neck to the lower edge of the mandible. Several areas of induration and keloid formation

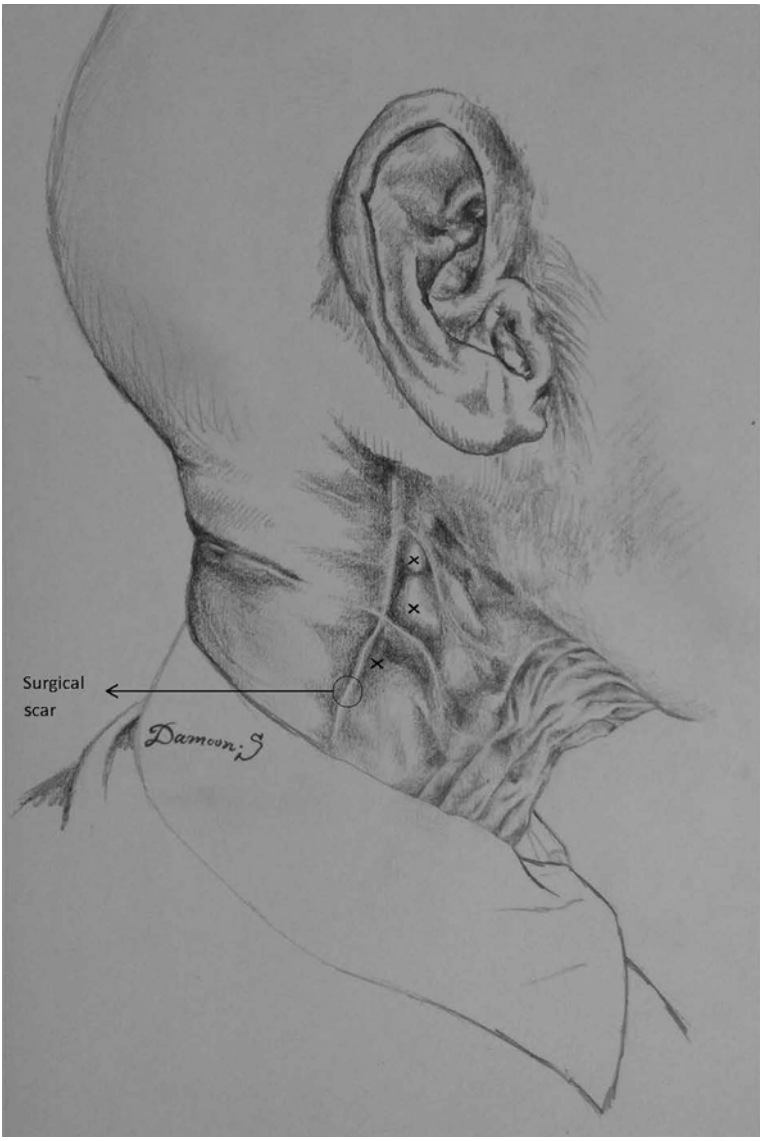

Fig. 15.1 Patient 15-1. onaA injection sites in the right side of the neck into areas of keloid, induration, and fibrosis. (Created by Damoun Safarhour, published with permission of © Bahman Jabbari 2014. All rights reserved.)

were present, the hardest and most painful being located anterior and slightly below the angle of the right jaw (Fig. 15.1).

Twenty units of onabotulinumtoxinA was injected into each of the three areas of indurated, scar tissue on the right side of the neck (Fig. 15.1). The dilution was 100 units/cc. A 0.75 in.-long, 27.5 gauge needle was used for injections. After a week,

patient reported total cessation of muscle spasms and burning pain as well as marked improvement of his swallowing and speech. He reported no side effects. The pain and discomfort returned after 6 months. Over the next 7 years, the patient continued to receive onaA injections into the same cervical regions, for the past 4 years with a slightly higher dose of onaA (30, 30, and 20 units). The injections have remained efficacious over 7 years when employed at 6 month intervals.

Case 2: Intense Left Cervical Pain Following Laryngectomy and Neck Dissections for Squamous Cell Carcinoma of the Pyriform Sinus

A 48-year-old man underwent laser supraglottic laryngectomy with bilateral neck dissections for squamous cell carcinoma of the left pyriform sinus. This was followed by courses of chemotherapy and radiation. Two years later, patient developed intense left cervical pain and left shoulder pain beginning with spasms of the left sternocleidomastoid (SCM) muscle. The pain was described as deep and aching, but at times sharp and jabbing. A variety of medications including fentanyl 25 mcg/h patch and hydromorphone 2 mg tablets, given as needed, provided no significant pain relief. He was then injected with a total dose of 200 units of onabotulinumtoxinA into the left cervical and shoulder muscles: left SCM, left trapezius, left splenius, and left levator scapulae muscles at several points, 15–20 units per site (Fig. 15.2). After a week, he reported marked reduction of pain (from VAS 8 to 1); on PGIC, he expressed the outcome as "very satisfactory." The response continued over a period of 3 years with repeat injections performed every 4 months. The patient did not report any side effects.

Case 3: Severe Spasms of Masseter Muscles 6 Months After Resection and Radiation of a Left Tonsillar Cancer

A 54-year-old male with a history of left-sided tonsillar cancer had undergone surgical resection and radiation therapy. Six months later, he noted painful spasm of the right masseter and pain during eating or jaw opening. This eventually spread to the left masseter and to the upper neck regions. The pain became excruciating during jaw opening, eating, and chewing. Baclofen, 20 mg daily, combined with a variety of analgesics offered little help. At Yale Botulinum Neurotoxin Clinic, he was injected with onaA into the masseter muscles bilaterally. Each masseter received 60 units of onaA, divided at two sites (30 unit per site). The total dose for both masseters was 120 units. Patient reported significant reduction of his pain after 10 days. The pain intensity score of 9 in VAS recorded at baseline changed to 1 at 4 weeks. He reported no side effects and in PGIC reported the change as "very satisfactory." Pain returned, though less intense, after 3 months. Repeat injections every 3 months thereafter had the same beneficial effect. Patient still visits Yale Neurotoxin

