Gabor B. Racz
Carl Edward Noe
Editors

Techniques of Neurolysis

Second Edition

Springer

Techniques of Neurolysis

Gabor B. Racz • Carl Edward Noe
Editors

Techniques of Neurolysis

Second Edition

Springer

Editors
Gabor B. Racz
Lubbock, TX
USA

Carl Edward Noe
Dallas, TX
USA

ISBN 978-3-319-27605-2 ISBN 978-3-319-27607-6 (eBook)
DOI 10.1007/978-3-319-27607-6

Library of Congress Control Number: 2016933055

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Foreword

Neurolytic techniques have evolved dramatically over the past decades. Injecting large volumes of alcohol and phenol has been largely displaced by targeted neurolytic procedures using radiofrequency thermocoagulation. Cryoneurolysis is resurging and molecular techniques may be developed for routine use. Neurectomy has become reserved for specific syndromes such as Morton's neuromas and thorascopic sympathectomy. Neuromodulation will continue to complement neurolytic techniques, and emerging technology may displace some neurolytic procedures.

Effectiveness is always the patient's primary desire, but safety must always be our primary concern. It is our hope that this book will advance both pain relief and patient safety. The PainCast video links are intended to reinforce this information in the book and give a glimpse into the future new techniques, ideas, and technologies.

Lubbock, TX, USA — Gabor B. Racz

Preface

Interventional pain procedures work. The first edition of *Techniques of Neurolysis* was published in 1989, as the field of interventional pain was starting to take shape. Six to seven years before the first edition, there was a clear need to train doctors in this new and evolving field, and an impetus was the availability of beautiful anatomical preparations in the anatomical laboratory that were done by Professor Selliger at Texas Tech University Health Science Center. We started a lecture-based training course and immediately added the lab component to incorporate the information of clinical anatomy from dissections that were beautifully performed in well-preserved anatomical specimens. In the second year, we decided to try and show the placement of needles under fluoroscopy to the lumbar sympathetic chain in cadavers. Additionally, we tried to demonstrate placing epidural catheters that we were using, to reach the dorsal root ganglion. Initially, this was done for nerve blocks and later for longer-lasting phenol blocks. The first edition reflects our feeling at the time when we had very limited number of tools available. Twenty-six years later, this second edition reflects changes in our desire and our continued desire, to consider using neural destructive techniques but in a much more targeted manner. The reader will gain a strong sense of this in Chap. 2 as better monitoring of cryoneurolysis is described along with images of the targeted nerve under ultrasonic guidance. This beautiful work of Trescot et al. presents the concept of imaging the cryoneurolysis ice ball encapsulating the nerve.

In Chap. 3, targeted radiofrequency lesion techniques by Calodney et al. present elegant refinements of basic procedures such as facet denervation along with new techniques such as pulsed radiofrequency procedures.

In Chap. 4, the wealth of experience of Drs. Koh and Loeser in the trigeminal nerve radiofrequency lesion procedure is presented. John Loeser's continued involvement and support has been very much appreciated and impressive as he has taken the FIPP examination after being established as an international figure.

In Chap. 5, we are fortunate to have Prithvi Raj describe his technique for the splanchnic nerve radiofrequency lesion procedure to replace a more hazardous alcohol neurolysis of the celiac ganglion that was presented in the first edition. New evidence shows that the splanchnic nerve radiofrequency lesion procedure in terminal cancer patients not only reduces pain but also suffering.

Chapter 6 describes the sympathetic and celiac plexus blocks and also discusses complex regional pain syndromes where there is a significant role of the sympathetic nervous system.

The hypogastric plexus block was developed by Plancarte, after the first edition was published, but technically, with the addition of blunt needle techniques, it has become a safer and better procedure as presented by Drs. Smith and Day in Chap. 7. The practice is slowly shifting away from the use of sharp needles as well as particulate steroids when sharp needles are used. The incidence of interneural injection and secondary injuries to the spinal cord is low but remains a significant concern.

Evaluation of the mechanism of actions of neuromodulation is looked at by Calvillo et al., and most of it is based on animal data and additional clinical observation which shows the relevance of DRG evolvement in development allodynia. The reversal of allodynia using site-specific dilute local anesthetic concentration infusion allows recognition of triggering

mechanisms, and the time-dependent pain blocking (4–5 days) of the DRG can reverse the development of painful spinal cord stimulation. However, the peripheral components need to be treated as well. Clearly this observation cannot be duplicated easily in the animal models but has a significant role in the effective use of neuromodulation.

Neuromodulation has been recognized to be possible by subthreshold high-frequency stimulation. Pope and Deer have done a nice Chap. 10 on this topic. The interventional peripheral nerve stimulation for chronic headache is an exciting evolving area that has definite peripheral and central actions and nicely presented by Ken Reed. A link to this procedure is http://www.reedmigraine.com/four-lead-neurostimulator-trial.php.

We have learned a great deal from the medicolegal arena, and some of our safer and better methods come out of it. This is a topic that needs to expand. We have assembled a nice group for international experts' observational input to make the field safer, Chap. 12. Intrathecal substance P-saporin is a new topic nicely addressed by Dr. Noe.

This second edition does have a link to PainCast and opportunity for the reader to look at actual cases and refer back to the chapters in the book.

I dedicate the book to the people who helped, and some of these people are no longer around, but our indebtedness remains to them, with them, forever. Dr. Ian McWhinney and his wife Betty took me into their home in Stratford-upon-Avon, England, after 4 days in a refugee camp in January 1957, unable to speak English, after we had escaped in November to Austria after the brutal soviet crackdown. They've helped, and we learned English from them. The McWhinneys and hard work helped me to become a physician. As fate would have it, Ian's cousin, Jack Leggate, was the dean at the medical school at the University of Liverpool. Ian's recommendation helped to get an interview, and I was able to continue medical education the next fall. Dr. Robert King's influence as a neurosurgeon paved the way to work with pain problems. This is an example of debt that can never be repaid but passed along to others.

Dr. Miles Day has been a wonderful colleague for 20 years and is doing a great job as a leader in interventional pain and fellowship training.

Twenty-six years later, we have come a long way, and many people have helped including the current coeditor, my long-term friend Dr. Carl E. Noe whose prompting I have needed to get to this point which is now the third book in our working together. Key individuals I could not have done without have been Professor James Heavener, whose logical and thorough scientific mind has kept us focused and kept us close to the truth the way that we know it and others accept; Prithvi Raj who has been a longtime colleague and friend; the people in WIP; the founders in addition to Raj, Ricardo Luiz Lopez, Serdar Erdine, David Niv, and Richard Rauck; and my friends in Hungary Edit Racz and Professors Lorand Eross and Istvan Nyary where we have the 20th international and best cadaver conference.

For the past 8 years, I've had an honorary consultant appointment at Guy's and Saint Thomas' Hospitals and enjoyed visiting, lecturing, and doing procedures under the leadership of Adnan Al-Kaisy.

Paula Brasher who relentlessly keeps and consistently keeps the system flowing and the delightful Angela Pranivong who manages to make the pieces fit together when they appear impossible.

We have been able to do a lot through the help of our families, my beautiful wife Enid Racz and my children Gabor J., N. Sandor, Tibor, and Yvonne and Dr. Noe's wife Laura Noe and their children Lillie and Robert.

Dr. Lax Manchikanti and the American Society of Interventional Pain Physicians have established the Raj and Racz lectures, and the honor and support is greatly appreciated.

Epimed's readiness and willingness to help in sponsoring were needed in timely studies. One of the many years' lessons learned was the need to work together for science and clinical practice just as much as lectures and practical on hand teaching of physicians at various levels of their education to make them better. This process has been very expensive, and funding for these educational badly needed opportunities could have not been possible without working together with industrial partners and their financial support. The process has been and had to

be transparent and appropriate at all times. I am grateful for the opportunities that we have been able to create for all involved.

None of this would be possible without opportunities for teaching and research through TTUHSC and first of all my patients and our patients who we are here to serve.

Lubbock, TX, USA — Gabor B. Racz
Dallas, TX, USA — Carl E. Noe

Contents

About the Author

The Visionary Prithvy Raj MD FIPP 1931–2016

Contributors

Adnan Al-Kaisy, MB, ChB, FRCA, FPMRCA, FIPP London Bridge Hospital, London, UK

Aaron Calodney, MD, FIPP, ABIPP Texas Spine & Joint Hospital, Tyler, TX, USA

Octavio Calvillo, MD, PhD, FIPP, ABIPP Department of Anesthesiology, Methodist Hospital Houston, Houston, TX, USA

Miles Day, MD, DABA, DABIPP, FIPP Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Timothy Deer, MD, DABPM, FIPP The Center for Pain Relief, West Virginia University School of Medicine, Charleston, WV, USA

Arthur E. Frankel, MD Hematology/Oncology Division, University of Texas Southwestern, Dallas, TX, USA

Abigail Gordon, BA Baylor College of Medicine, Houston, TX, USA

Hans Hansen, MD The Pain Relief Centers, Statesville, NC, USA

James E. Heavner, MD, PhD, DVM Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Denise Higgins, BS Advanced Targeting Systems, San Diego, CA, USA

Andrew L. Ko, MD Department of Neurological Surgery, University of Washington, Seattle, WA, USA

Douglas A. Lappi, PhD Advanced Targeting Systems, San Diego, CA, USA

Sang Chul Lee, MD, PhD, FIPP Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul, Korea

John D. Loeser, MD, FIPP Department of Neurological Surgery, University of Washington, Seattle, WA, USA

André Mansano, MD, PhD, FIPP Singular-Pain Control Center/Brazil, Campinas, SP, Brazil

Tomikichi Matsumoto, MD, FIPP Jikei University School of Medicine, Tokyo, Japan

Shiga University of Medical Science, Shiga, Japan

Rajesh Munglani, MBBS, DA, DCH, FRCA, FFPMRCA West Suffolk Hospital Cambridge University Trust, Bury St Edmunds, UK

Laszlo Nagy, MD Department of Pediatric Neurosurgery, Texas Tech University Health Sciences Center and Covenant Medical Center, Dallas, TX, USA

Carl E. Noe, MD Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

Hugh Nymeyer, PhD Hematology/Oncology Division, University of Texas Southwestern Medical Center, Dallas, TX, USA

Jason E. Pope, MD, DABPM, FIPP Summit Pain Alliance, Santa Rosa, CA, USA

Gabor B. Racz, MD, ABA, FIPP, ABIPP Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX, USA

P. Prithvi Raj, MD, FIPP, FRCA Texas Tech University Health Science Center 5–10, Lubbock, TX, USA

Ken Reed, MD Reed Migraine Center, Dallas, TX, USA

Richard Rosenthal, MD, DABPM, FIPP Utah Center for Pain Medicine and Research, Provo, UT, USA

Michelle Smith, MD Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Andrea Trescot, MD, ABIPP, FIPP Pain and Headache Center, St. Augustine, FL, USA

Robert E. Wright, MD, DABPM, FIPP Denver Pain Management, Greenwood Village, CO, USA

Nimbus Concepts, LLC, Denver, CO, USA

Introduction to Lysis of Adhesions

1

Gabor B. Racz and James E. Heavner

The results of epidural lysis of adhesions from the first series of patients presented in the first edition of *Techniques of Neurolysis* in 1989 are now reinforced with data from numerous studies. The first published case in the first edition was related to an on-the-job injury which the procedure was denied by workers' compensation. This was the first documented observation of scar formation in the epidural space without a history of surgery. The post-lysis discogram showed a leaky disk. The workers' compensation panel ruled that the lysis procedure and surgery was a "flight into health" and declared experimental. This case was eventually presented in court, and the judge ruled that the lysis procedure and surgery were compensable. The procedure is becoming accepted worldwide and used with the goal of reducing both unnecessary surgeries and additional procedures in patients who have a variety of indications, such as multilevel disk protrusions. The more people in academic centers who look at these procedures and do studies, the more we learn. Multiple studies from a number of specialties have been recognized in the way of CPT codes in the USA by the AMA CPT code committee: 62263 and 62264. Significant studies have come from our multispecialty colleagues in interventional pain, neurosurgery, orthopedic surgery, and others. The late Dr. Sam Hassenbusch, representing neurosurgery on the committee, was most influential after seeing results in his patients that he not only referred to us but also observed the outcomes in patients he treated himself with the procedure. The work and studies of Lax Manchikanti led to the 62264 code for the one-day percutaneous neuroplasty procedure. There are animal, clinical, and laboratory studies that are not completely transferable to clinical practice, and there were some new experiences and information that very much improve our understanding of the basic principles that have evolved during the last 30 years. For example, a laboratory study concluding that the Racz® catheters are not stiff enough to carry out mechanical lysis of adhesions is misleading. The attempt was to interpret the catheter lysis as it is a mechanical procedure by the catheter alone [1]. The principle used from the beginning has been to place the catheter in the appropriate location and tissue plane for the injected fluid to find the path of least resistance. The injected fluid will open up the immediate surrounding compartment and find the path of least resistance to spread and open up the adjoining compartment. This compartmental filling principle has been nicely described by Angelo Rocco from Harvard. So long as lysis is carried out laterally and safe runoff is verified, fluid dissection can be safely performed. Flexion and rotation, especially in the cervical area, is an important addition to the technique to allow neuroforaminal runoff by increasing the size of the neuroforamina. An important principle of interventional pain management is that there is a learning curve for the procedures and gaining knowledge and improving the techniques is vital. Birkenmeyer et al. studied the effect of injection components during the lysis procedure and found that hyaluronidase has no impact on the human fibrocyte culture, but steroid and hypertonic saline inhibit fibrocyte regeneration and growth [2]. This study has provided significant information and an explanation for the long-lasting effect of the lysis procedure, where re-scarring does not occur for multiple years in the location where the hypertonic saline has been applied in the epidural space. These observations have been possible in patients where long-term follow-up contact has been possible. One of these patients has been written up in multiple textbooks [3–5].

G.B. Racz, MD (✉) • J.E. Heavner, MD
Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX, USA
e-mail: gbracz@yahoo.com

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_1

In the epidural space, hypertonic saline only inhibits scar formation in the area where it is applied. Hyperosmolar solutions, including hypertonic saline, have been used in prolotherapy techniques to scar and stiffen ligaments around painful joints. This does not occur in the epidural space. Our long-term observations of patients show scar inhibition only in the area of the application of epidural hypertonic saline, as is represented by the cases described hereafter.

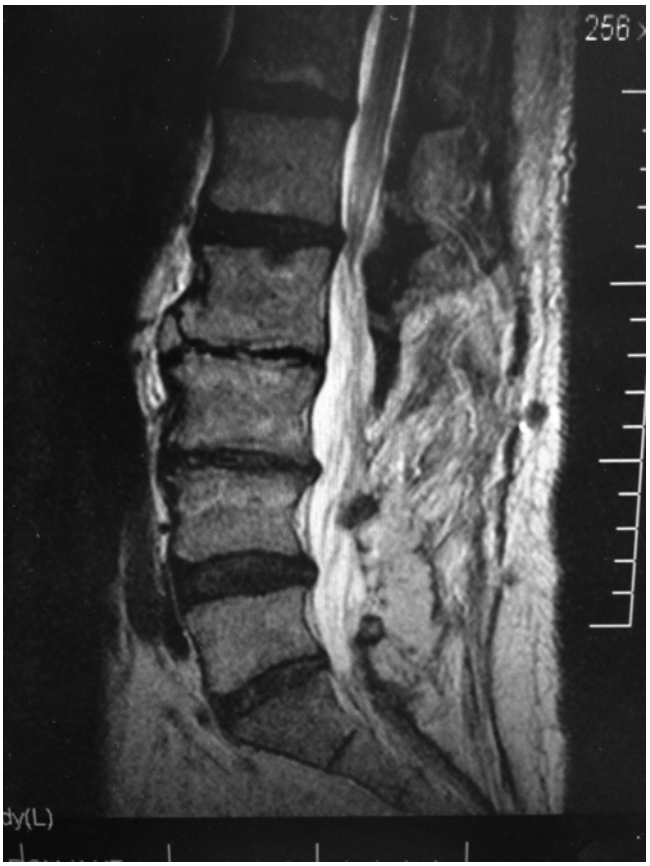
The use of fluid for dissecting the correct tissue plane has been used by neurosurgeons in various neurosurgical procedures [6].

One of the unrecognized and extremely dense scarring areas has been identified by a group of spine surgeons to be a unique cavity within the lower area of the lumbar epidural space bilaterally between the L5 and S1 dorsal root ganglia. This space is 0.921 mL and communicates circumferentially in the ventral epidural space. The authors noted that a small volume injection can travel a long way, but also that this space is big enough to accept the average loose disc fragment. It is located off midline above the L5–S1 disc and below the L4–L5 disc bilaterally. The authors failed to recognize the inflammation and scar formation related to the nucleus pulposus and disc material. The recognition of dense scar formation was acknowledged over the years but not understood by our group. Attempts to force stiffer catheters or scopes usually were not successful, and in rare instances, forcing rigid devices to open up the L5–S1 nerve roots could lead to additional pain or failure to reverse weakness and dysesthesia of the lateral calf and the lateral foot. Transforaminal approaches with a second catheter have helped, but incompletely. S1 and S2 radiculopathy may remain as residual pain syndromes. We have seen numerous surgical failures from microdiscectomies, disc replacements, and fusions where the same pain remained or returned very rapidly following procedures. Contrary to the laboratory testing model of the catheter not being stiff enough [1], the solution of this dilemma came from a clinical finding by Matsumoto [7]. He discovered that by using a posterior transsacral S1 approach with an 18 g RX-2® Coudé® Needle and placing a 21 g VERSA-KATH®, it is possible for the uniquely constructed smaller catheter to slip into the triangular-shaped, densely scarred area that was identified by Teske et al. [8]. The described evolution of the lysis technique suggests following the recommendation of Gerdesmeyer that lysis should be the first intervention after conservative measures have been used [9]. A very common associated finding is the combination of back, hip, and leg pain. It is our belief that the scarring between the posterior longitudinal ligament and the dura is a leading cause of back pain. The description in Chap. 7 of the "dural tug" accurately pinpoints the location of presence of the scarring impact from the scarring triangle. An additional finding often seen is the presence of motor block evidenced by foot drop. Degenerative changes commonly include spondylosis, spinal stenosis, and pain. To show the technique, three video presentations can be accessed below in PainCast website.

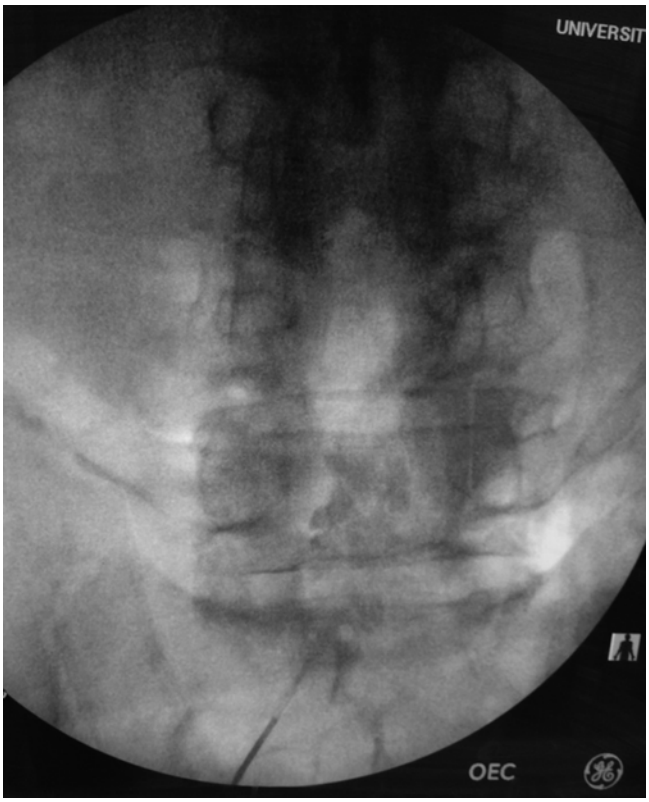
Case 1.1 Ten-and-a-half years ago, a 75-year-old patient had a decompressive laminectomy at L3–L4–L5 due to degenerative changes and spinal stenosis in his lumbar spine. The spinal stenosis resulted in 5 years of very good outcome. Spinal stenosis recurred five-and-a-half years later, one segment above the surgical procedure at L2–L3 which leads to back and leg pain. Caudal lysis of adhesions to the L5 nerve root in combination with an L2–L3 transforaminal catheter lysis and injection of contrast, hyaluronidase, local anesthetic, and steroid followed by hypertonic saline, repeated three times, resulted in five-and-a-half years of very good recovery. The pain returned, and the repeat MRI documented a wide opened L2–L3 area and stenosis of L1–L2, one segment above the previous site of pathology. 7 months ago, a transsacral S1 placement of a VERSA-KATH® to the scarring triangle and an L1–L2 midcanal transforaminal Brevi-Kath® lysis of adhesions were followed up with excellent pain relief and functional recovery in this very youthful 75-year-old patient.

A repeat MRI study revealed spinal stenosis one segment higher at L1–L2. It was noteworthy that the formal lysis areas showed less scar formation at L5 and L2–L3. Likely, it was because of the three times reinjection of hypertonic saline. The decision made was to perform a transsacral S1 lysis with a 21 g VERSA-KATH® into the "scarring triangle" and a second transforaminal L1–L2 Brevi-Kath® lysis with three repeat injections through both catheters using hyaluronidase and 10 % hypertonic saline each time [1]. The patient had rapid reversal of spinal stenosis-related symptoms and pain from radiculopathy. However, the L3–L4 area was not widely opened; therefore, it is very likely that the patient needs a repeat L3–L4 transforaminal and caudal lysis.

Visit PainCast (www.paincast.com) *to view video*, "*Techniques of Neurolysis – 2nd Edition*" *of patient in Case* 1.1 *with patient permission*.



Case 1.1A MRI (2015) showing postsurgical scarring L3–L4–L5 previous L2–L3 spinal stenosis site where lysis of adhesions was carried out 5 ½ years ago and current L1–L2 stenosis that has been resulted in reversal of pain and functional limitations following the lysis procedure.



Case 1.1B Transsacral S1 to the scarring triangle, high-pressure injection of contrast (10 mL) hyaluronidase (Hyalgan 150 units/10 mL), and local anesthetic-steroid (10 mL .2 % ropivacaine and 40 mg triamcinolone) 30 min later (10 mL 10 % NaCl)

Birkenmaier et al. evaluated the various injected substances on human fibrocyte culture and found convincing evidence for the reason why there was no recurrence of stenosis in Case 1.1. The human fibrocyte culture showed inhibition of fibrocyte growth and regeneration, which is the most likely explanation for the long-term favorable outcomes following lysis of adhesions in the lumbosacral as well as in the cervical epidural space. The lack of effect on fibrocyte by hyaluronidase is also very reassuring, as hyaluronidase is a hugely important part of the technique. It is dramatically effective in opening up the tissue planes while high pressure is used to inject, so that the local anesthetic and steroid, which again inhibits fibrocytes, can be delivered to the most effective area. We have found in other cases, which will be presented in video form linked to PainCast (www.paincast.com), where the hypertonic saline inhibits scar formation on the side of the epidural space where it is injected and the other side scars down 4 years later. The dural tug maneuver is an accurate test to localize levels for catheter placement.

Neuromodulation is partially effective for many patients but patients often have residual back pain that may respond to the lysis procedure. The dural tug maneuver is useful for determining the level of pathology in patients with multi-level spine disease. Figures 1.1 and 1.2 show the level and location of pain with the dural tug maneuver. The painful spot was marked the day before and was reproduced with the dural tug. This localization information is useful for determining the level for a transforaminal lysis procedure to treat back pain that is not covered by neuroaugmentation (Fig. 1.3). Also, a 3 day lysis procedure is useful for salvaging neuroaugmentation systems that have been initially effective but have become less effective (Fig. 1.4).

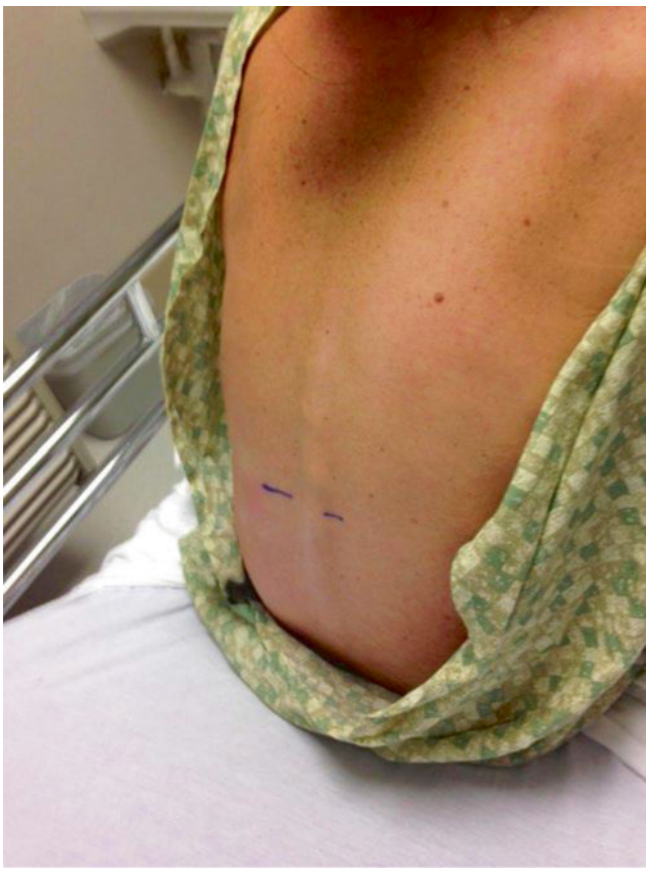


Fig. 1.1 The painful level was marked the day before the procedure

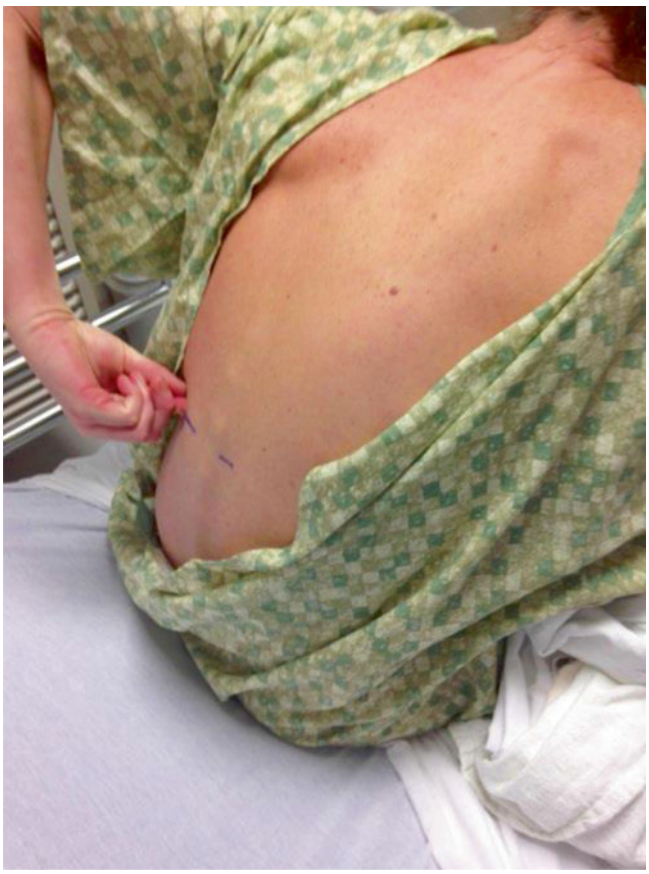


Fig. 1.2 The dural tug maneuver is performed and the patient localizes pain at the same level as was marked the previous day. This level was targeted for catheter placement and epidural adhesions were found

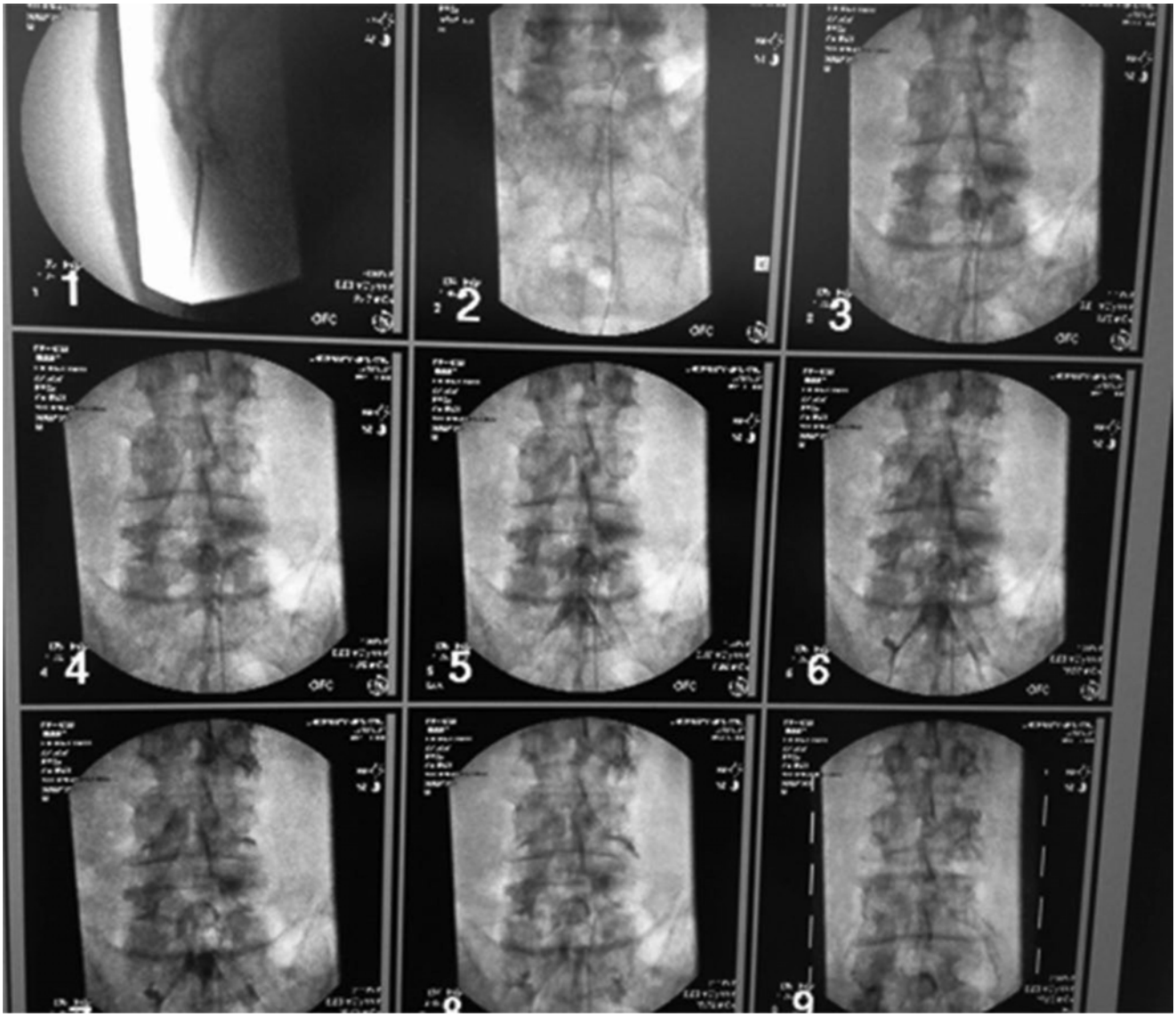


Fig. 1.3 L5 lysis procedure that relieved symptoms from right sided stenosis and symptoms did not recur on the treated side

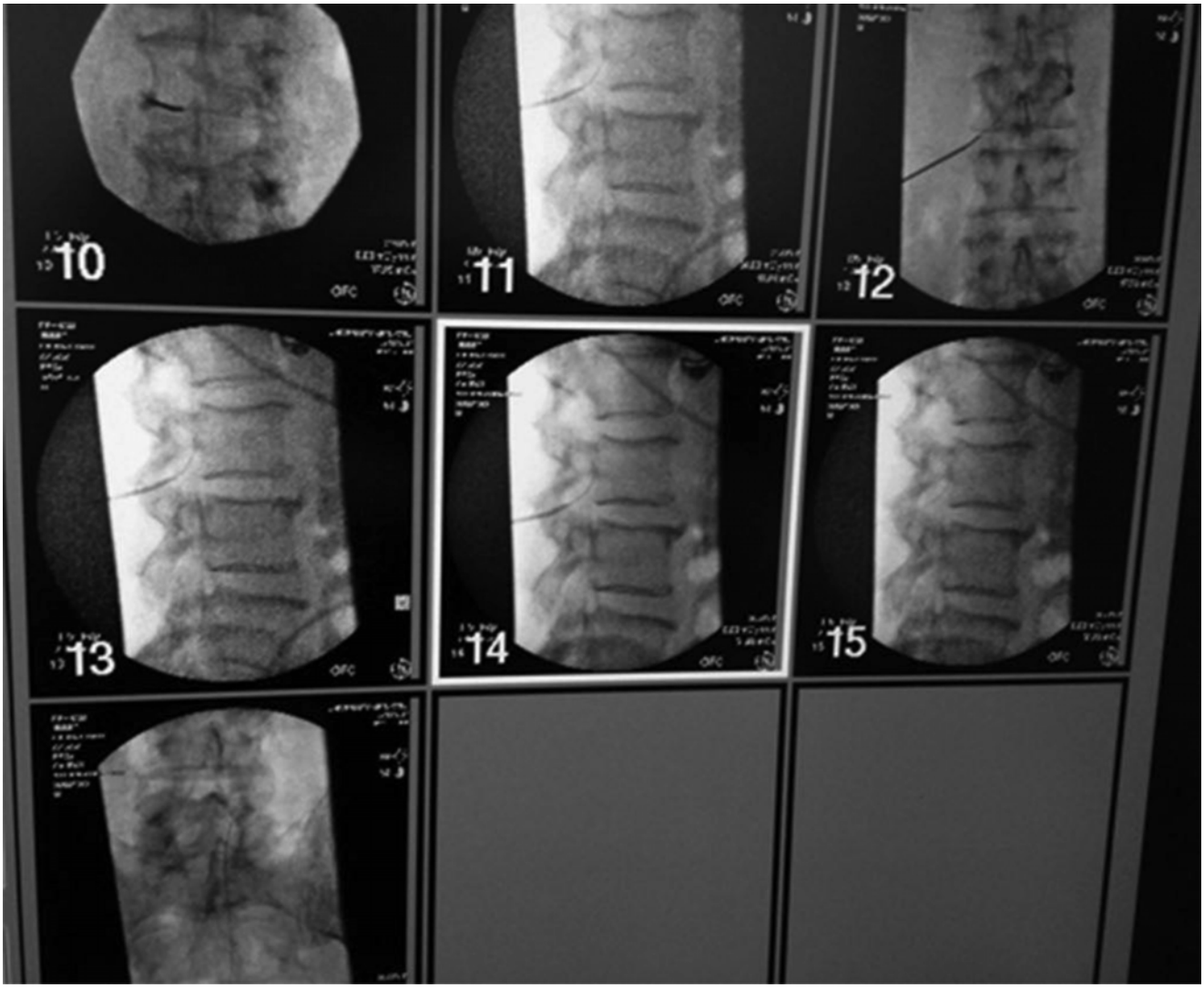
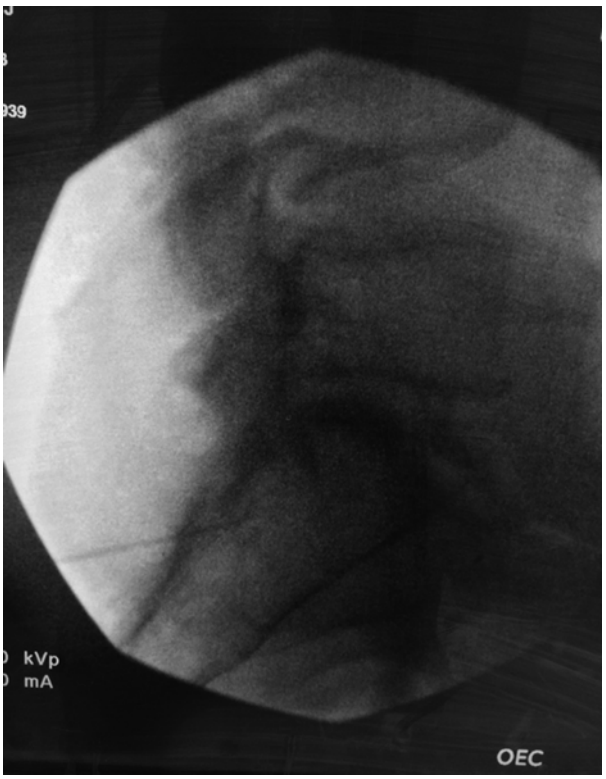
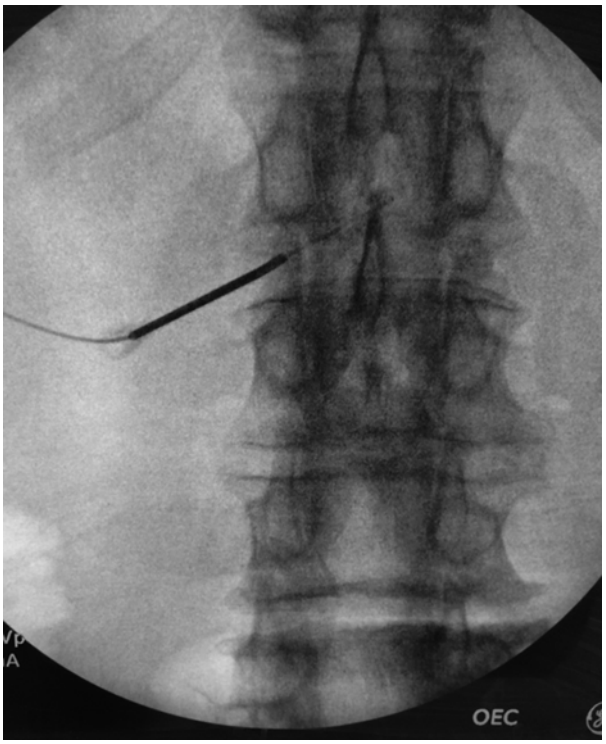