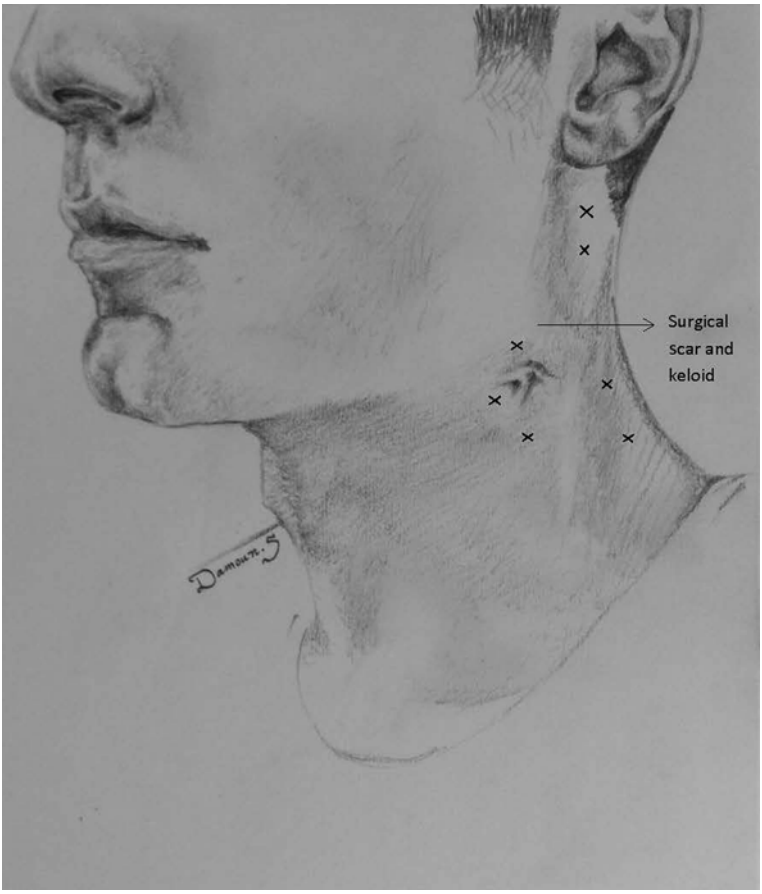

Fig. 15.2 Patient 15-2. onaA injection sites in the left side of the neck and shoulder into the sternocleidomastoid, levator scapulae, splenius, and trapezius muscles. (Created by Damoun Safarhour, published with kind permission of Bahman Jabbari 2014. All rights reserved.)

Treatment Clinic every 3 months (6 years follow-up). The dose for the past 2 years has been reduced to 50 units per masseter.

Comments

Botulinum neurotoxins can influence and reduce pain via a variety of mechanisms (Hallett 2000). These include inhibition of pain mediator (CGRP, SP, glutamate) release from nerve endings and dorsal root ganglia and at the spinal level. Reduction of local inflammation, inhibition of sodium and purinergic channels (ATP), and decrease discharge of sympathetic neurons are among other factors contributing to the analgesic effects of BoNTs. These effects collectively subdue peripheral and

ultimately central sensitization and lead to a powerful analgesic effect (see Chap. 2 of this book for more details).

Results of the four aforementioned, prospective studies (open label) with BoNTs for treatment of postradiation/postsurgical pain among cancer patients are encouraging. This form of pain is hard to treat, and introduction of a novel therapeutic modality with a safe and low side effect profile is welcome given the fragility of the patients and their higher propensity for developing side effects with potent conventional analgesic medications. These preliminary results demonstrate a few points of clinical significance:

- In at least half of our patients, the analgesic response to BoNT lasted 6 months rather than the usual 3 months duration of relief noted in treatment of movement disorders.
- The available information demonstrates that onaA, incoA, and aboA all can alleviate postradiation/postsurgical pain in patients with cancer.

Controlled and blinded studies are necessary to substantiate the validity of these data, although blinded studies are difficult to perform in cancer patients with disabling pain.

Botulinum Neurotoxin Treatment of End of Life Cancer Pain

The mechanism of focal pain in advanced cancer and end of the life cancer pain is multifactorial. In a majority of patients, pain has a peripheral origin and results from direct invasion of neural tissue by cancer or reactive issue post surgical or radiation therapy. Centrally, it can result from activation of pain mechanisms by a central nervous system cancer that may cause either a neuropathic pain or painful muscle spasms (Fu et al. 2013). Examples are provided below from the author's experience:

Case 1: Severe Jaw Pain and Trismus Due to the Direct Invasion of Masseter Muscle and Jaw Bone by a Non-small Cell Cancer of the Lung

A 69-year-old female with stage IV non-small cell carcinoma of the lungs with metastasis to bone (femur and petrous bone) and brain underwent multiple courses of chemotherapy and radiation therapy. Three months after completion of radiotherapy, she complained of jaw stiffness, inability to open the mouth fully, and right masseter pain when attempting to open the mouth. Over a few weeks, the problem reached a point that she refrained from eating. Her medications, oxycodone (10 mg, twice daily) and fentanyl (25 mcg patch every 72 h), provided temporary pain relief but did not alleviate the trismus. An MRI showed enlargement of right masseter due to neoplastic involvement (Fig. 15.3).

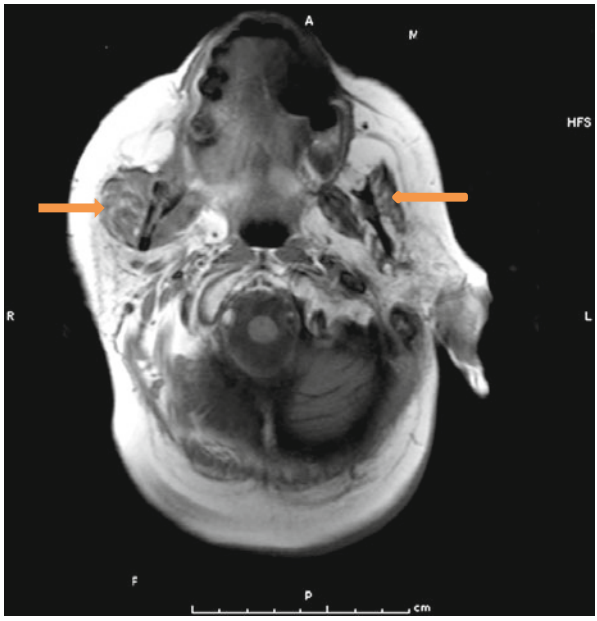

Fig. 15.3 Patient 15-3. Magnetic resonance imaging with special base view showing the right masseter enlargement presumably from cancerous involvement (*arrows*)

Injection of onabotulinumtoxinA (50 units) into the right masseter and 20 units into the right temporalis decreased the right masseter pain and improved jaw opening for 6 weeks. Subsequent injections of a larger dose of onaA into the right masseter (70 units) with additional injection into the left masseter (30 units) improved her quality of life (pain relief, less eating difficulty) over the next 18 months before her demise from complications of cancer.

Case 2: Disabling, Deep Neck and Shoulder Pain Due to an Extensive Pontomedullary Astrocytoma

A 29-year-old male with a grade 3 pontine astrocytoma (Fig. 15.4) experienced painful spasms of the neck and shoulder muscles 6 months following radiation therapy. Tizanidine, 2 mg three times a day, had minimal effects, and nonsteroidal anti-inflammatory analgesics were not helpful. Abnormal neurological findings included a left sixth and seventh nerve paresis, left side spasticity, and gait ataxia.