Fig. 1.4 L23 transforaminal lysis procedure 2 years ago after an L5 lysis procedure (left) resulted in continued pain relief at present

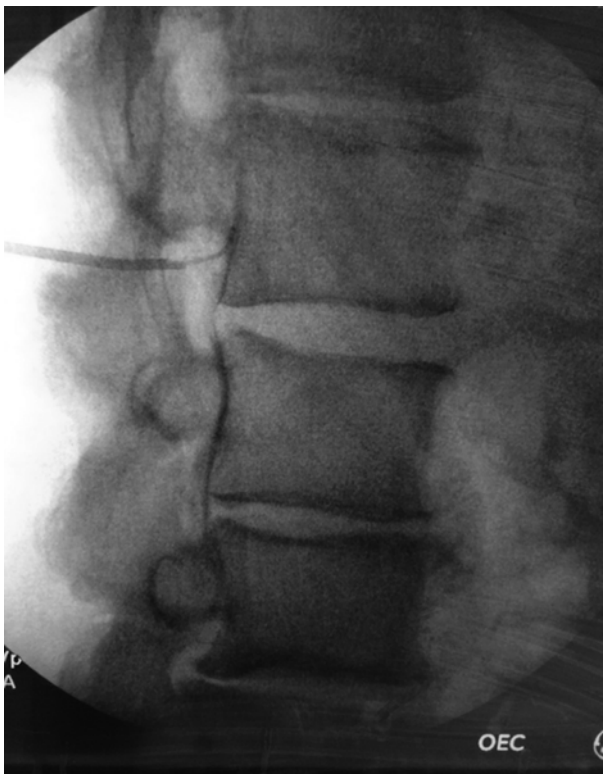
The concerning issue is that the allegation of complications and neurogenic injury that triggered the reason for this study simply is not substantiated by facts. The Stan Helm Systematic Review had not a single hematoma from lysis of adhesions for lumbar spinal stenosis. Large studies confirm, as in the original Heavner paper, that additional procedures as well as surgeries were required less often following lysis of adhesions. Multiple studies by Manchikanti, Park, Gerdesmeyer, and Veihelmann point to the remarkable safety of the technique. The lack of clinical experience by the procedure may be an explanation, as there are no clinical studies forthcoming from Birkenmaier et al.



Case 1.1C Observe opening up of the ventral epidural space and bulging disc at L4–-L5



Case 1.1E Mid-canal L1–L2 Brevi-Kath® documenting wide open formally stenotic segment. Also note the widely open L2–L3 segment the site of 5 ½ years before lysis.



Case 1.1D Lateral view of L1–L2 showing wide opening of ventral and the epidural space with similar injections as the low lumbar but 5 mL each.

Case 1.2 A failed microdiscectomy, including re-exploration, finds dense scarring tissue. Three years prior, there was the development of foot drop on the left side and severe back pain and left lower extremity pain. The procedure was the proposed step one in the treatment algorithm. A transsacral approach VERSA-KATH® to the scarring triangle and trans L4–L5 catheter placement to mid-canal, ventral epidural space, as well as injections of contrast, hyaluronidase, local anesthetic, and steroid was followed by recovering of the foot drop and rapid recovery of his back and leg pain. A 1-month follow-up tape shows the patient is able to walk on toes with remarkable recovery of his foot drop.

Visit PainCast (www.paincast.com) *to view video, "Techniques of Neurolysis – 2nd Edition" of patient in Case 1.2 with patient permission.*

Case 1.3 Sixteen-year-old female with unexplained onset of left foot drop was found to have tethered cord and spondylosis. Surgery for tethered cord was followed by recovery of the foot drop. Postsurgery, the foot drop returned that responded to physical therapy. One year postsurgery, a spinal fluid leak developed that was treated because of

the headache with epidural blood patch. Post procedure, she developed progressive foot drop. Dural tug reproduced low back pain, and a trans S1 scarring triangle targeted lysis of adhesions was followed by rapid recovery of foot drop.

Visit PainCast (www.paincast.com) *to view video*, "*Techniques of Neurolysis – 2nd Edition*"*of patient in Case* 1.3 *with patient permission*.

The First Edition Case of Lysis of Adhesions Procedure in 1986

The first published case of epidural lysis of adhesions was related to an acute injury, but the epidurogram showed scarring on the left L4–L5, S1 area. A catheter was placed in the ventral lateral epidural space without difficulty. The patient had a discogram that demonstrated an annular tear, and the patient did well after a fusion. This case led to the hypothesis that the leak or herniation of nucleus pulposus may produce inflammation and scarring. Rick McCarron studied dogs in a model of epidural adhesion formation by experimentally injecting disk material into the epidural space [10].

The concepts established from the first case have stood the test of time. The patient remained pain-free as of a 20-year follow-up telephone call. He has established his own successful business. Twenty-two years later, he developed pain in the same area and the procedure was repeated. The epidurogram was remarkably similar to the first with scarring of the left side, but not at the scarring triangle. This suggests that hypertonic saline acts to prevent fibrocyte scar formation as Birkenmaier has demonstrated [2]. If there is dense scarring in the scarring triangle, it often leads to surgery because most surgical techniques are addressing the lateral recess and the neuroforaminal issues. Here the scarring is more medial and adheres to the L5 and S1 nerve roots. Patients often complain of back pain, hip and leg pain, and foot drop together with L5–S1 distribution dysesthesia, allodynia, and pain. Freeing the space with the transsacral approach, a ventral epidural small 20-gauge VERSA-KATH® through an 18-gauge RX-2™ Coudé® needle can reverse foot drop and back pain. The painful lateral recess-related radiculopathies are addressed in a month or two, possibly together with the transforaminal catheter placement for the maximally stenosed segment (Figs. 1.5, 1.6, and 1.7).

As the patient had no previous surgery or injury, only a rotational lifting injury, the decision was to do a discogram, which showed a leaky disc at L5–S1. A fusion was also done at that level.

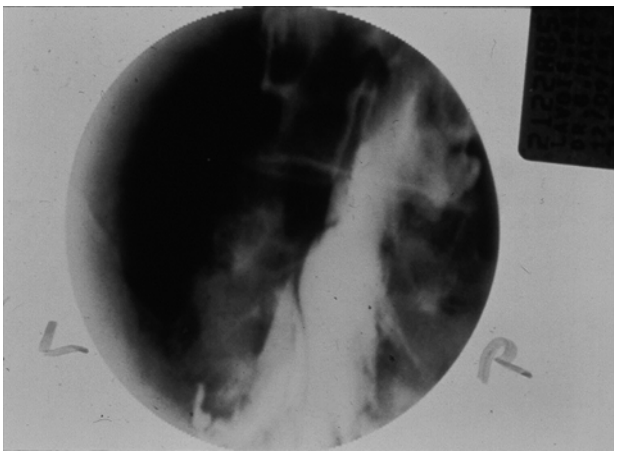


Fig. 1.5 Patient with severe radiculopathy with straight leg provocation affecting the left side. Multiple diagnoses were considered following neurologist referral from a long distance away. The epidurogram outlined the L4–L5 epidural scarring

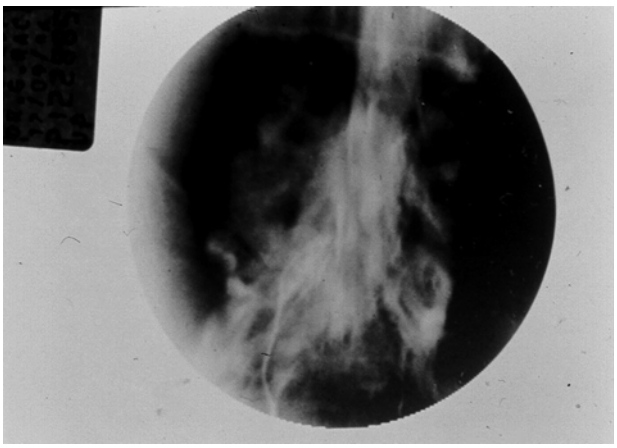


Fig. 1.6 A caudal epidural Racz® catheter was threaded toward the L4 dorsal root ganglion within the scar tissue (no mechanical attempts to do the lysis of adhesions)

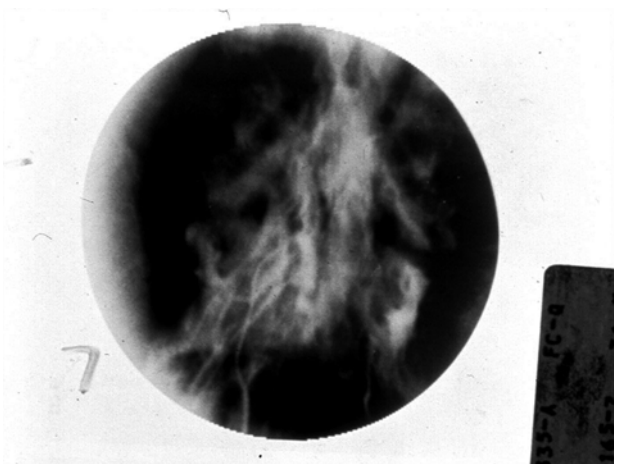


Fig. 1.7 Injection of local anesthetic and steroid shows opening of the L4–L5 nerve roots bilaterally

Patient Twenty-Two Years Later in 2008 (Figs. 1.8, 1.9, 1.10, 1.11, and 1.12)

In 2008, we did not know about the scarring triangle. Today we should be addressing this area and the related back pain with a trans S1 VERSA-KATH® technique. Surprisingly, these types of patients with multiple surgeries, back pain, foot drop, and possibly a negative straight leg provocation, but S1–S2 allodynia, showed dramatic response to this newly recognized aspect of the lysis of adhesions procedure.

In the early 1970s, Dr. Ted Hartman referred his patients to Alon Winnie for spinal steroid injections and published the

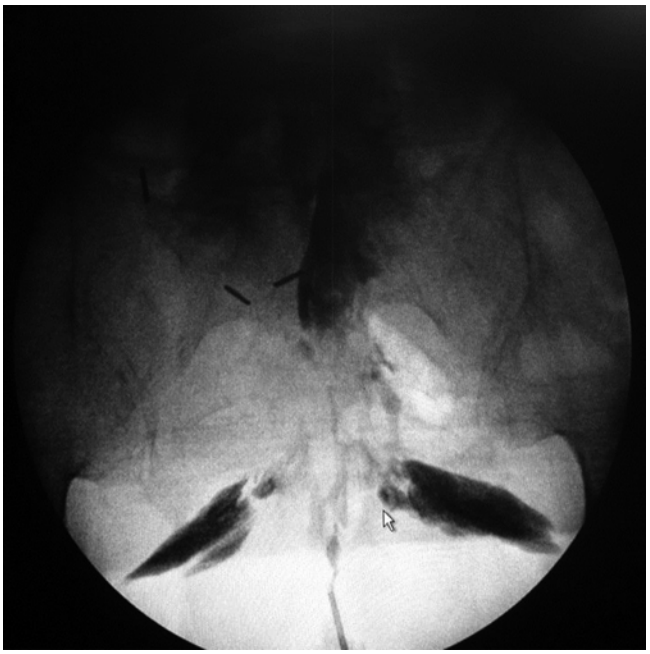


Fig. 1.8 Twenty-two years later, the pain has returned and repeat lysis, showing a filling defect on the left side of the lumbosacral epidural space above S4

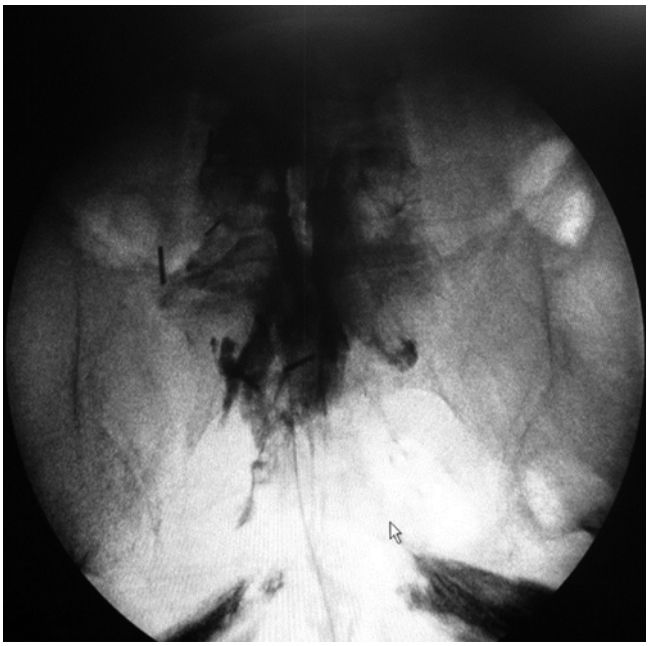


Fig. 1.10 Pain has returned, and scarring is more lateral, and the scarring triangle may be involved, encapsulating part of L5 and the upper end of S1

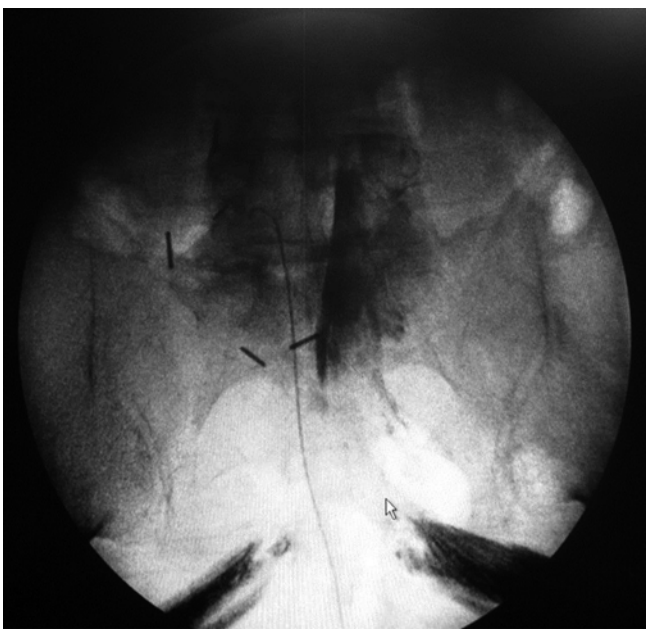


Fig. 1.9 The caudal epidural catheter appears to travel just lateral to the scarring triangle and curves under the L5 nerve root

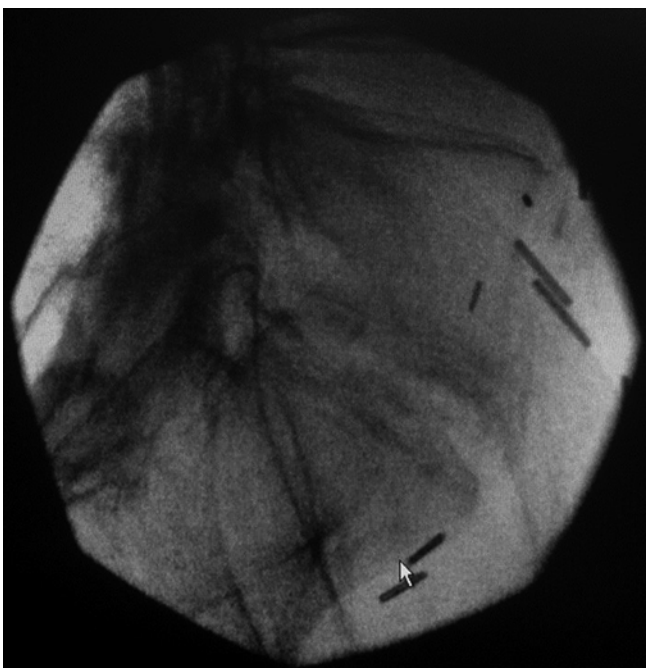


Fig. 1.11 The catheter is unable to pass in the ventral epidural space, and the tip of the catheter slides under the L5 nerve root to the lateral epidural space

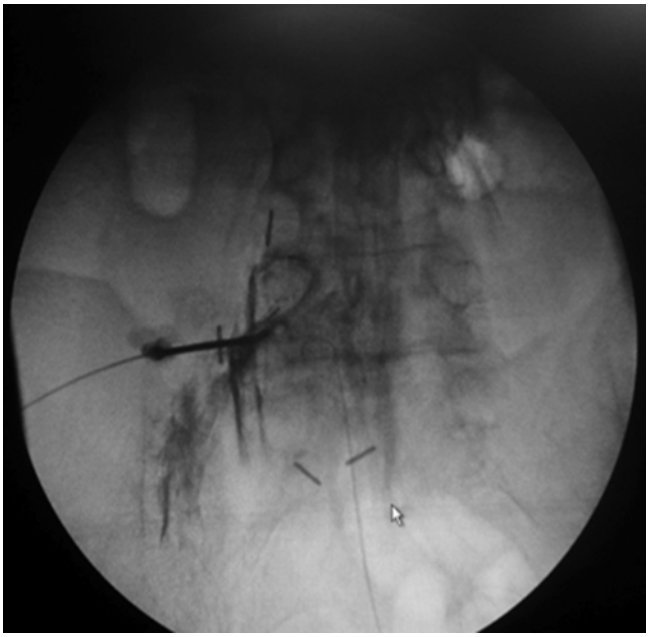


Fig. 1.12 Tip of a transforaminal epidural catheter at L5–S1 goes superior to the L5 nerve root, and a nice "boomerang" appearance is visible from the contrast spread

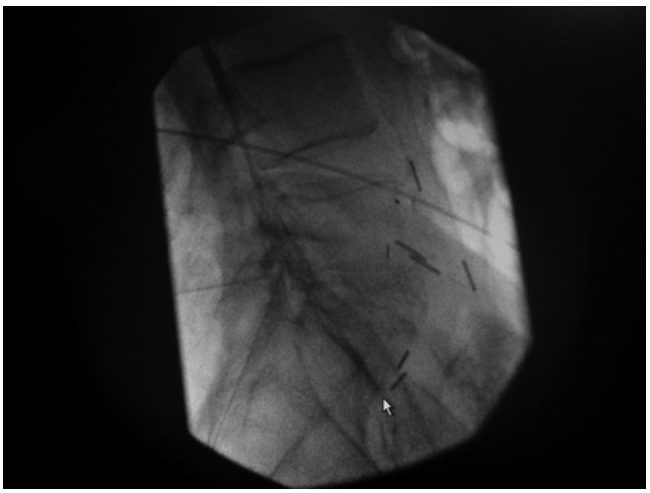


Fig. 1.13 Lateral view shows the scarring area-related filling defect that goes above the disc line as well as below

series of patients in one of the only international journals with a focus on pain, *Anesthesia and Analgesia*, in 1973. This same journal also published early neuromodulation studies. Dr. Hartman's recollections are available on PainCast.

Dr. Hartman developed back trouble as a tank driver in World War II. He developed L5 and later L4 radiculopathy. He became Professor and Chair of Orthopedics at Texas Tech University Health Science Center and later became the medical director for west Texas for Blue Cross/Blue Shield and Medicare.

Twenty five years ago, he developed neck and arm pain and went to see Dr. Winnie for a cervical epidural steroid injection. The series of radiographs from 1982, 1993 (1998 is missing), 2002, 2007, and 2015 are available to see the progression (Fig. 1.14).

In 1993, he developed a severe right L4 radiculopathy and underwent a lysis of adhesions with a series of three injections, as described in the chapter on epidural lysis. He did well until 1998 when it was repeated for recurrent symptoms. In 2002, he developed severe degenerative disk disease and L2–L3 stenosis. He underwent a repeat caudal lysis and a transforaminal L2–L3 lysis. He did well until 2015. He has a pulmonary embolus and had a vena cava filter placed between 2002 and 2015. He had recurrent cervical problems and had a cervical lysis in 2003. He also had a left shoulder replacement and a cervical lysis procedure in 2014. After the first cervical lysis, he had a suprascapular-pulsed radiofrequency treatment that was very helpful. Considering he introduced epidural steroid injections in the USA, he has had no repeat epidural steroid single shot injection since 1993.

The long-lasting hyaluronidase for spreading effect and human fibrocyte recovery inhibition by the hypertonic saline explains the long-lasting functional restoration from increased space and reduced scarring in the epidural space.

At the 33-year follow-up, lateral view x-rays of the lumbosacral spine show disappearance of the disk spaces where there is mainly bone on bone, but the patient is not complaining of back pain, and the patient remains functional at age 90. Age should not be a deterrent to consider the lysis procedure in light of the significant pain relief and functional restoration in the 90-year-old Dr. Hartman.

Pain relief comes from the hypertonic saline's effects on C fibers of the sinuvertebral system and increased blood supply because of the reversal of spinal stenosis and the prevention of re-scarring in the spinal canal.

Visit PainCast (www.paincast.com) *to view additional procedure videos*.

This patient represents the site-specific impact of hypertonic saline ion the epidural space. The patient at age 70 presented with right-sided back and leg pain and a positive dural tug sign. The pain relief lasted for 4 years following a caudal and transforaminal lysis of adhesions with a series of three injections of hypertonic saline and one time injection of hyaluronidase. A year and a half ago, his pain returned on the left side, and an MRI showed spinal stenosis on the affected left side. Repeat treatment was performed with caudal and transforaminal injection of Omnipaque, hyaluronidase for facilitating spreading local anesthetic, and hypertonic saline on the affected left side. He remains pain-free and working. The epidurogram showed drawing in on the left side and the filling defect as visualized by a lack of spread to the contrast injection. Hyaluronidase has helped the spreading and opening up of the epidural scarring by the compartmental filling principle followed by injection of local anesthetic and steroid 30 min later.

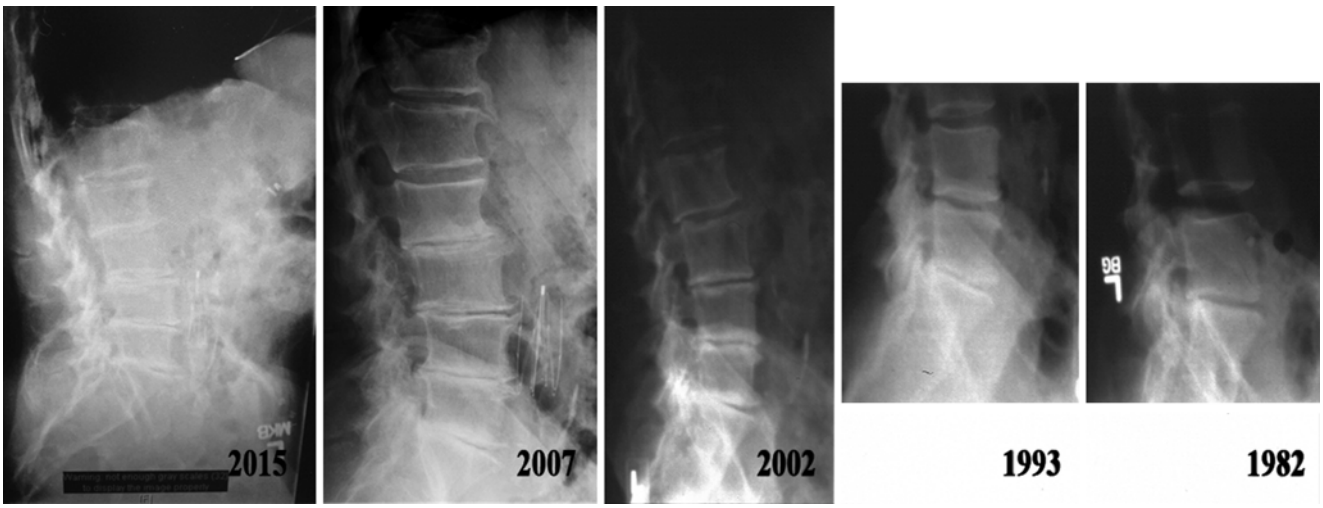


Fig. 1.14 Dr. Hartman, 2015 x-ray at age 90. No back and leg pain present

Injection of hypertonic saline and repeated two more times 6–8 h apart.

The lysis of epidural adhesion technique as originally described fostered the introduction and development of the use of a flexible fiberscope to examine the epidural cavity (epiduroscopy) [12]. Epiduroscopy, a minimally invasive technique, confirmed direct visual inspection of various degrees of fibrosis in the spinal canal of patients with low back pain and/or pain radiating to the legs [13, 14]. It also documented the presence of engorged blood vessels in these patients, especially in patients with spinal stenosis. Value added by using epiduroscopy in addition to diagnostic imaging such as MRI and CT scans was demonstrated [15]. Evidence was found that confirms the role of pathology within the epidural cavity in patients with low back pain and/or pain radiating to the legs [16, 17, 18].

The first report included over 100 cases, and now over three million lysis procedures have been performed worldwide. One hospital in South Korea has performed over 10,000 cases in 4 years. The online procedure information has been downloaded 14,000 times in 83 countries [11].

References

1. Birkenmaier C, Baumert S, Schroeder C, Jansson V, Wegener B. A biomechanical evaluation of the epidural neurolysis procedure. Pain Physician. 2012;15(1):E89–97.
2. Birkenmaier C, Redeker J, Sievers B, Melcher C, Jansson V, Mayer-Wagner S. An evaluation of medications commonly used for epidural neurolysis procedures in a human fibroblast cell culture model. Reg Anesth Pain Med. 2011;36:140–4.
3. Lauretti GR, Corrêa SWR, Anita L, Mattos AL. Efficacy of the greater occipital nerve block for cervicogenic headache: comparing classical and subcompartmental techniques. Pain Pract. 2015;15(7):654–61.
4. Racz GB, Day MR, Heavner JE, Smith JP. The Racz procedure: lysis of epidural adhesions (percutaneous neuroplasty), chapter 50. In: Deer T, Leong M, editors. Comprehensive treatment of chronic pain by medical, interventional, and integrative approaches. Springer New York; 2013. p. 521–534.
5. Racz GB, Day MR, Heavner JE, Scott J. Lysis of Epidural Adhesions: the Racz technique, chapter 169. In: Waldman S, editors. Pain management. 2nd ed. Elsevier Philadelphia Saunders; 2011. p. 1258–72.
6. Csokay A, Nagy L, Novoth B. Avoidance of vascular compression in decompressive surgery for brain edema caused by trauma and tumor ablation. Neurosurg Rev. 2001;24(4):209–13.
7. Matsumoto T, Kitagawa H. Treatment of lower back and leg pain using the Racz Catheter-Matsumoto way (via S1 intervertebral foramen). Poster. WIP Maastricht; 2014.
8. Teske W, Zirke S, Nottenkamper J, Lichtinger T, Theodoridis T, Kramer J, Schmidt K. Anatomical and surgical study of volume determination of the anterolateral epidural space nerve root L5/S1 under the aspect of epidural perineural injection in minimal invasive treatment of lumbar nerve root compression. Eur Spine J. 2011;20(4):537–41.
9. Gerdesmeyer L. Percutaneous epidural lysis of adhesions in chronic lumbar radicular pain: a randomized, double-blind, placebo-controlled trial. Pain Physician. 2016;16:185–96.
10. McCarron RF, Wimpee MW, Hudkins PG, Laros GS. The inflammatory effect of nucleus pulposus. A possible element in the pathogenesis of low back pain. Spine. 1987;12:760–4.
11. Gabor B. Racz, James E. Heavner, Jeffrey P. Smith, Carl E. Noe, Adnan Al-Kaisy, Tomikichi Matsumoto, Sang Chul, Laszlo Nagy. Epidural lysis of adhesions and percutaneous neuroplasty, pain and treatment. Gabor Racz, Editors. InTech Rijeka Croatia; 2014. ISBN 978-953-51-1629-5. doi:10.5772/58753. Available from: http://www.intechopen.com/books/pain-and-treatment/epidural-lysis-of-adhesions-and-percutaneous-neuroplasty.
12. Heavner JE, Bosscher H, Wachtel M. Lumbosacral epiduroscopy. In: Benzon H et al., editors. Raj's practical management of pain. 4th ed. Philadelphia: Mosby Elsevier; 2008. p. 1127–39.

13. Heavner JE, Bosscher HA, Wachtel M. Cell types obtained from the epidural space of patients with Low back pain/radiculopathy. Pain Pract. 2009;9:167–72.
14. Bosscher HA, Heavner JE. Incidence and severity of epidural fibrosis after back surgery: an endoscopic study. Pain Pract. 2010;10: 18–24.
15. Bosscher HA, Heavner JE. Diagnosis of the vertebral level from which low back or leg pain originates. A comparison of clinical evaluation, MRI and epiduroscopy. Pain Pract. 2012;12: 506–12.
16. Bosscher HA, Heavner JE. Lumbosacral epiduroscopy finding predict treatment outcomes. Pain Pract. 2014;14:506–14. doi:10.1111/papr.12112PMID:24118805. Article first published online: 2 OCT 2013.
17. Kallewaard JW, Vanelderen P, Richardson J, Van Zundert J, Heavner JE, Groen GJ. Epiduroscopy for patients with lumbosacral radicular pain. Pain Pract. 2014;14:365–77.
18. Heavner JE, Bossher, H. Lumbosacral epiduroscopy. In: Jankovic D, Peng P, editors. Regional nerve blocks in anesthesia and pain therapy. Springer New York; 2015. p. 641–54.

Part I

Neurolytic Techniques

Cryoneurolysis

2

Andrea Trescot and André Mansano

Introduction

Cryoneurolysis, also known as *cryoanalgesia* or *cryoneuroablation*, is a technique that uses extreme cold to provide long-term relief for patients suffering from chronic pain due to sensory nerve involvement. The word is derived from the Ancient Greek "κρύος" ("krúos," "icy cold," "chill," "frost"), "νεῦρον" (neuron, "nerve," "cordlike structure"), and "lysis" ("loosening," "dissolving," "dissolution").

History

The use of cold in pain medicine dates from 1000 years ago when Hippocrates de Cós (460–377 BC) reported that snow had been used over wound with analgesic properties [1]. Avicenna of Persia (980–1037 AD) and Severino of Naples (1580–1656) described the use of ice as an anesthetic technique for surgical procedures [2]. In the nineteenth century, Baron Dominique Jean Larré, Napoleon's military surgeon, noted that soldiers underwent painless limb amputations during the severe battlefield winter [3]. Trendelenburg was the first to report that cooling nerves produces prolonged and reversible loss of its function [4].

The clinical use of cryoneurolysis started with James Arnott (1797–1883), an English physician, who reported the benefits of cold in treating several diseases, such headaches, neuropathic pain, and some gynecological cancers [5]. He also developed a cryotherapy device which was presented in 1851 at the Great Exhibition in London as a mode of applying cold as a therapeutic agent [6].

In contemporary medicine, cryosurgery gained popularity in 1961 with the introduction of automated cryosurgical devices by Cooper and Lee that created cryolesions with liquid nitrogen [7]. After this important boost, there was a rapid growth of use of cryosurgeries such as cryohypophysectomy [8], transurethral freezing of the prostate [9], skin cancer ablation [10], treatment of Meniere's disease [11], hemorrhoidectomy [12], tonsillectomy [13], and even retinal detachment surgeries [14].

It was Lloyd and his colleagues that coined the term *cryoanalgesia* for its use in pain management [15].

Technical Aspects and Equipment

The cryoprobe consists of a hollow tube with a smaller inner tube. A high-pressurized gas (usually CO_2 or N_2O), at 600–800 psi, goes through the smaller tube and is released into the larger, low pressure, outer tube through a microscopic aperture (0.002 mm) (Fig. 2.1). The cryogenic gas (Table 2.1) expands quickly at the distal tip in an adiabatic process fashion, dropping the distal tip to a temperature as low as −70 °C (Joule-Thompson effect) [16], creating an ice ball (Fig. 2.2). The gas then travels back to the machine where it is scavenged through a ventilated outlet, making no contact with the patient tissues.

The bigger the tip probe, the bigger the ice ball generated. While the 1.4 mm probe makes a 3.5 mm ice ball, a 2.0 mm probe creates a 5.5 mm ice area. An accurate gas flow is mandatory to create an adequate and safe freezing lesion because a low gas output cannot extract enough heat, and a flow that is too high could result in an excessively cold lesion.