Administration of onabotulinumtoxinA into the neck and shoulder muscles resulted in significant pain relief. The following muscles were injected: left and right splenius capitis (40 units each), left and right trapezius (40 units each), left and right levator scapulae (40 units each), and left and right sternocleidomastoid (20 units each). The total dose was 280 units. Each muscle received two injections, except for the sternocleidomastoid muscle (one injection, upper part). Injections were repeated every 3 months for 2 years until the patient passed away from complications of cancer. Each injection relieved pain for 2.5 months.

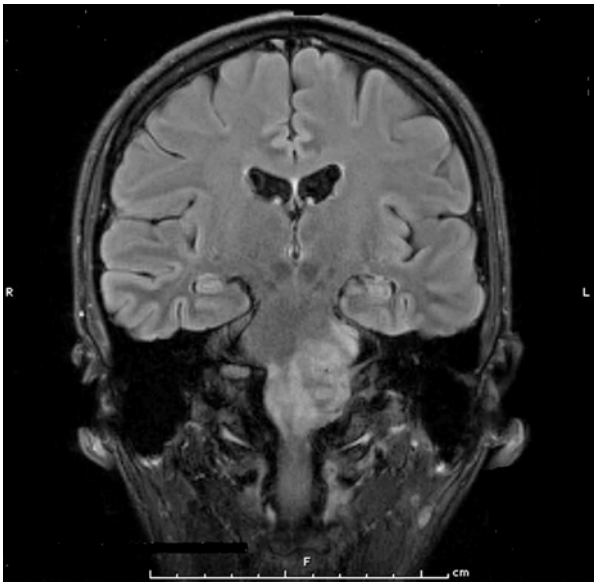

Fig. 15.4 Patient 14-5. Brain MRI showing a large pontomedullary mass

Case 3: Disabling, Painful and Dystonic Upper Limb Contractions After Gamma Knife Surgery for Recurrent Frontoparietal Brain Tumor

A 79-year-old gentleman was referred to the Yale Botulinum Neurotoxin Treatment Clinic for evaluation of painful muscle contractions affecting the left shoulder and left arm muscles. Patient had had recurrent meningiomas in the right posterior frontal region for the past several years which had resulted in focal motor seizures of the left side. These seizures were treated with a variety of medications, most recently with a combination of Depakote (750 mg daily) and Klonopin (2 mg daily). The recent abnormal movements, however, had begun 3 months ago shortly following a Gamma Knife surgical excision of a recurrent right posterior frontal lobe tumor. The movements were different from those associated with his seizures in that they occurred as episodic "very painful" contractions of the left upper limb muscles associated with "wandering movements" of that limb. These painful contractions failed to respond to non-opioid analgesics and to 10 mg three times daily of baclofen.

On examination, the patient had a mild left hemiparesis. Several episodes of involuntary movements of the right upper limbs were noted during examination. These were characterized by dystonic posturing of the limb with elbow extension, elbow flexion, arm adduction, and wrist flexion and extension. The affected arm also, at times, wandered around aimlessly. These dystonic muscle contractions and postures were painful, unnerved the patient during the day and interfered with his sleep. A magnetic resonance imaging showed areas of edema in the white matter deeper than the posterior frontal mass lesion, possibly related to radiation necrosis from the Gamma Knife procedure (Fig. 15.5).

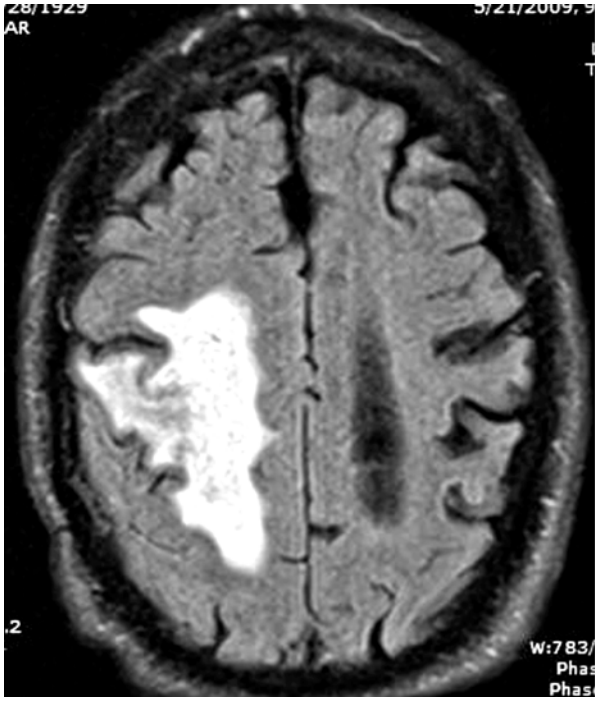

Fig. 15.5 Patient 15-5. T1-weighted brain MRI shows the right frontal mass and edema

Over the next 2 years, the patient was treated with intramuscular injections of onabotulinumtoxinA into the left upper limb and shoulder muscles: biceps (100 units), triceps (100 units), pectoralis (100 units), deltoid (40 units), trapezius (60 units), flexor carpi ulnaris (60 units), and flexor carpi radialis (40 units) for a total of 500 units per session. This treatment reduced the frequency of patient's painful episodic dystonia by 80 % as well as lowering the intensity of each episode by 50–70 %. BoNT therapy was repeated every 3–4 months. Patient and his wife repeatedly commented on the improvement of his quality of life. The patient died from complications of his brain tumor 2 years after initiation of BoNT therapy.

Comment

Although no blinded and prospective studies are available on the role of BoNT therapy for pain in advanced cancer, the aforementioned observations illustrate that BoNT therapy provides an avenue for treatment for end of life cancer pain which is effective and has a low side effect profile. The infrequency of treatment (every 3–4 months) is an advantage for patients who are too sick to take or remember tasking additional daily medications. Each of the three patients presented above enjoyed a significant improvement of the quality of their final months of life. In case of patient 1, BoNT therapy enabled the patient to eat and with less pain. Patient 2 experienced considerably less neck and shoulder pain. Patient 3 had less daily pain, better rest, and better sleep.

Conclusion

Preliminary data demonstrate that local injection of botulinum neurotoxins (ona, abo, and inco) can significantly reduce the local pain experienced by cancer patients after surgery and radiation therapy. The BoNTs seem to have an analgesic effect both in neuropathic pain and pain resulting from muscle spasms. Onabotulinumtoxin A, in a limited number of patients, has improved the end of life quality for cancer patients through its analgesic effect.