The cryoprobe has a built-in sensory (100 Hz) and motor (2 Hz) nerve stimulator that allows a precise positioning on the target. The freezing (and consequently the nerve damage) depends on:

A. Trescot, MD, ABIPP, FIPP (✉)
Private Practice, Pain and Headache Center,
4 Oceanside Circle, St. Augustine, FL 32080, USA
e-mail: DrTrescot@gmail.com

A. Mansano, MD, PhD, FIPP
Private Practice, Singular-Pain Control Center/Brazil,
Rua Coronel Quirino, 1343 apto 61, Campinas,
SP 13010-912, Brazil
e-mail: andremarquesmansano@gmail.com

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_2

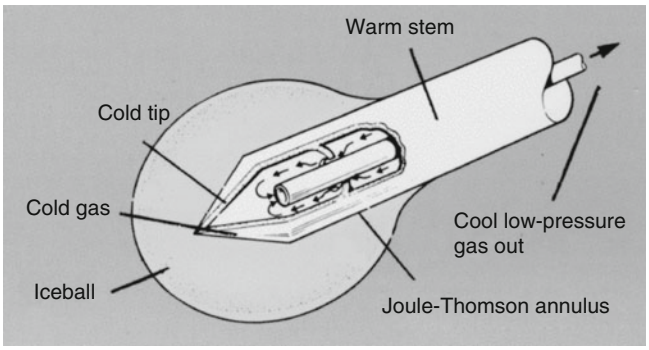


Fig. 2.1 Anatomy of the cryoprobe (Image courtesy of Epimed®, with permission)

Table 2.1 Compounds used in cryotherapy

Cryogenic gas	Boiling point (°C)
Dichlorotetrafluoromethane (*Freon 114*)	3.8[a]
Dichlorodifluororomethane (*Freon 12*)	−29.8
Chlorodifluoromethane (*Freon 22*)	−40.8
Carbon dioxide, solid	−78.5[b]
Nitrous oxide, liquid	−89.5[b]
Argon, liquid	−185.7
Nitrogen, liquid	−195.8

[a]When sprayed on skin surface, the fluorinated hydrocarbons yield colder temperatures (*Freon 114* approximately −33 °C; *Freon 12* approximately −60 °C; *Freon 22* approximately −70 °C)
[b]Sublimes at 1 atmosphere

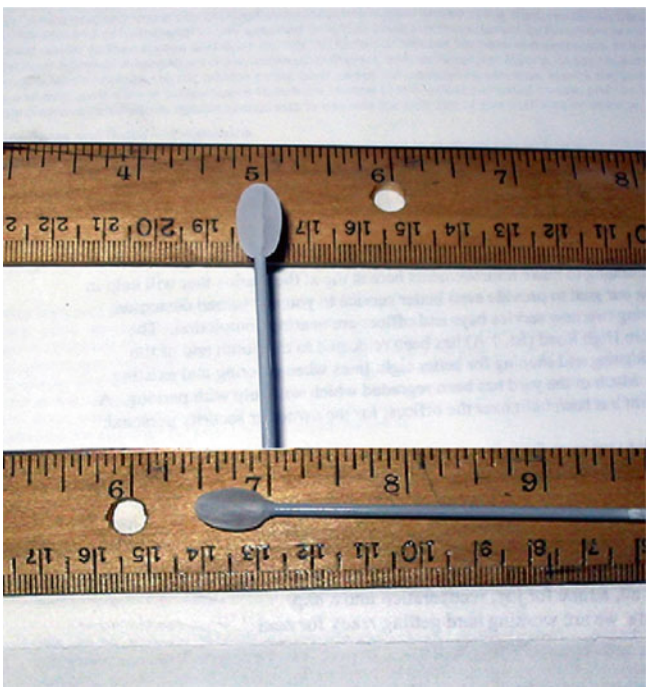


Fig. 2.2 Ice ball formation (Image courtesy of Epimed®, with permission)

- Correct diagnosis, which requires knowledge of anatomy and clinical syndromes
- Small volume (less than 1 cc) diagnostic injections
- The proximity of the probe to the nerve, which involves landmark, fluoroscopy, CT, or ultrasound guidance as well as meticulous nerve stimulation
- The size of the cryoprobe
- The size of ice ball formed
- The rate and duration of freezing

Mechanisms of Cold-Induced Cell Injury

It is well established that temperatures bellow −20 °C are lethal to human cells [17–20], although there are no *in vivo* studies that support this finding. Actually, *in vitro* research offers no data about the local blood flow changes that freezing promotes, which can be important in cell lesioning. It is also believed that mild but prolonged low temperature exposures can result in cell death [21, 22].

As the tissue temperature goes down, the extracellular fluid gets crystallized, which promotes a hyperosmotic environment leading to severe cell dehydration. As time goes by, the rise of some intracellular ions and intracellular ice generation usually induces cell death, by shrinkage and membrane rupture [23–27].

Cooling directly disrupts the blood supply tissues. There is an initial vasoconstriction and, after thawing, a microcirculatory stasis caused by vasodilatation, endothelial changes, increased vascular permeability, increased platelet aggregation, and microthrombus formation [28–30].

The faster the freezing rate, the bigger is the cell destruction [24, 31]. Regarding the target temperature, studies show that cell death occurs between −5 and −70 °C [24, 32]. As a result, there is damage to the vasa nervorum, which promotes severe endoneurial edema, increased of endoneurial fluid pressure, and a wallerian degeneration (Fig. 2.3) with preservation of the myelin sheath [33]. The Schwann cell basal lamina is preserved, which allows regeneration (Fig. 2.4). When the endoneurium remains uninjured, there is no neuroma formation and the nerve is able to regenerate at a rate of 1–1.5 mm/week [34].

Sunderland described five stages of nerve injury based on histological findings and prognosis [34]:

- First degree (neuropraxia): minimal histological changes with days to months' loss of nerve function.
- Second degree (axonotmesis): loss of axonal continuity without endoneurium injury. This occurs when the nerve is frozen to – 20 °C (the range of cryoneuroablation).
- Third, fourth, and fifth degree (neurotmesis): neural and stromal destruction with low regeneration possibility.

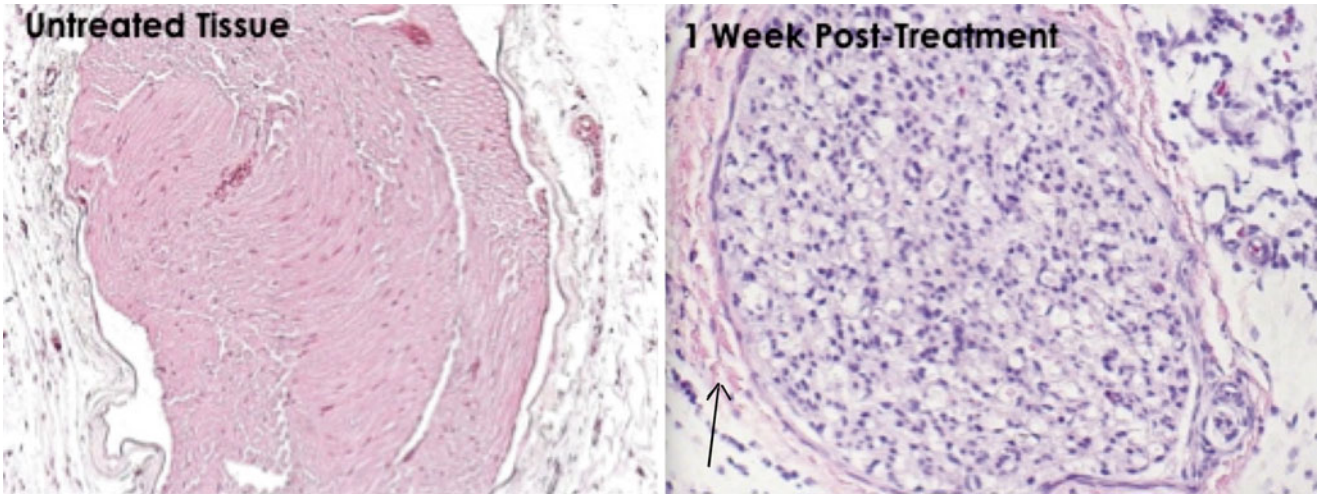


Fig. 2.3 Histology after cryoneurolysis (Image courtesy of Myoscience®, with permission)

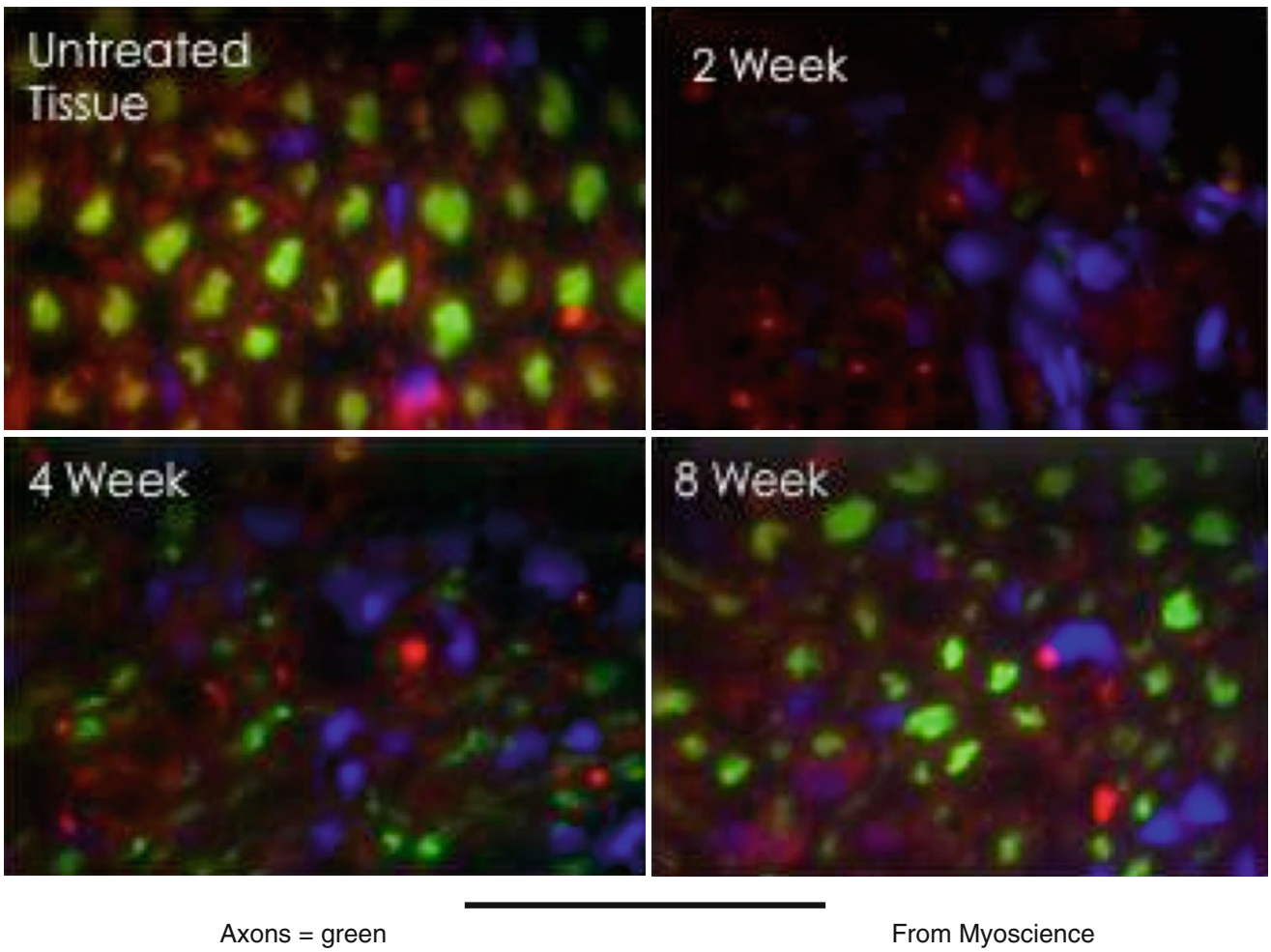


Fig. 2.4 Regeneration after cryoneurolysis (Image courtesy of Myoscience®, with permission)

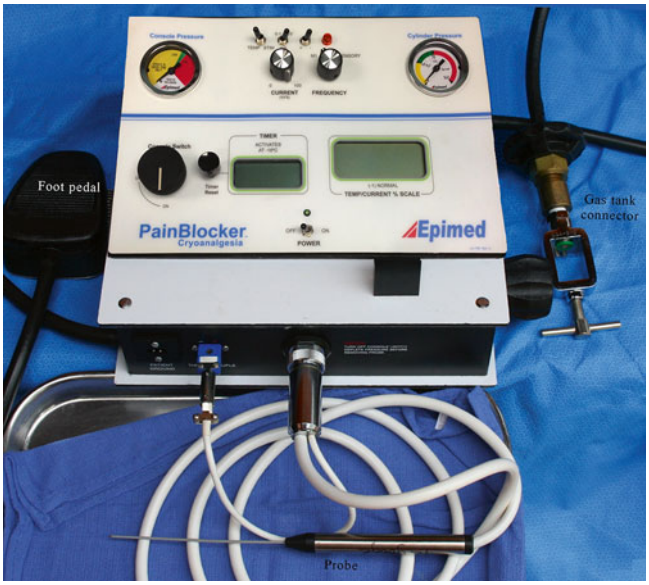


Fig. 2.5 Epimed/Wallach PainBlocker® (Image courtesy of Epimed®)

Fig. 2.6 Cryo-S cryoneuroablation machine (Image courtesy of Metrum Cryoflex®)

There are several cryoneurolysis machines now available with built-in nerve stimulators, gas flow monitors, and temperature thermistors (Figs. 2.5 and 2.6).

Techniques

For deeper structures, it is useful to direct the cryoprobe under fluoroscopy or ultrasound guidance, but the use of sensory and motor stimulation to identify nerve structures is key to success of this technique. Some steps should be followed to perform a safe and effective procedure:

1. A sterile prep and drape.
2. Skin and subcutaneous local anesthetic.
3. A small amount of saline with freshly added epinephrine 1:200.000 is infiltrated for hemostasis.
4. A small incision is made on the skin.
5. An IV introducer (size 12 or 14 gauge, depending on the size of the probe) is advanced to the target area.
6. The stylet is removed and the cryoprobe is then advanced through the catheter.
7. Withdrawing the catheter into the subcutaneous tissues exposes the tip of the probe.
8. Sensory stimulation (100 Hz), preferably below 0.5 mV, is used to identify the nerve.
9. Motor stimulation (2 Hz) is used at 2 mVolts to ensure that the probe is far enough from any motor nerves.
10. Gas flow is then turned up to 10–12 liters per minute (for the 2.0 mm probe) or 8–10 liters per minute (for the 1.4 mm probe).
11. A series of three 2-minute freezes with a 30-s thawing period between each cycle is performed.
12. The patients usually describe a burning pain in the first seconds of the first freezing cycle, which usually resolves within 30 seconds.

Some studies evaluated patients undergoing repeated cryoneurolysis sessions in a long-term fashion and concluded that this treatment demonstrated to provide safe, effective, and reversible outcomes [35–37].

Craniofacial Pain

Supraorbital and Supratrochlear Nerves

The supraorbital and supratrochlear nerves are branches of the frontal nerve all from the first division of trigeminal nerve. They are responsible for the forehead innervation, and their entrapment can cause frontal headache (often misdiagnosed as migraine or sinusitis).

The supratrochlear nerve can be found about 16 mm lateral from the medial orbital border aspect and 7 mm below the orbital upper margin, while the supraorbital nerve exits the supraorbital notch or supraorbital foramen about 29 mm lateral to the midline and 5 mm below the supraorbital upper margin (Fig. 2.7) [38].

Infraorbital Nerve

The infraorbital nerve (ION), a purely sensory nerve, is a maxillary nerve terminal branch. It is responsible for the cutaneous sensation of the zygomatic, paranasal, and paraorbital areas [39]. After emerging onto the face through the

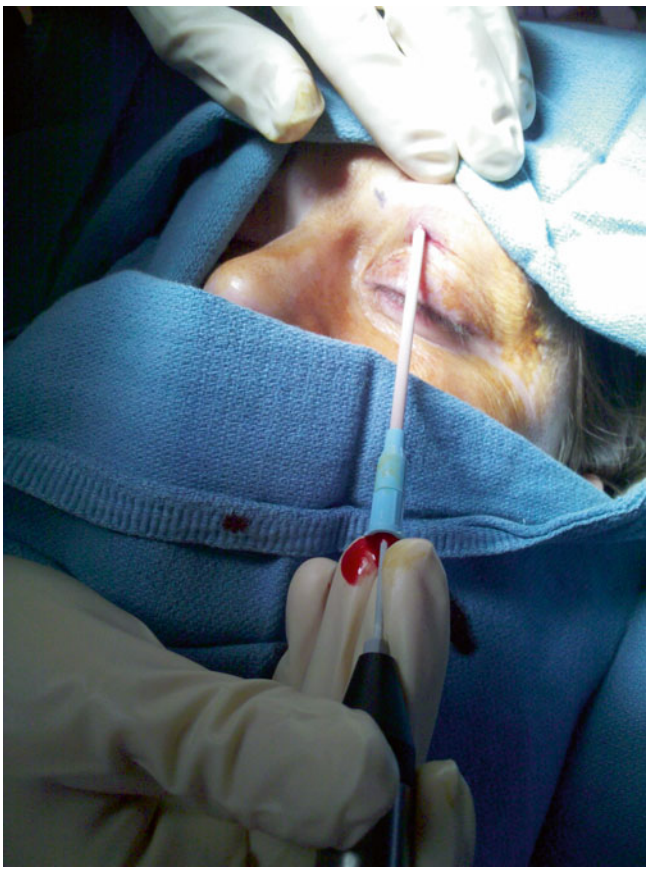


Fig. 2.7 Cryoneuroablation supraorbital nerve (Image courtesy of Andrea Trescot, MD)

infraorbital foramen, the ION gives out the inferior palpebral, nasal, and superior labial branches [40, 41]. It can be damage by trauma (especially malar fractures), surgical procedures, and sinusitis. It can be easily reached by a percutaneous or intraoral approach (Fig. 2.8) just outside the infraorbital foramen, avoiding deeper needle introduction, which can cause global penetration [42].

Maxillary Nerve

The maxillary nerve neuralgia usually causes upper jaw and cheek pain. The nerve can be entrapped proximal to the infraorbital foramen and can be one of the branches involved in the trigeminal neuralgia, occuring in as many as 80% of the cases. The maxillary can be accessed by the lateral pterygopalatine fossa approach with the probe perpendicular to lateral pterygoid plate.