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Chapter 16
Botulinum Neurotoxin Treatment of Unusual and Rare Painful Disorders

Abstract Botulinum neurotoxins (BoNTs) can relieve painful muscle spasms through inhibition of acetylcholine release and alleviate neuropathic pain via blocking the release of pain mediators such as calcitonin gene-related peptide (CGRP), glutamate, substance P (SP), and others (detailed in Chap. 2). In addition to the common pain disorders discussed in the preceding chapters, data is now available on the possible efficacy of BoNTs in alleviating pain in uncommon and rare disorders.

In this chapter, three uncommon and rare conditions—stiff-person syndrome, painful legs–moving toes, and painful camptocormia—are discussed. The limited data from the literature about the use of BoNT in these conditions is presented. Case reports and video clips are included from the author's experience to illustrate the clinical features and the technique of BoNT injection employed to relieve pain.

Keywords Stiff-person syndrome • Painful legs–moving toes • Camptocormia • Botulinum toxin • Botulinum neurotoxin • Onabotulinum toxin • Abobotulinum toxin • Incobotulinum toxin

Introduction

Focal pain is a common complaint in some of the rare and uncommon neurological disorders. These disorders are characterized by a wide spectrum of symptoms ranging from intense increase in muscle tone to involuntary movements and unusual and abnormal postures. In most patients, conventional analgesics are only partially helpful, providing suboptimal pain control.

This chapter focuses on the effect of BoNTs on alleviation of the pain that presents as a major complaint in several rare disorders. The discussion of these rare conditions—stiff-person syndrome, painful legs–moving toes, and painful

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camptocormia—will be complimented with case reports and videotape clips from the author's experience to illustrate the patients' clinical features and the appropriate injection techniques.

Stiff-Person Syndrome (SPS)

Stiff-person syndrome is an autoimmune disorder characterized by progressive increase in muscle tone (rigidity) associated with painful, trigger-induced muscle spasms, predominantly affecting the axial and proximal limb muscles (Ciccotto et al. 2013). The exact pathophysiology of SPS is not known, but presence of antibodies against GABA decarboxylase (GAD), the rate limiting enzyme which makes GABA, suggests an inherent dysfunction of inhibitory spinal cord mechanisms (Solimena et al. 1990). Increased levels of GAD65 antibody are found in 60–80 % of the patients with SPS; however, the level of anti-GAD antibody does not correlate with the severity of the disorder (Ciccotto et al. 2013). Approximately 30 % of the patients with SPS have type1 diabetes, with autoantibodies to the same isoform of GAD65 shared by both disorders (Raju and Hampe 2008). Electromyography shows continuous muscle activity and firing of motor unit potentials which are easily triggered by photic or acoustic stimuli. This increased activity is seen in both agonist and antagonist muscles, and unlike a normal muscle, volitional activation of the agonist muscles does not reduce or stop the activity of the antagonist muscles (Rakocevic and Floeter 2012).

McKeon et al. (2012) defined SPS as a rare disorder based on their experience at the Mayo Clinic, observing an average of four new patients per year. Of their 99 patients diagnosed over 25 years, 67 were female (68 %) and 89 were Caucasian (91 %). They subdivided the clinical picture of SPS into classic SPS (65 patients), with predominantly lower trunk involvement conforming to the original description of Moersch and Woltman (1956), and a partial variant (31 patients) with involvement of one or more (usually lower) limbs. This variant is also called stiff limb syndrome (SLS) by others in the field. Included among the 99 patients, were 3 with the poorly understood disorder of progressive encephalomyelitis and rigidity (PERM). Eighteen of 99 patients (10.6 %) were seronegative for anti-GAD antibody. Seronegativity was more common among patients with the partial variant of SPS (12 out of 31 versus 6 out of 65, $P<0.05$).

SPS is occasionally a manifestation of an occult neoplasm. Paraneoplastic SPS accounts for 5 % of SPS patients and has been described in association with carcinoma of the breast, lung, colon, thymus, and lymphoma (Hadavi et al. 2011). The SPS symptoms may precede detection of the neoplasm by months or even years. Presence of antiamphiphysin antibodies in these patients correlates with adenocarcinoma of the breast or small cell carcinoma of the lung (De Camilli et al. 1993; Nguyen-Huu et al. 2006). Maurinson and Guarnacia (2008) emphasized epidemiological and clinical features of SPS with amphiphysin antibodies; these features include older age, marked predominance among women, absence of diabetes,

and cervico-brachial rigidity. Approximately 50 % of the patients complained of substantial muscle pain.

Treatment of SPS is aimed at reducing muscle tone, alleviating pain, and preventing further damage to the central nervous system (CNS). High doses of diazepam (40–100 mg daily) are commonly used for reducing muscle stiffness in SPS. Reduction of muscle tone can be achieved also by baclofen (including intrathecal route), tizanidine, or dantrolene. Levetiracetam, vigabatrin, valproic acid, clonazepam, and gabapentin are used to reduce CNS hyperexcitability. Anecdotal observations claim improvement of SPS symptoms with short courses of steroids (Blum and Jankovic 1991). Intravenous gamma globulin (IVIG) therapy is often employed to prevent further damage to the CNS. The recommended total dose is 2 g/kg, over 3–5 days, and may be repeated every 4–6 weeks. More severe cases and especially those with compromised respiratory function due to severe spasms of the thoracic muscles may require plasma exchange (PE).

A recent review of this subject (Pagano et al. 2014) found 18 publications describing the response to PE in 26 patients with SPS. Overall, 41 % of the patient had significant improvement of their symptoms after plasmapheresis, and two experienced adverse effects (one transient hypotension and one infection at the site of catheter insertion). Although a small controlled study showed no advantage for rituximab over other modes of therapy in SPS (Dalakas et al. 2009), two recent case reports claim its effectiveness against SPS symptoms (Fekete and Jankovic 2012; Sevy et al. 2012).

Pain is a common complaint in patients with stiff-person syndrome. In the classic form of SPS, rigidity of the lumbar and lower thoracic, abdominal, or paraspinal muscles is often associated with lumbar lordosis and deep pain (Bastin et al. 2002). Paroxysmal local pain in the form of muscle spasms is also common in the trunk and thigh muscles. Some patients with partial SPS and lower limb involvement manifest neuropathic pain with a significant burning quality (personal observations).