Zygomaticotemporal Nerve (ZN)

The ZN is one of the branches of the maxillary nerve. The ZN is responsible for the sensory innervation of a small area of the forehead and the temporal region. It can be squeezed

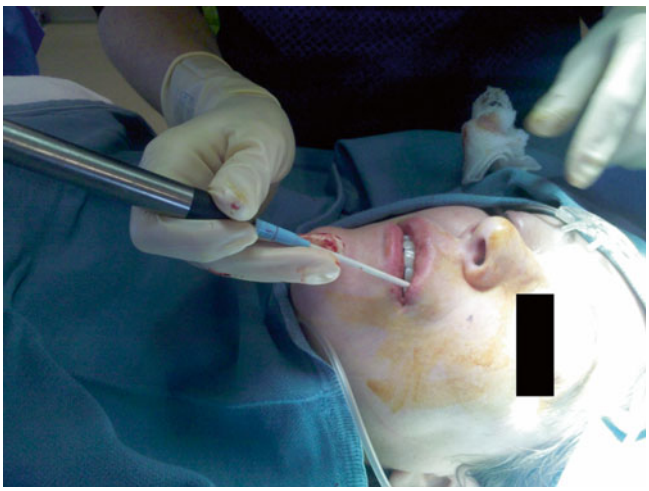


Fig. 2.8 Intraoral cryoneurolysis infraorbital nerve (Image courtesy of Andrea Trescot, MD)

at the zygomaticotemporal foramen or by the temporalis muscle (Fig. 2.9).

The ZN can be blocked 10–17.5 mm posterior to the frontozygomatic suture and 22–24.8 mm above the zygomatic arch [38].

Auriculotemporal Nerve (ATN)

The ATN is a branch of the posterior trunk of the mandibular division of the trigeminal nerve. It is responsible for the sensory innervation of the tragus and the anterior aspect of the ear as well as the temple. In some instances, the ATN can be compressed by temporal artery, which can cause headaches. The ATN can be accessed at a point 10–15 mm anterior to the upper origin of the helix of the ear (Fig. 2.10) [38].

Mandibular Nerve

The presentation of mandibular nerve (the third trigeminal branch) neuropathy is pain involving the mandibular, dental, and lateral tongue areas. It can be compressed by bone, muscle, and fibrous band [43–45]. In the cryoneurolysis technique, the probe is placed perpendicular to the lateral pterygoid plate and advanced posteriorly [46].

Inferior Alveolar Nerve

The inferior alveolar nerve, also called inferior dental nerve, is a branch of the third division of the trigeminal nerve. Its involvement produces a clinical picture of lower jaw and dental pain, which usually occurs after jaw trauma or dental surgery [47]. The nerve can be accessed intraorally at the medial aspect at the angle of mandible (Fig. 2.11).

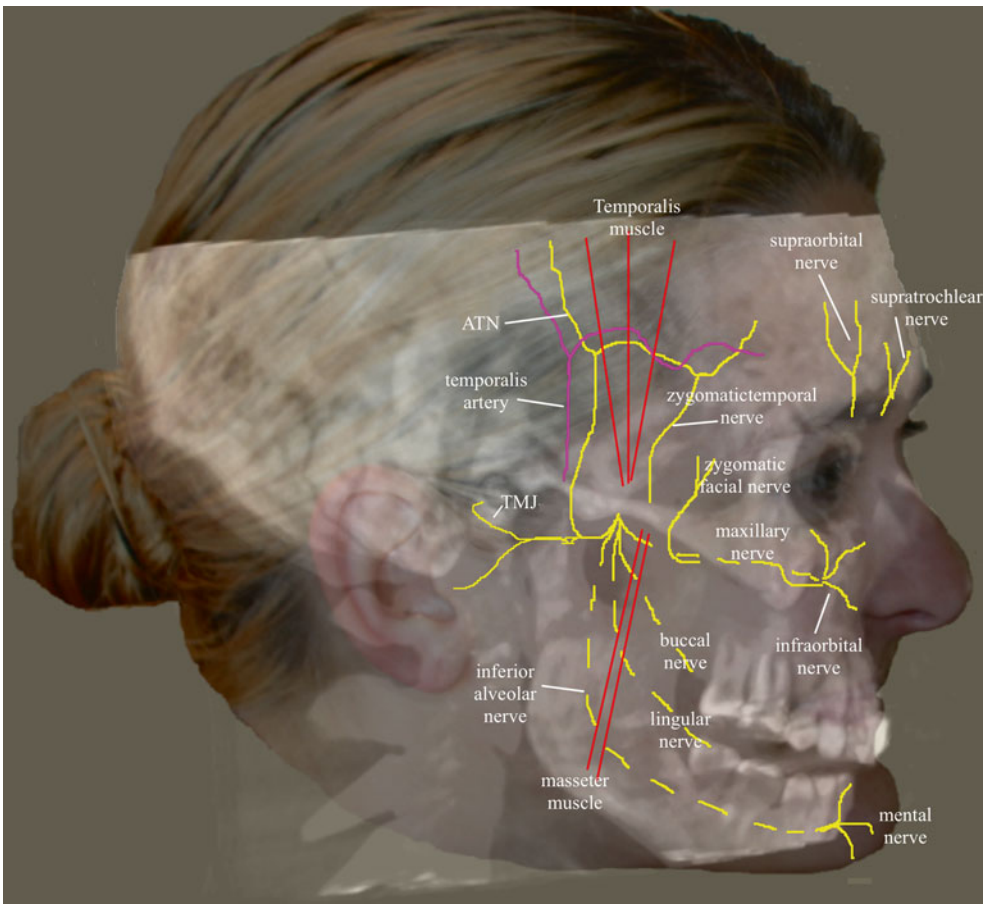


Fig. 2.9 Anatomy of the facial nerves (Image courtesy of Andrea Trescot, MD)

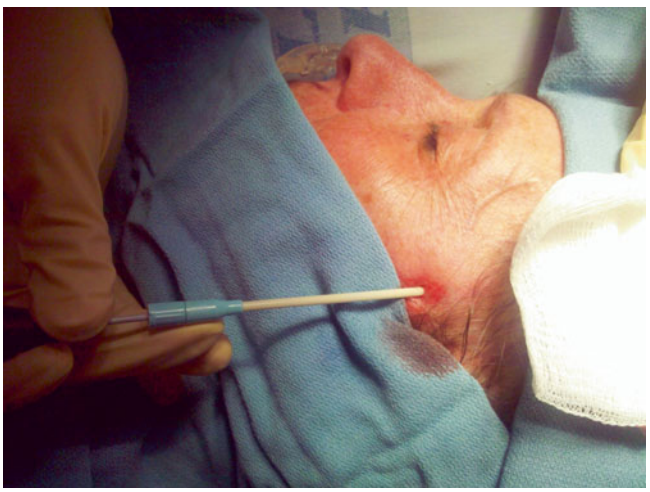


Fig. 2.10 Cryoneurolysis of the auriculotemporal nerve (Image courtesy of Andrea Trescot, MD)

Fig. 2.11 Intraoral inferior alveolar nerve injection (Image courtesy of Andrea Trescot, MD)

Mental Nerve

The mental nerve (MN) is a terminal branch of the mandibular nerve. The MN is responsible for the lower chin, lower incisors, and lower lip sensory innervation, and its damage causes pain and sensory disturbances in those areas. The MN exists at the mandible through the mental foramen, usually at the second premolar level.

The MN can be blocked by the intraoral and extraoral approach, both techniques through the mental foramen.

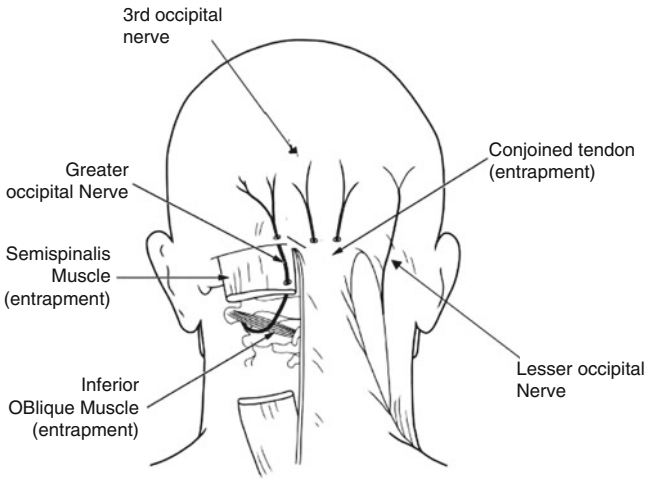


Fig. 2.12 Occipital nerve entrapment sites (Image courtesy of EpiMed®)

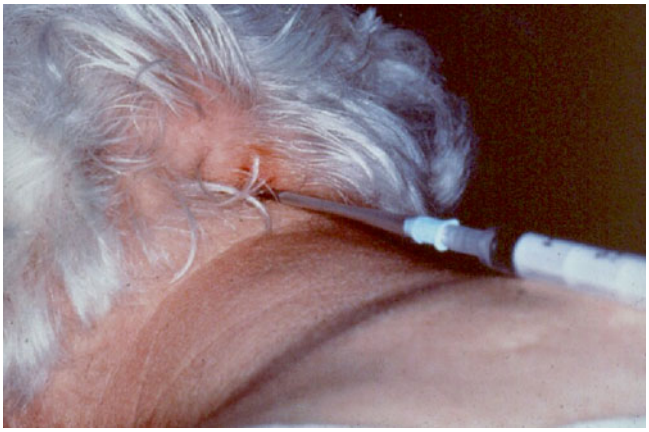


Fig. 2.13 Occipital nerve cryoneurolysis (Image courtesy of Epimed®)

Greater Occipital Nerve (GON)

The GON originates from the medial branch of the dorsal ramus of the C2 spinal nerve and also can communicate with branches from the dorsal branch of the C3 spinal nerve [48]. The GON entrapment typically produces occipital pain that can radiate to the frontal and periorbital areas. The GON pierces the trapezius muscle, the semispinalis capitis muscle, and the inferior oblique muscle (Fig. 2.12) in, respectively, 45 %, 90 %, and 7.5 % of cases [49]. These muscles are typical sites of nerve entrapment [50].

The GON blockade is performed blindly or under ultrasound guidance at a point 3–5 cm laterally and 2–3 cm below the inion (Fig. 2.13).

Lesser Occipital Nerve (LON)

The LON originates from the ventral rami of C2 and C3 nerve roots and travels superiorly along the posterior border of the sternocleidomastoid muscle. Communicating branches with the GON are very common (Fig. 2.14). Lesser occipital pathology usually manifests as a cervicogenic headache; it can be frozen at a point approximately 7 cm lateral to the external occipital protuberance or under ultrasound guidance.

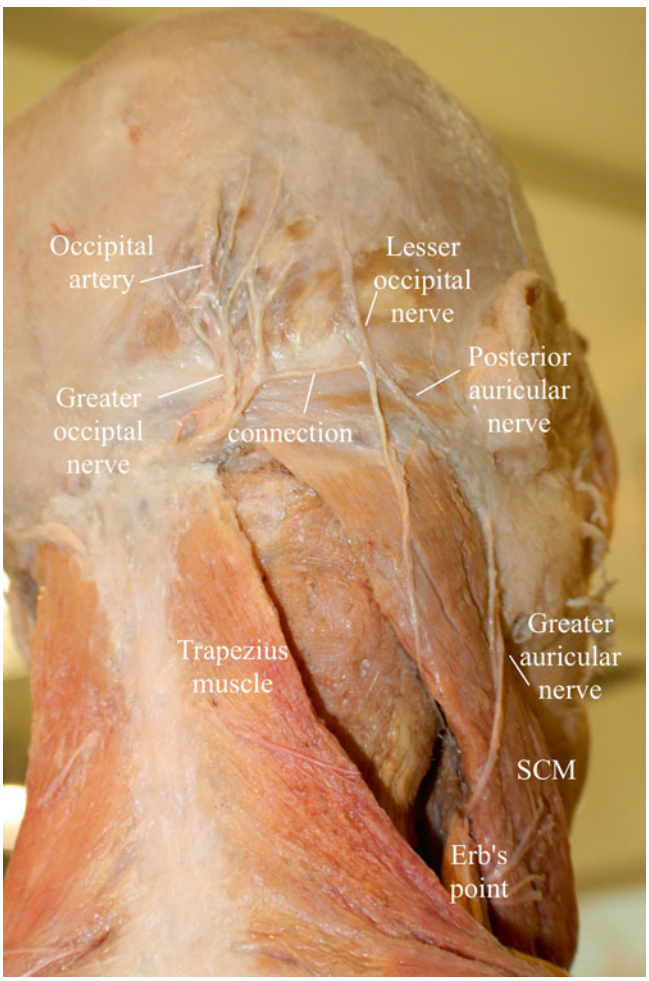


Fig. 2.14 Occipital nerve dissection showing connection between the greater and lesser occipital nerves (Image courtesy of Andrea Trescot, MD, from *Bodies, The Exhibition,* with permission)

Upper Extremity Pain

Suprascapular Nerve

The suprascapular nerve originates from the fifth and sixth cervical nerves and is responsible for the motor innervation of the supraspinatus and infraspinatus muscles as well as the sensory innervation of the shoulder [51]. It can be entrapped by the supraspinatus muscle or by an ossification of the suprascapular ligament [52] and is also a great target for shoulder pain [53] and even chronic headache control [54].

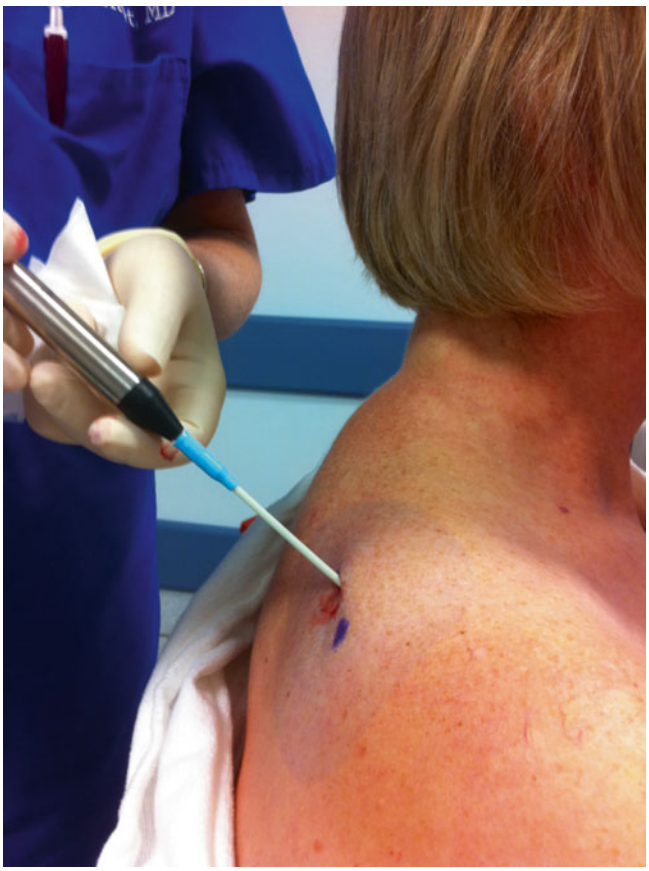


Fig. 2.15 Cryoneurolysis of the suprascapular nerve (Image courtesy of Andrea Trescot, MD)

The suprascapular nerve can be lesioned with landmark, ultrasound, or fluoroscopic guidance (Fig. 2.15).

Chest Wall Pain

Intercostal Nerve

The intercostal nerves arise from the ventral roots of thoracic spinal nerves from T1 to T11. They can be injured during thoracotomy or by rib fractures or shingles. The intercostal nerve lies posterior and cephalad to the inferior border of the rib. The cryoprobe should be placed tangentially to the inferior border of the rib, slipping beneath the inferior rib (Fig. 2.16). It is strongly recommended that ultrasound or fluoroscopy guidance be used to avoid pneumothorax [55].

Abdominal/Pelvic Pain

Iliohypogastric/Ilioinguinal Nerve

The iliohypogastric nerve arises from the L1 nerve root with a contribution from T12 in some patients. It travels from the ventral aspect of the quadratus lumborum muscle (at L1/L2 intervertebral disc level), passing behind the middle or lower pole of the kidney and piercing the aponeurosis of the transversus abdominal muscle above the iliac crest.

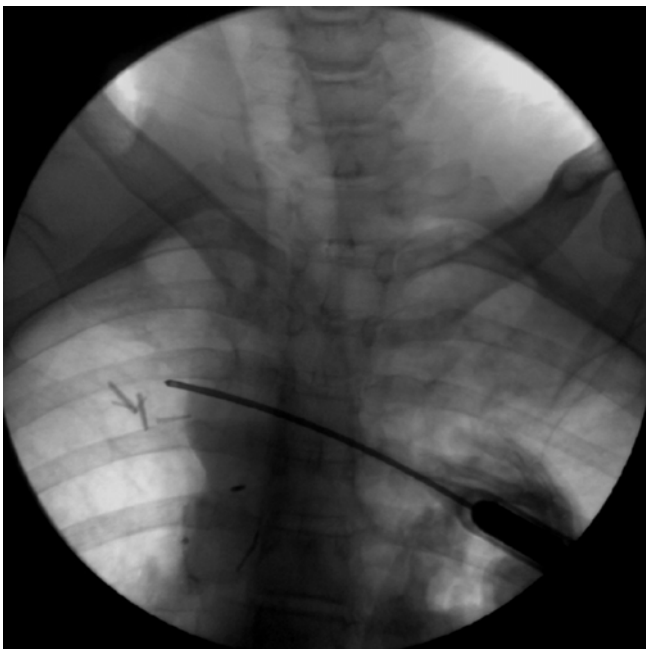


Fig. 2.16 Fluoroscopic image of cryoneurolysis of the intercostal nerve (Image courtesy of Andrea Trescot, MD)

The iliohypogastric nerve is frequently injured during inguinal repairs and appendectomies [56] or even during pregnancy (due to traction of the nerve secondary to expanding abdomen) or after Pfannenstiel incision [57]. Patients may complain about neuropathic pain in the skin over the pubis and lower flank region.

The ilioinguinal nerve is also derived from the L1 nerve root with possible contribution from T12. Ilioinguinal injury may also cause lower pelvic and groin pain.

The iliohypogastric and ilioinguinal nerves can be easily visualized under ultrasound (Fig. 2.17) and cryoneurolysis performed with landmark guidance (Fig. 2.18) or ultrasound visualization.

Genitofemoral Nerve

As with the iliohypogastric and ilioinguinal nerves, the genitofemoral nerve arises from the L1 nerve root with T12 contributions in some patients. Its femoral branch provides sensory innervation to a small area on the medial aspect of the thigh, while its genial branch passes through the inguinal canal and is responsible for the sensory innervation of round ligament of the uterus and labia majora in women or the lower part of the scrotum in men.

The genitofemoral nerve can be injured in some surgeries such as appendectomies, inguinal hernia repairs, and cesar-

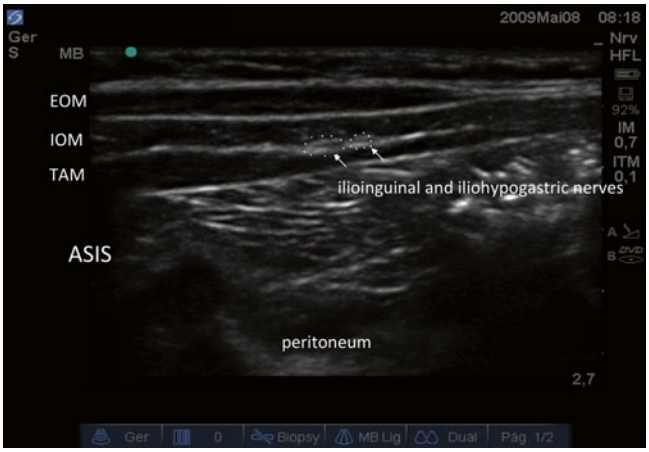


Fig. 2.17 Ultrasound images of the iliohypogastric and ilioinguinal nerves (Image courtesy of Thiago Nouer Frederico, MD, modified by Charles de Oliveira, MD)

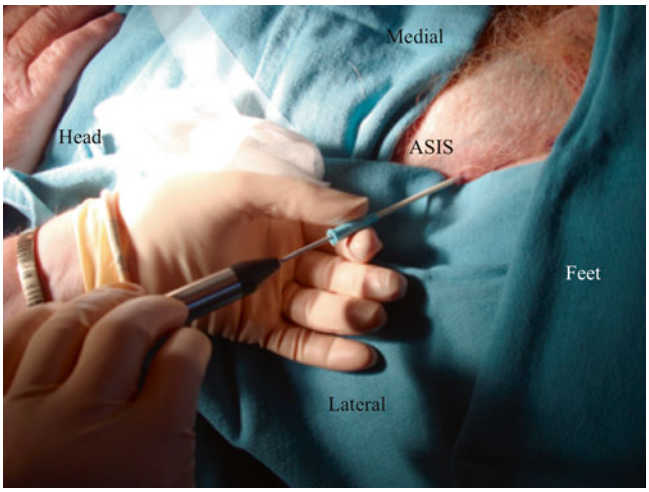


Fig. 2.18 Cryoneurolysis of the ilioinguinal nerve (Image courtesy of Andrea Trescot, MD)

ean sections. The genitofemoral nerve can be safely accessed by ultrasound guidance in the thigh (Fig. 2.19) [58], or at the pubis (Fig. 2.20) or proximally at the spine (Fig. 2.21) under fluoroscopy.

Pudendal Nerve

The pudendal nerve is derived from the S2, S3, and S4 nerve roots. It leaves the pelvis through the greater sciatic notch around the sacrospinatus ligament and runs through the pudendal canal (Alcock's canal) to innervate the anus, perineum, and scrotum/vagina.

Four primary types of pudendal entrapment syndromes had been described: type I, entrapment at the exit of the greater sciatic notch in concert with piriformis muscle spasm; type II, entrapment at the level of the ischial spine, sacrotuberous ligament, and lesser sciatic notch entrance; type III, entrapment in association with obturator internus muscle spasm at the entrance of the Alcock's canal; and type IV, distal entrapment of terminal branches [59].

The clinical picture of pudendal nerve entrapment is pain from the anus through the penis or clitoris, usually predominantly experienced while sitting. The presence of sphincter motor disorders suggests more proximal sacral nerve involvement [60].

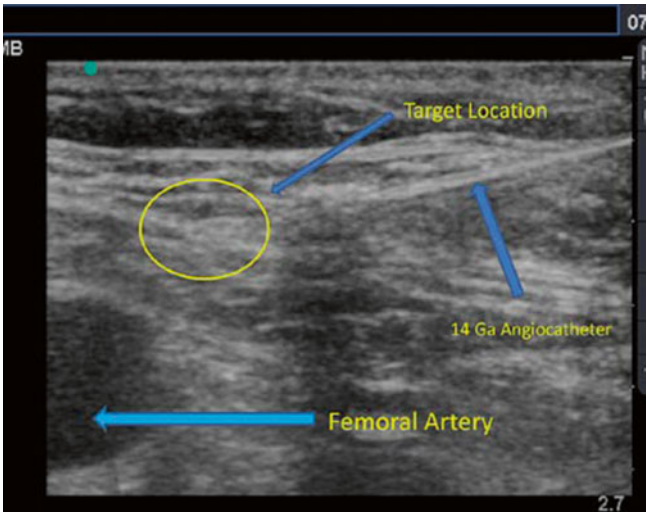


Fig. 2.19 Cryoneurolysis under ultrasound of the femoral branch of the genitofemoral nerve (Image courtesy of John Chiles, MD)

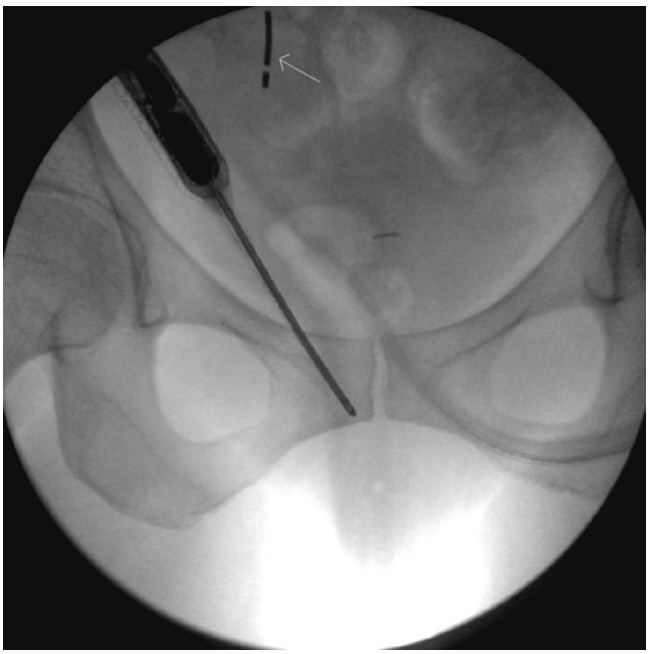


Fig. 2.20 Cryoneurolysis of the genitofemoral nerve at the pubic tubercle. Note the *white arrow* showing the Interstim® placed for interstitial cystitis pain that offered no relief (Image courtesy of Andrea Trescot, MD)

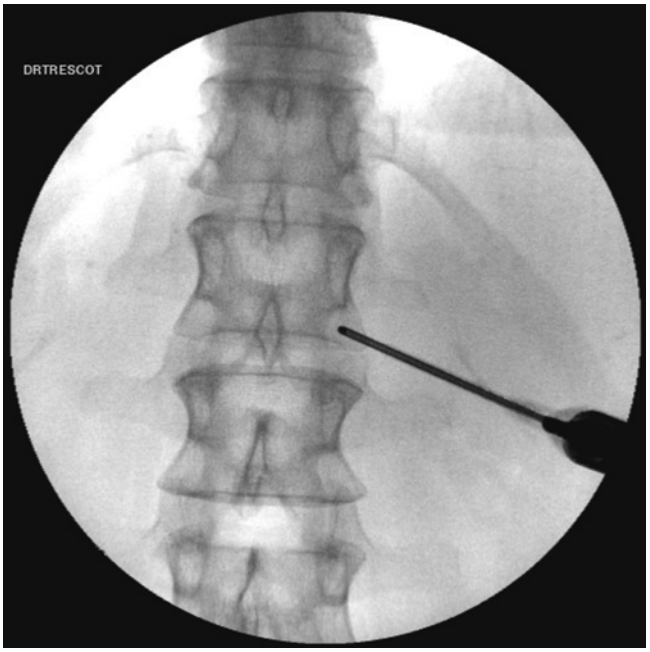


Fig. 2.21 Cryoprobe positioned on the proximal genitofemoral nerve at L1 (Image courtesy of Andrea Trescot, MD)

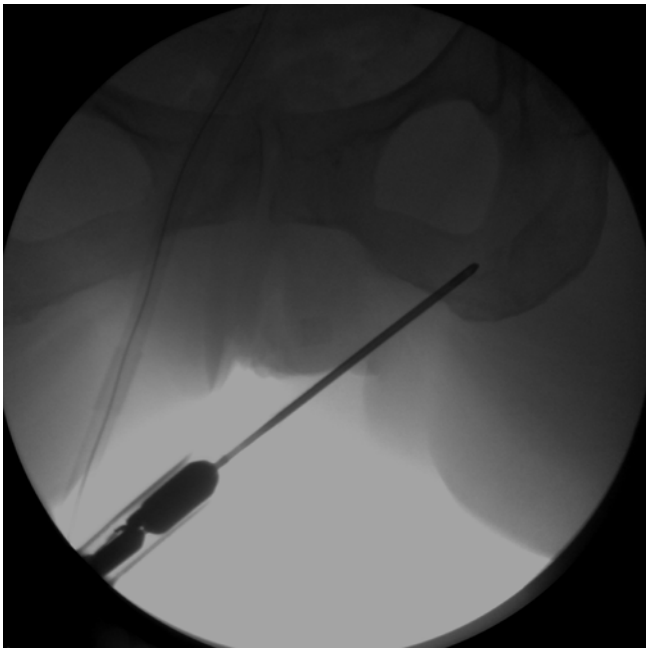


Fig. 2.23 Cryoneurolysis at the pudendal canal (Image courtesy of Andrea Trescot, MD)

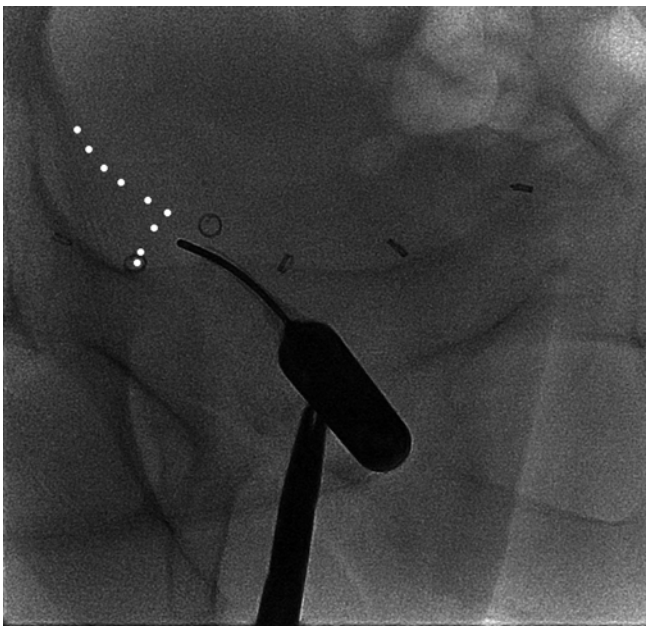


Fig. 2.22 Cryoneurolysis at the ischial spine (outlined in *white*) (Image courtesy of Agnes Stogicza, MD)

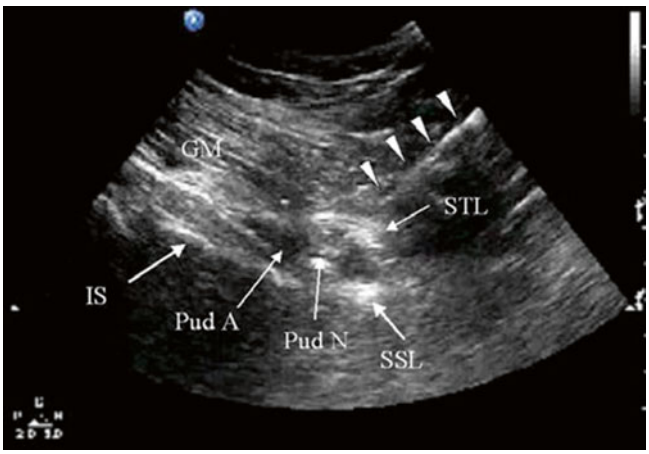


Fig. 2.24 Ultrasound picture of the pudendal nerve during injection. *STL* sacrotuberous ligament, *SSL* sacrospinous ligament, *Pud A* pudendal artery, *Pud N* pudendal nerve, *IS* ischium at ischial spine level, *GM* gluteus maximus. The needle is identified by the *solid arrows* (Image from Peng [89], with permission)

The pudendal nerve cryoneurolysis can be accomplished proximally or distally, by fluoroscopic [61] or ultrasound visualization, with patient in prone or lithotomy position. Figure 2.22 shows cryoneurolysis proximally at the ischial spine, and Fig. 2.23 shows cryoneurolysis at the pudendal (Adcock's) canal, both under fluoroscopic guidance, while Fig. 2.24 shows the pudendal nerve under ultrasound.

Lower Extremity Pain

Superior Cluneal Nerve

The superior cluneal nerve is composed of the cutaneous branches of the dorsal rami of L1, L2, and L3 [62]. Although classically it had been seen as a cause of pain after iliac bone harvest surgery, superior cluneal pathology may occur more frequent as result of a spontaneous entrapment of the nerves as they pass through the thoracolumbar fascia [63]. The

Fig. 2.25 Location of cluneal nerve entrapment (Image courtesy of Andrea Trescot, MD)

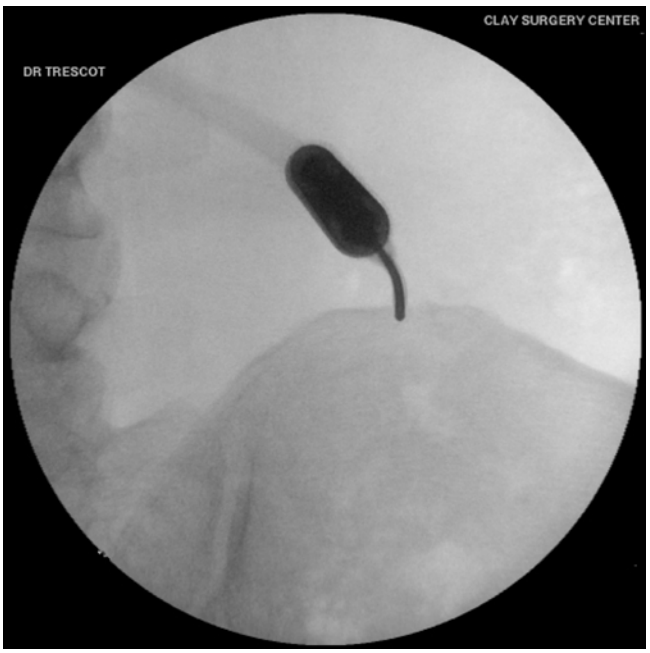


Fig. 2.26 Cryoneurolysis of the cluneal nerve (Image courtesy of Andrea Trescot, MD)

patient usually complains about low back pain that radiates to the gluteal region. The symptoms can be reproduced by manual palpation of the iliac crest at a point approximately 7 cm lateral to the midline (Fig. 2.25). Cryoneurolysis is performed at the iliac crest (Fig. 2.26) or more proximately at the spinal foramen.

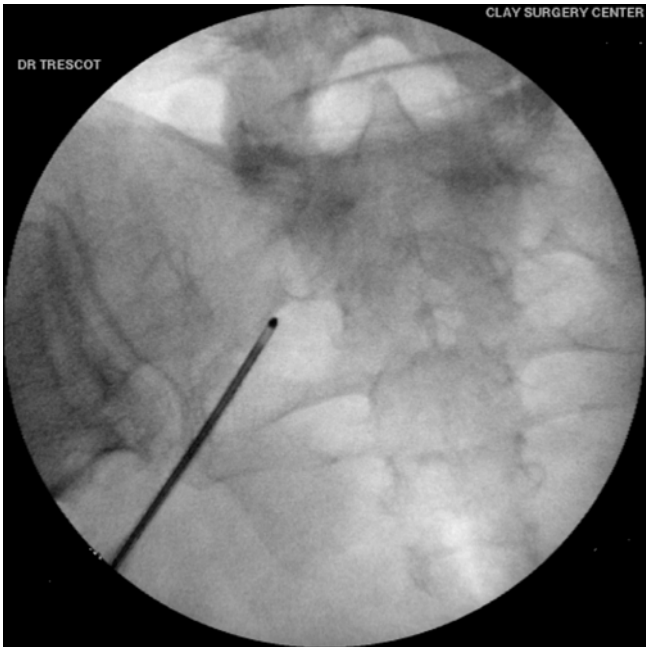


Fig. 2.27 Cryoneurolysis of the posterior ramus of the sacral nerves (Image courtesy of Andrea Trescot, MD)

Sacral Nerve

The sacral nerve pathology can produce sacroiliac joint pain with tenderness over the medial aspect of the posterior iliac. Pain can be referred from the buttocks to the foot. The cryoprobe must be placed at the lateral border of the foramen to freeze the posterior ramus of the sacral nerves (Fig. 2.27).

Infrapatellar Saphenous Nerve

The infrapatellar branch of saphenous nerve (IPS) is a pure sensory nerve that is responsible for the infrapatellar skin and anterior knee capsule innervation [64]. The nerve crosses the inferior knee from medial to lateral (Fig. 2.28) where it could be injured in many surgical procedures such as total knee replacement [65], patellar and hamstring tendon harvest [66], and tibial nailing as well as by anterior knee trauma [67].