BoNT Treatment of Pain in Stiff-Person Syndrome

Davis and Jabbari (1993) first reported marked improvement of low back pain and reduction of paraspinal rigidity in SPS after injection of onabotulinumtoxinA into the paraspinal muscles of a 36-year-old African American gentleman who had developed progressive stiffness of the thighs, lower abdominal, and back muscles over an 18-month period. Initially, his problems were attributed to lumbar osteoarthritis, and he was treated with nonsteroidal anti-inflammatory agents. However, he gradually developed lumbar lordosis and severe, painful muscle spasms in the thigh, back, and abdominal muscles. These spasms were easily triggered by physical activity. His sister had non-insulin-dependent diabetes and hypothyroidism, but his past medical history was normal. On examination, pertinent physical findings were lumbar lordosis; markedly increased tone in the thigh, abdominal, and low back muscles bilaterally; inability to change position from supine to standing position unassisted; and an

awkward, hesitant, and short-stepped gait. In addition, he had diffuse hyperhidrosis. An extensive laboratory workup including muscle biopsy of the right thigh muscles and cerebrospinal fluid values was normal with the exception of electromyography (EMG) and the level of anti-GAD antibodies. On EMG, the involved muscles showed continuous motor unit firing at rest in both the agonist and antagonist muscles. Serum GAD antibody was positive at a dilution of 1/122,000, and the CSF anti-GAD level was 1/128 (normal values from Mayo Clinic were <1/120 and <1/2, respectively). Treatment with a combination of baclofen and diazepam partially improved muscle rigidity. Patient was injected with 560 units of onabotulinumtoxinA into the erector spinae and thigh muscles. Within a week, the patient reported cessation of muscle spasms and significant improvement of back and thigh rigidity. A repeat injection 6 months later produced similar effects.

In 1997, Liguori et al. described the results of the BoNT-A (aboA) injection into the affected muscles of two patients with Stiff-person syndrome. Both patients were women with the partial variant of SPS (Stiff limb syndrome). Both patients had detectable serum anti-GAD antibodies, but the exact level was not mentioned. In one patient, a total of 700 units of abobotulinumtoxinA (aboA) was injected into different muscles of one thigh. The second patient received a total of 1,000 units of aboA into the upper limb muscles (deltoid, biceps, brachioradialis). The outcome for rigidity was assessed blindly at baseline and following injections, with the Unified Parkinson Disease Rating Scale (UPDRS). The spasms were evaluated on a scale of 1–5 (5 being 30 or more spasms per day). Treatment with abobotulinumtoxinA reduced both pain and rigidity for up to 7 months, and repeat injections were also successful over a follow-up period of 2 years.

Anagnustou and Zambelis (2012) reported a 40-year-old man with a history of left leg stiffness for 9 years. The patient gradually developed painful knee extension spasms. Treatment with diazepam was partially helpful. Serum anti-GAD antibody level was 500 units/ml (normal <5/ml). Injection of 900 units of abobotulinumtoxinA into the leg muscles (350 units into vastus lateralis, 350 units into vastus medialis, 200 units into rectus femoris) eliminated the painful extension spasms of the leg and reduced the muscle tone (Ashworth scale: 4, before injection; 1, 4 weeks after injection). In this patient with stiff limb syndrome, previous injections of aboA with doses smaller than 900 units had resulted in either no or only modest improvement.

Case Report 16-1

A 44-year-old man was referred to the Yale Movement Disorder Clinic for evaluation of “muscle pain and muscles stiffness.” His symptoms had begun 3 years earlier with increased daily fatigue and low motivation for engaging in physical activity. He was told by a physician to keep well hydrated and consume potassium-rich foods. Subsequently, the patient developed a chronic sensation of “tightness/stiffness” in his lower limbs and severe episodic cramping of muscles in his thighs,

calves, toes, and flanks as well as his jaw muscles. Intermittent cramping and pain in the jaw muscles made speaking difficult. The more severe episodes lasted 30 min but only occurred after physical exertion, about five times per week. The patient also reported continuous twitching of his right quadriceps and intermittent twitching of his left quadriceps and bilateral calve muscles. He had also noticed involuntary jerking of his limbs during the day and night. The patient felt his right thigh has grown larger in the last year and had noticed increased hair growth on his right upper thigh extending to the gluteus region. Diazepam, 10 mg twice daily, and Percocet, 10–325 mg two to three times daily, offered only modest relief of the symptoms.

Neurological examination demonstrated normal cognition and speech and intact cranial nerves, cerebellar, and sensory functions. There was increased muscle tone in the right thigh (Ashworth score of 3) and lower abdominal muscles. Painful muscle twitches could be provoked easily in the right thigh muscles by passive and active stretch or pressing the right foot on the floor. The rest of the neurological examination was normal. Electromyography showed continuous muscle activity at rest in the right vastus medialis and rectus femoris muscles (Video 16.1). The serum anti-GAD antibody level was 3 (normal, <0.5), significantly elevated from 0.07 obtained a year earlier. Serum glucose, total CK l, HgA1c, TSH, insulin autoantibody (<5.0), and striational and acetylcholine receptor antibodies were all normal as well as the paraneoplastic panel which included the antiamphiphysin antibody. Magnetic resonance imaging of the spine showed moderate cervical arthritic changes.

The patient was treated with intravenous immunoglobulin (IVIG), 2 g/kg given over a period of 3–5 days at 4-week intervals. This treatment improved the muscle rigidity after 3 months, but the effect on painful muscle spasms was modest. The patient then received an intramuscular injection of 400 units of botulinum toxin A (onaA) into the right thigh muscles. A total of 100 units was injected at two sites (50 units/site) into each of the following four muscles: vastus medialis, rectus femoris, vastus lateralis, and hamstring (Video 16.1). After 2 weeks, the patient reported reduction in frequency and in intensity of muscle cramps in the right vastus lateralis and rectus femoris muscles. However, the spasms of the gastrocnemius muscles responded less favorably.

Comment

Pain is a major symptom in many patients with Stiff-person syndrome. The observations listed above demonstrate that both onaA and aboA injections into rigid and painful muscles can alleviate pain in patients with SPS. In my experience with BoNT injections in a dozen patients with SPS, onabotulinumtoxinA effectively reduced pain and rigidity and improved the patients' quality of life. Due to the rarity of SPS, however, clinical trials are hard to perform. An important caveat of BoNT treatment in SPS is sufficiency of the injected dose. The involved muscles are large

muscles and, therefore, it is easy to under-dose. For bilateral low back muscles, I recommend a total dose of 400 units of onaA for a patient of average weight. This can be given at five lumbar levels into the erector spinae, 40 units/level for a total of 200 units on each side. The technique of BoNT injection into the lumbar erector spinae is shown in Video 5.1 (Chap. 5, low back pain). A comparable dose of aboA would be 500 units for each side (using 1:2.5 ratio). For the large thigh muscles, I recommend 100–200 units of onaA per muscle. It is important to remember that BoNT treatment is only for symptomatic relief and not a substitute for modulation of the immune system which is often needed for these patients.

Painful Legs–Moving Toes

This syndrome was originally described in six patients who presented with involuntary toe or foot movements associated with pain in the toes, feet, or leg (Spillane et al. 1971). The pain often precedes the movements and has been described variably as aching, burning, jabbing, throbbing, and so forth. Movements are often slow and writhing with a flexion–extension pattern (Videos 16.2 and 16.3). Subsequently, a number of variants of this syndrome were described and designated as painful hand moving fingers and painless moving toes/painless moving fingers. The movements can start in one limb and gradually progress to the other limb or move from the lower limb to the upper limb (Ebersbach et al. 1998; Jabbari et al. 2000). The syndrome is rare with only 14 cases observed among 4,780 patients referred to the Mayo Clinic for evaluation of movement disorders over a 10-year period (Alvarez et al. 2008).

Nathan (1978) and Schott (1981) proposed that the condition results from injury to the peripheral nervous system (nerves, plexus, roots), citing several examples of this association. Support for this view has emerged from cases of cervical and lumbar spine disease that have improved after surgical intervention. Miyakawa et al. (2010) reported a patient with painful arm–moving fingers with cervical spondylosis at the C5–C6 level in whom foraminectomy stopped both the finger movements and the arm pain. Their second patient had developed leg pain and toe movements (PLMT) 2 weeks after L5–S1 discectomy. The pain and movements disappeared after lumbar nerve blocks. Others have also reported various levels of pain relief following lumbar epidural block or spinal cord stimulation (Okuda et al. 1998; Takahashi et al. 2002).

In the largest series of patients reported to date with this syndrome, Dressler et al. (1994) noted a variable age of onset in adults (youngest, 28 years of age) and a predominance among women (14 out of 20). Also, a majority of their patients had peripheral nervous system injury. Due to bilateral symptom distribution in some patients, the authors proposed existence of a central generator for the movements which presumably develops by a cascade of events after the peripheral injury. Presence of a “central oscillator” above the spinal cord level has been strongly suggested from transcortical magnetic simulation of the left motor cortex which has

demonstrated failure of cortical facilitation in a patient with bilateral finger movements and painful hands. A detailed electrophysiological assessment of this case showed no abnormality of the spinal inhibitory mechanisms (Jabbari et al. 2000). In another patient with bilateral finger movements, presence of out-of-phase discharges in the involved hand muscles suggested existence of two independent central generators (Ebersbach et al. 1998).

In the series reported from Mayo Clinic, 11 of 14 patients also had electrophysiological evidence of peripheral nervous system dysfunction and were affected by a variety of neuropathies caused by diabetes, vitamin deficiencies, lupus, and Sjogren's syndrome (Alvarez et al. 2008). In most affected patients, electromyography (EMG) demonstrated rhythmic 1–3 HZ discharges with duration of each discharge ranging from 0.5 to 2 s. In several patients, the pattern of EMG discharge resembled that of myokymia.

Treatment of pain in PLMT is challenging and was called "notoriously difficult" by Dressler et al. (1994). In the Mayo Clinic series (Alvarez et al. 2008) which was published 12 years after Dressler's series, most patients were treated with gabapentin and pregabalin (GABAergic and calcium channel blocker) which provided the patients with partial pain relief. Others have used opioids in patients with persistent pain. A more extensive description of clinical features and therapeutic measures in PLMTs has been published by Reich (2011) in a recent review.

BoNT Treatment of Painful Legs–Moving Toes

Three open-label observations have reported on the effect of local BoNT injection in PLMT syndrome. In collaboration with Dr. Carlos Singer's group in the University of Miami, we described significant reduction of pain and movements in two patients with PLMT syndrome after injection of onaA into the affected muscles (Eisa et al. 2006). One of the patients, a 62-year-old man, complained of low back pain for a year followed by development of pain in both calves and feet associated with involuntary flexion–extension of the toes bilaterally. OnabotulinumtoxinA was injected into the following muscles bilaterally: gastrocnemius (50 units, each side), flexor digitorum brevis (45 units, each side), and lower lumbar paraspinal muscles (60 units on each side). The second patient, a 72-year-old female, also had bilateral PLMTs with irregular toe movements and pain in the feet. Injection of 25 units of onaA into the flexor digitorum brevis of each foot relieved pain and slowed down the movements.

Schoffer (2010) described a 17-year-old boy who developed burning sensation and cramps in the calf and writhing involuntary movements of the fourth and fifth toes a year after a hamstring injury. Injection of 20 units of onabotulinumtoxinA into the adductor digiti minimi and 10 units into the flexor digiti minimi eliminated the movements and the calf pain.

Rodriguez and Fernandez (2013) reported a 43-year-old man who developed adduction–abduction movements of the right big toe and, to a lesser extent, other

toes with significant foot and lower leg pain. Injection of onabotulinumtoxinA (onaA) under electromyographic guidance into the foot muscles stopped the movements and significantly reduced the pain intensity. The dose was as follows: 25 units in the flexor hallucis brevis, 25 units in the adductor hallucis, and 50 units in the flexor digitorum brevis. A long-term follow-up of 3 years showed continued efficacy of treatment with onaA injections every 3 months.

Comment

Painful legs–moving toes is a rare disorder but can be a cause of significant pain and discomfort to the patients. The observations cited above suggest efficacy of local BoNT injection in the management of pain and movements in patients with this syndrome. The mechanism of pain relief is probably multifactorial, partly related to suppression of muscle spasms via inhibition of acetylcholine release from the neuromuscular junction and partly related to other analgesic effects of the BoNTs (Chap. 2). The technique of injection needs to be individualized according to the patient's symptomatology. In the case of PLMT, injections of BoNT-A into the gastrocnemius and flexor digitorum brevis as well as flexor or adductor pollicis when the big toe is involved have been helpful. With experience, refinement of injection techniques can lead to better results.

Camptocormia

Camptocormia is an abnormality of posture characterized by marked thoracolumbar flexion which manifests during standing and walking and abates in the position of repose (Video 16.5). The term camptocormia was coined by two French neurologists Souques and Rosanoff-Saloff describing the posture in shell-shocked soldiers who fought in trenches during World War I (Souques and Rosanoff-Saloff 1914). The authors suspected a psychogenic cause for this form of camptocormia. However, almost a century earlier, another neurologist had used the term "bent spine" describing the posture of a Spanish painter (Brodie 1818). It is now clear that most cases of camptocormia are not psychogenic and camptocormia can be caused by a large number of pathologic conditions (Finsterer and Strober 2010). Typical camptocormia is usually seen in neurodegenerative disorders, especially Parkinson's disease (PD) and multiple system atrophy (MSA) (Azhar and Jankovic 2005; Melamed and Djaldetti 2006; Jankovic 2009), and in myopathies of posterior trunk muscles. Other common causes include drug-induced camptocormia, spine and disc disease, and even certain neuropathies. Most recently, acute camptocormia has been described as a manifestation of tetanus (Kaji et al. 2014). Camptocormia of PD or MSA seems to be related to basal ganglia dysfunction, a view which is supported by significant improvement of camptocormia in some of

such patients after bilateral pallidal or bilateral subthalamic deep brain stimulation (Reese et al. 2014; Lyons et al. 2012). Margraf et al. (2010), however, hold the view that camptocormia in PD is a myopathy of the paraspinal muscles. In a study of 15 such patients, both electromyography and muscle biopsy have demonstrated a pattern of myopathy. Also a case of inclusion body myositis (proved by biopsy) has been reported as the cause of an isolated camptocormia (MA et al. 2013). Treatment of camptocormia is difficult. Pharmacological treatment is not usually effective. Anecdotal reports indicate that some patients may respond to dopaminergic drugs (Bloch and Houeto 2006; Ho et al. 2007; Oravivattanakul et al. 2014). Improvement of camptocormia has been reported after transcranial magnetic stimulation, but the effect is transient (Arii et al. 2014).

BoNT Treatment of Camptocormia

In recent years, several medical groups have reported on the effects of BoNT injections into abdominal and iliopsoas muscles of patients with camptocormia. The Baylor group (Azher and Jankovic 2005) noted moderate to marked improvement of camptocormia in four of nine patients with neurodegenerative disorders. OnabotulinumtoxinA, 300–600 units, was injected into the rectus abdominis muscles bilaterally. Presence of pain or the effect of injections on pain was not mentioned. No side effects were reported.

In contrast, Van Coellen et al. (2008) reported no improvement of camptocormia after BoNT injection in four patients with PD and MSA. AbobotulinumtoxinA was injected, 500 units per side, into the deep iliopsoas muscle under ultrasound guidance. Injections were repeated every 4–6 months with escalating doses of 1,000 and 1,500 units per side. Patient's posture was monitored at baseline and every 4–6 months; there was no mention of problems with pain in these four patients.

Fietzek et al. (2009) also injected BoNT-A (incoA), 100–300 units, either into the rectus abdominis or iliopsoas muscles of ten patients with camptocormia. Patients were asked to choose an outcome goal for the study. Six patients chose improvement of posture while three chose alleviation of pain as a desired outcome. None of the patients showed any improvements when assessed at 3 weeks postinjection. Two other patients were also reported in whom ultrasound-guided injection of onabotulinumtoxinA, 100 units per each iliopsoas, failed to improve camptocormia (Colosimo and Salvatori 2009).

Comment

Some patients with camptocormia have significant pain (Fietzke et al. 2009; Dupeyron et al. 2010, and personal observations). The literature on the effect of botulinum toxins on pain of camptocormia is very limited. Of the two techniques

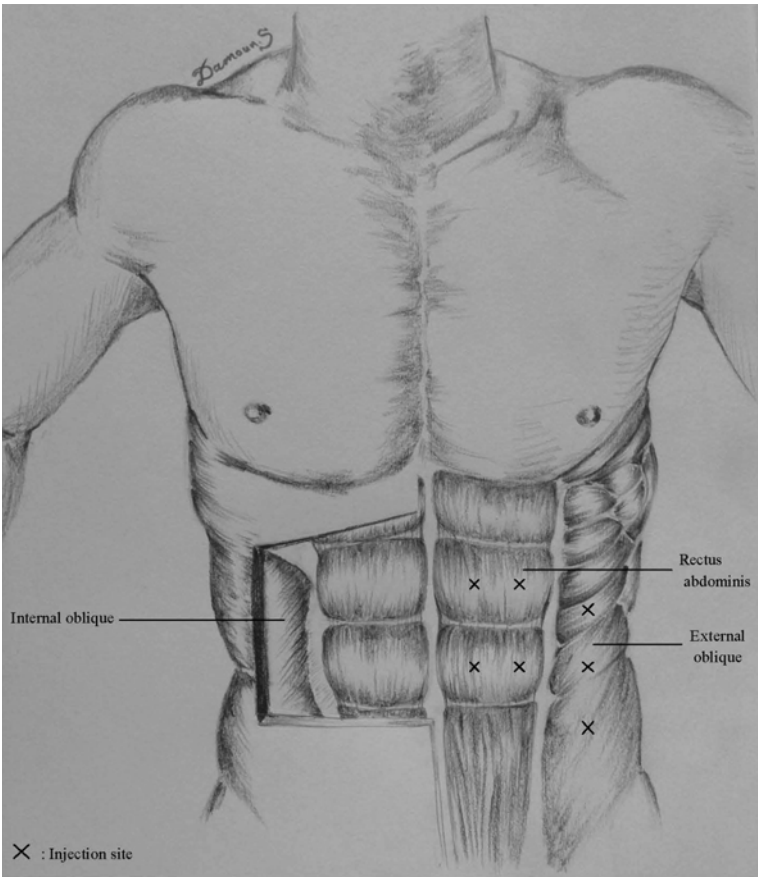

Fig. 16.1 Position of the rectus and oblique abdominal muscles and points of injections for camptocormia (created by Damoun sufarpouz, published with permission from © Bahman Jabbari 2014. All rights reserved

employed for treatment of camptocormia, negative results on pain have been reported with the iliopsoas injection method. This method seems to be ineffective also in improving the camptocormic posture itself.

Botulinum toxin treatment of camptocormia requires significant familiarity with anatomy of the abdominal muscles and a solid background in electromyography. In my experience with onabotulinumtoxinA in six patients with camptocormia, three have demonstrated notable improvement with a technique which combines injection of the rectus abdominis and oblique abdominal muscles (Fig. 16.1, Video 16.6). In one of these three patients who had painful camptocormia, onaA injections also significantly alleviated the pain (pain level of VAS 7 was lowered to VAS 2). I have used a total of 200 units for the rectus abdominis and 150 units for the abdominal oblique muscles on each side, a total of 700 units per session. The injections were

done under electromyographic guidance. No side effects were noted. (Video 16.7) Treatment of camptocormia is difficult due to the heterogeneity of the causative factors. Larger and preferably blinded studies are needed for assessing the efficacy of BoNT treatment of painful or painless camptocormia. These studies should focus on the techniques which have produced positive results as cited in the aforementioned open observations.

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Chapter 17
Future Prospects of Pain Treatment with Botulinum Neurotoxins

Abstract Treatment of pain with botulinum neurotoxins is now entering a new era due to the emergence of newly engineered compounds which by targeting the sensory neurons can offer a more effective means of pain control. The preliminary data from cell culture and animal experiments suggest a significant potential for these toxins/toxin chimeras and toxin/antibody compounds in relieving human pain.

Keywords Botulinum toxin • Botulinum neurotoxin • Tetanus toxin • A/E chimera • Antibody • P2X3 receptor • Pain

Introduction

Botulinum neurotoxins (BoNTs) have been shown to inhibit the release of pain mediators (glutamate, calcitonin gene-related peptide, substance P, and others) from sensory nerve endings and sensory neurons (Meng et al. 2007; Lucioni et al. 2008; Marinelli et al. 2010; Marino et al. 2014). The type A toxin is already widely used in clinical practice for treatment of a variety of pain disorders including chronic migraine and neuropathic pain (Chaps. 3 and 4).

It has been shown that SNARE proteins (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) which play a role in vesicular release of pain mediators are also expressed on the surface of sensory neurons (Matak et al. 2012). In the past few years, there has been a vigorous attempt in the scientific community to produce new molecular variants of BoNTs that specifically target the sensory neurons to attain better pain relief. As a result, we have witnessed the development of a variety of engineered BoNT chimeras which specifically target sensory neurons and have a potential for more effective management of pain. These chimeras have been already successful in alleviating pain in some animal models (Ferrari et al. 2013). Human studies are currently underway to test the clinical efficacy of these compounds.

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Botulinum Neurotoxin Chimeras and Their Role in Pain Management

The molecular structure of botulinum neurotoxins contains three functionally distinct domains: binding, translocating, and catalytic. As discussed in Chap. 1, the first two domains are included in the heavy chain (HC) of the toxin, whereas the light chain (LC, 50 KD) catalyzes and inactivates the SNARE proteins and prevents the release of neurotransmitters from the presynaptic vesicles. The HC is a 100 KD protein and has two terminals, N and C. Through its C terminal, the heavy chain binds to the synaptic membrane receptors (ganglioside, SV2). Following binding, HC translocates the toxin molecule through the synaptic membrane to the cell's interior. The light chain is a zinc-endopeptidase protein which is bound to the HC by a disulfide bond. Once inside, the light chain is detached from the HC and acts upon the synaptic proteins (SNARE) to block their function (vesicular membrane fusion and transmitter release).

The function of the various domains of the toxin varies between different BoNT serotypes. For instance, the binding domain of one toxin may show strong affinity for one cell receptor and weak affinity for another.

Botulinum neurotoxin chimeras are genetically engineered molecules with combined domains from different toxins in order to improve the overall function of the toxins. Usually, a chimera is stronger than either of the two parent toxins. In recent years, the use of such chimeras in animal models has been able to induce less or more paralytic toxin effect and longer duration of toxins' action or more specifically target certain cells (neuron or non-neuron). Pertaining to pain treatment, there are toxin chimeras which target specifically the sensory neurons.

The efficacy of BoNT-A in the treatment of chronic migraine has been attributed, at least in part, to the inhibition of the release of calcitonin gene-related peptide, a potent pro-inflammatory pain mediator (Cernuda-Morollón et al. 2014) which is also implicated in the burning pain resulting from exposure to capsaicin (the chemical contained in hot pepper). However, neither BoNT-A nor BoNT-E by itself alleviates or prevents the neuropathic pain caused by exposure to this agent. Capsaicin exerts its effect by activating the transient receptor potential vanilloid receptor type 1 (TRPV1), expressed abundantly on the surface of sensory neurons, dorsal root ganglia (DRG) (Nagy et al. 2014). Activation of TRPV1 is essential for exocytosis of CGRP and requires an intact SNAP25 function. BoNT-E is more potent than BoNT-A and acts faster than BoNT-A on SNAP25, but it has a shorter duration of action. It has been postulated that failure of BoNT-E in alleviating capsaicin-induced pain may be related to the paucity of specific binding receptors for this toxin on the surface of sensory cells. It has been hypothesized that an A/E toxin chimera may be effective against capsaicin-induced neuropathic pain using the powerful binding action of the type A toxin. A BoNT-A/E chimera has been engineered in which the HC domain of BoNT-A binds the toxin to sensory neuron's surface and by making a channel in the cell membrane translocates the E-protease into the synapse. This chimera effectively blocks the release of CGRP

from TRPV1 receptors in response to capsaicin exposure in cell cultures of sensory neurons (Meng et al. 2009). Additional studies have shown that A/E chimera also prevents the emergence of capsaicin-induced pain in animals as judged by alleviation of the behavioral manifestations of pain after peripheral exposure. Clinical trials with A/E chimera in human with pain disorders are currently being conducted.

Ferrari et al. (2013) assembled a chimera of BoNT-A and tetanus toxin using a new technology of "protein stapling." Through this method, the C domain protease of BoNT-A was combined with the binding domain of the tetanus toxin. Tetanus toxin naturally attaches itself to central neurons. The flaccid or spastic paralysis, characteristic of exposure to BoNT-A and tetanus toxin, was not observed in the rats injected intrathecally with the chimera. Measurements of the paralytic effect of the chimera have shown that it is negligible and 11,000 times less than either of the parent toxins. The rats were then injected with Freund's adjuvant in the hind paw to cause local inflammation, inflammatory pain, and mechanical hypersensitivity. The animals pretreated with the novel chimera demonstrated significantly less mechanical hypersensitivity compared to the control animals which had been pretreated with saline. Cleavage of SNAP25 was noted in approximately half of the sensory dorsal root ganglia neurons indicating resistance of a population of sensory neurons to this chimera. The investigators concluded that pain-conducting mechanoreceptors in the rat are located in tetanus toxin-binding neurons, and the novel chimera of BoNT-A/tetanus toxin has a potential for treating pain in human subjects.

Botulinum Toxin as a Protein Transporter

The capacity of the botulinum neurotoxin molecule to move a 50KD protein (light chain, LC) through the synaptic membrane has inspired attempts to use BoNTs as vehicles to carry small-sized proteins into cells for therapeutic purposes. A variety of approaches has been used in recent years including gene transfer into neuroblastoma cells and transport of viral vectors into neural cells (Maysuyer et al. 2014).

New ideas and approaches are now emerging in the area of pain research based on the protein transporting properties of BoNTs. Very recently, Ma et al. (2014) engineered a recombinant small molecule antibody, scFv, which works against the P2X3 nociceptive receptor; P2X3 is believed to play a major role in the development of inflammatory pain (Burnstock 2014). Drugs that reduce the action of this purinergic ATP-activated receptor have been shown to alleviate neuropathic inflammatory pain (Dai et al. 2004). A fused protein was generated by ligating the gene of scFv antibody to the gene of BoNT-A (Ma et al. 2014). This compound enters the sensory neurons that have P2X3 receptors and cleaves the SNAP25. The cleavage of SNAP25 with this novel protein occurs in much lower concentration (at 0.1 nm level) compared to BoNT alone (at 100 nm). The novel protein also inhibited the release of CGRP from the sensory neurons (DRG).

Comment

A/E chimera and BoNT/antibody molecules are novel compounds that have demonstrated a significant potential for more effective alleviation of neuropathic pain. The encouraging data on the efficacy of these compounds derived from cell culture and animal studies, however, need to be carefully and safely tested in human subjects to determine if they are indeed more potent than and at least as safe as the sole BoNT molecules that are currently used for pain management.

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