The IPS can be cryolesioned at the inferior medial tibial plateau, medial and inferior to the tibial tuberosity (Fig. 2.29). It is useful to palpate and locate the maximum tender point over the nerve. It is important to be prudent and avoid skin freezing since the nerve is superficial.

Superficial Fibular (Peroneal) Nerve

The superficial fibular nerve (also known as the superficial peroneal nerve) is a branch of the common fibular nerve and

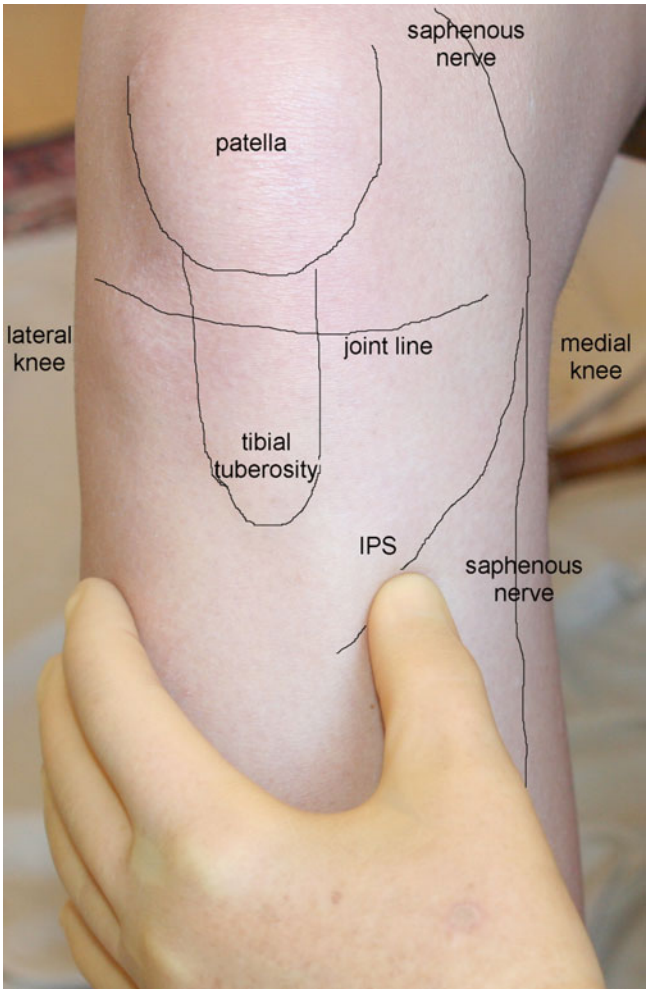


Fig. 2.28 Physical exam of the infrapatellar saphenous nerve (Image courtesy of Andrea Trescot, MD)

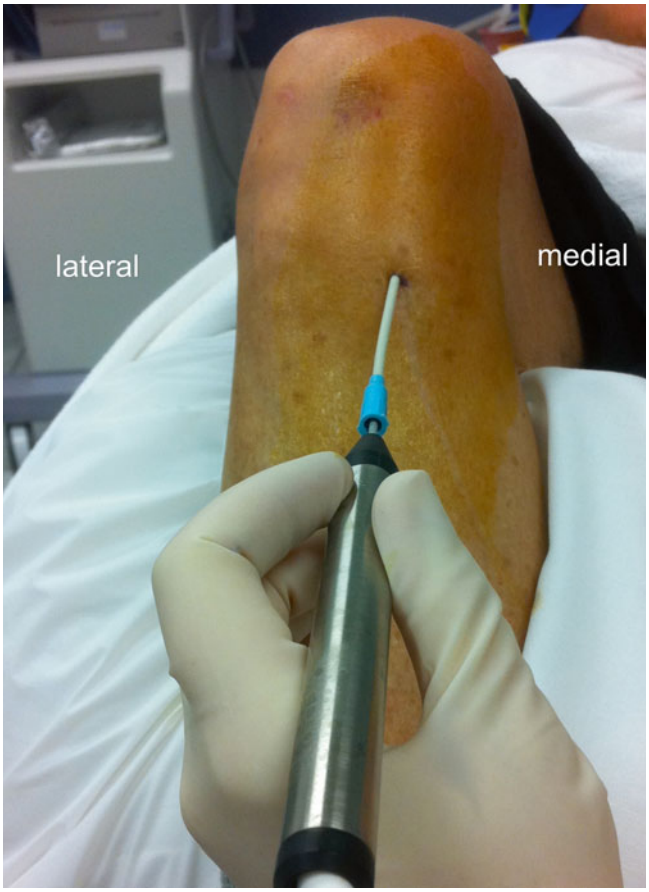


Fig. 2.29 Cryoneurolysis of the infrapatellar nerve (Image courtesy of Andrea Trescot, MD)

innervates the fibularis longus and fibularis brevis muscles and the skin over the greater part of the dorsum of the foot. The nerve lies between the lateral malleolus and the extensor retinaculum, and it can be injured frequently after inversion foot injuries, mimicking complex regional pain syndrome [68]. The patient may experiment dull lateral ankle pain that radiates to the dorsal of the foot.

The probe should be placed parallel to the nerve, and, since the nerve is quite superficial, one needs to be careful about skin freezing (Fig. 2.30).

Superficial Saphenous Nerve

The saphenous nerve is the largest branch of the femoral nerve, derived from the L3 and L4 spinal roots. The nerve runs along the adductor canal (also known as subsartorial or Hunter's canal) and becomes superficial as it approaches the knee. More distally, the nerve passes anterior to the medial malleolus, the site for cryoneurolysis of the superficial saphenous nerve (Fig. 2.31). The superficial saphenous nerve is frequently injured during saphenous vein surgeries (for aesthetic or vein graft harvest purposes) or after foot eversion injuries. The patient usually complains about a dull medial ankle pain that may radiate down to the great toe.

Medial and Inferior Calcaneal Nerves

The medial and inferior calcaneal nerves are branches of the posterior tibial nerve, and they are responsible for the medial and inferior heel innervation, respectively (Fig. 2.32) [69]. They can be compressed by tight-fitting shoes or injured by trauma and cause pain in the innervated area.

The medial and inferior calcaneal nerve cryoneurolysis may be useful targets for the recalcitrant plantar fasciitis (Fig. 2.33); inferior calcaneal neuralgia may need treatment

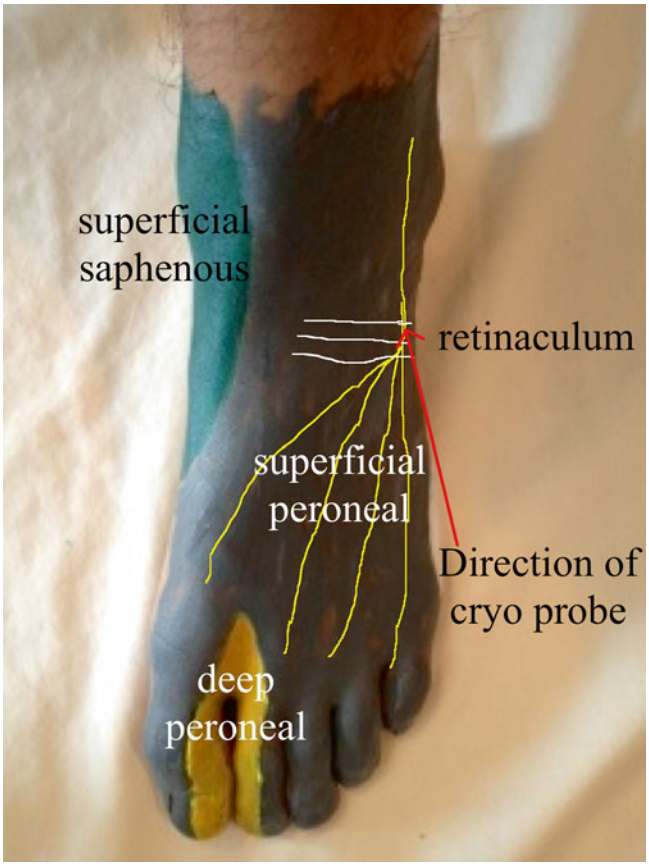


Fig. 2.30 Site of cryoneurolysis of the superficial peroneal nerve (Image courtesy of Terri Dallas-Prunskis, MD)

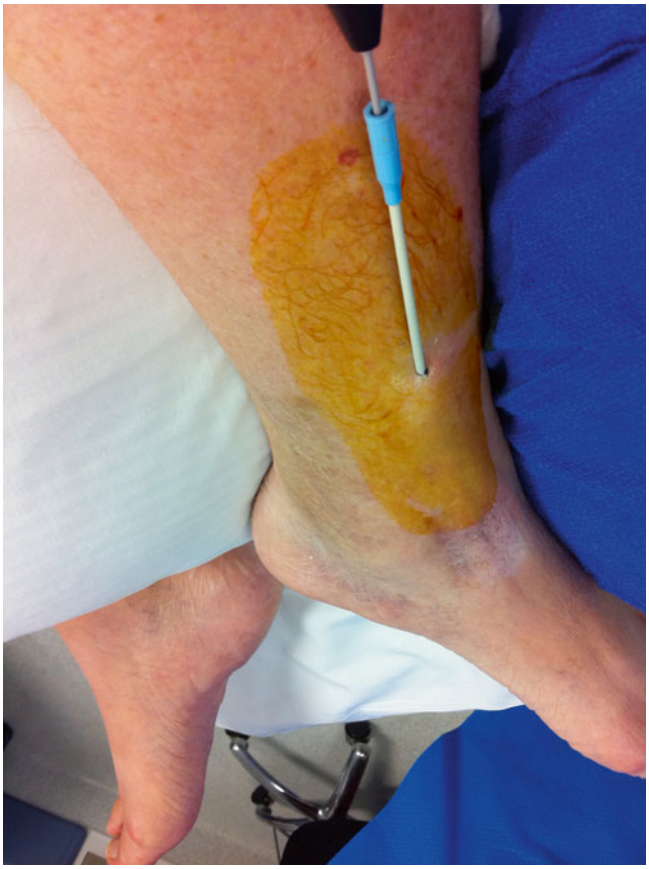


Fig. 2.31 Cryoneurolysis of the superficial saphenous nerve (Image courtesy of Andrea Trescot, MD)

for its own entrapment (also known as Baxter's neuropathy) [70–72].

Digital Nerve

The plantar digital nerve entrapments can produce a poorly localized foot pain, mainly at the ball of the foot and between the toes. The deep peroneal nerve functions as a digital nerve and is treated the same way. The most common mechanism of entrapment is compression by the metatarsal heads. Cryoneurolysis is an attractive option to alcohol injections and open surgery (Fig. 2.34).

Outcome Data

Cryoneurolysis is used for non-spinal pain in multiple sites. Although the technique has a great clinical efficacy, the evidence has been scarce. Most of studies are case reports, case series, or observational studies.

Craniofacial Pain

Zakrzewska et al. [73] reviewed 475 trigeminal neuralgia patients over a 10-year follow-up period. The patients were subgrouped as follows: 145 submitted to cryotherapy, 265 underwent radiofrequency thermocoagulation, and 65 underwent microvascular decompression. The recurrence probability among the patients submitted to cryotherapy was lower, and none of the cryoneuroablation patients developed anesthesia dolorosa, which occurred in 8 % of patients in the radiofrequency group.

Sidebottom et al. [74] tested cryoneuroablation in the management of intractable pain of the temporomandibular joint (TMJ). They observed a decrease at the visual analogue pain scale from 6.8 (range 4–10) to 2 (range 0–7), after applying the cryoablation at the auriculotemporal nerve region and at the TMJ in 17 patients.

Thoracic Pain

Cryoneurolysis had been used to treat intercostal neuralgia and even for post-thoracotomy pain control.

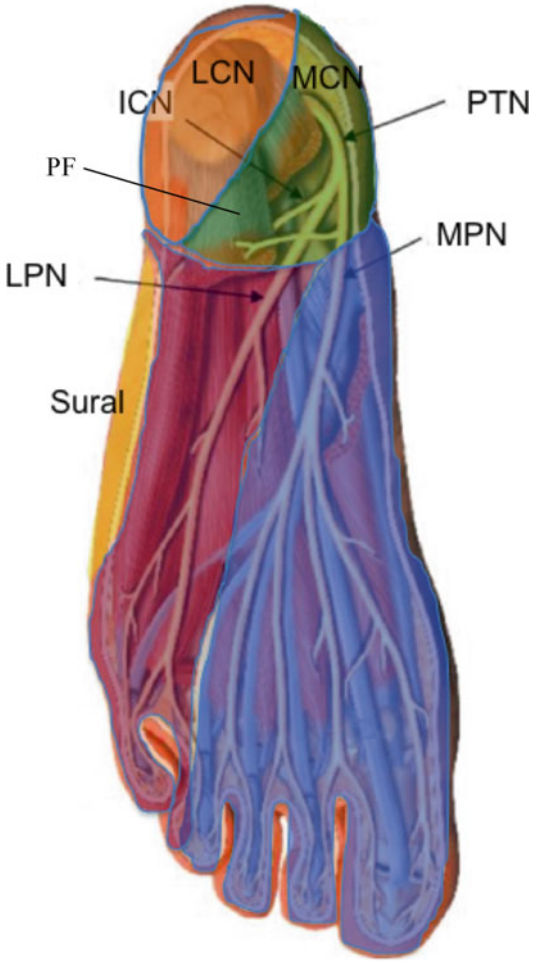


Fig. 2.32 Anatomy of the plantar nerves: *PTN* posterior tibial nerve, *MPN* medial plantar nerve, *LPN* lateral plantar nerve, *ICN* inferior calcaneal nerve, *LCN* lateral calcaneal nerve, *MCN* medial calcaneal nerve, *PF* plantar fascia (Image courtesy of Andrea Trescot, MD)

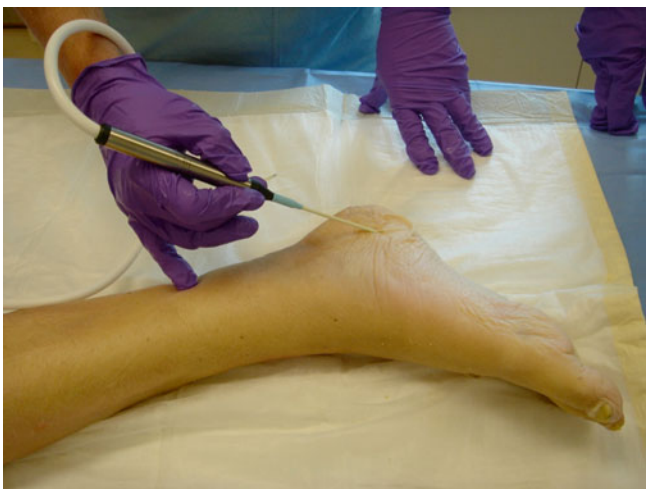


Fig. 2.33 Cryoneurolysis of the medial calcaneal nerve (Image courtesy of Andrea Trescot, MD)

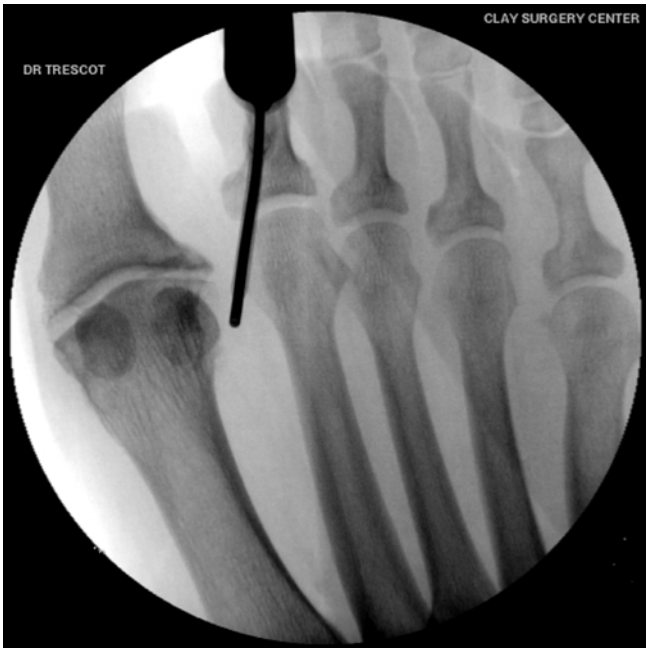


Fig. 2.34 Cryoneurolysis of the deep peroneal nerve (digital nerve) (Image courtesy of Andrea Trescot, MD)

Momenzadeh et al. [75] compared the effects of intercostal cryoneurolysis on post-thoracotomy pain. The postoperative pain was classified in three groups according to the intensity: 0–1 (mild), 2–3 (moderate), and 4–10 (severe). On the second day, the incidence of severe pain was 33 % and 0 in the control and cryoanalgesia groups, respectively. The opioid consumption was significantly lower in the cryoanalgesia group.

Ju et al. [76], in a randomly prospective fashion, compared the efficacy of intercostal cryoablation and epidural analgesia in 107 patients undergoing thoracotomy. They found the same pain relief with lower pruritus incidence in the cryotherapy group.

Green et al. [77] retrospectively studied the effects of cryoneurolysis in 43 patients with chronic chest wall pain due to intercostal neuralgia. The mean VAS score dropped from 8.2 (preprocedure) to 2.7 in a 3-month follow-up. Three months after cryoanalgesia, 50 % of the patients continued to report significant pain relief.

Lumbar Pain

One of the uses of cryoanalgesia for low back pain is the treatment of lumbar facet pathology. When diagnostic lumbar facet injections (either pericapsular or median branch blocks [78]) have given good but only temporary relief, one option for further treatment is cryoneuroablation of the medial branches (see Fig. 2.35). The American Medical Association (AMA) has confirmed that the facet neurolytic codes (64633/64634

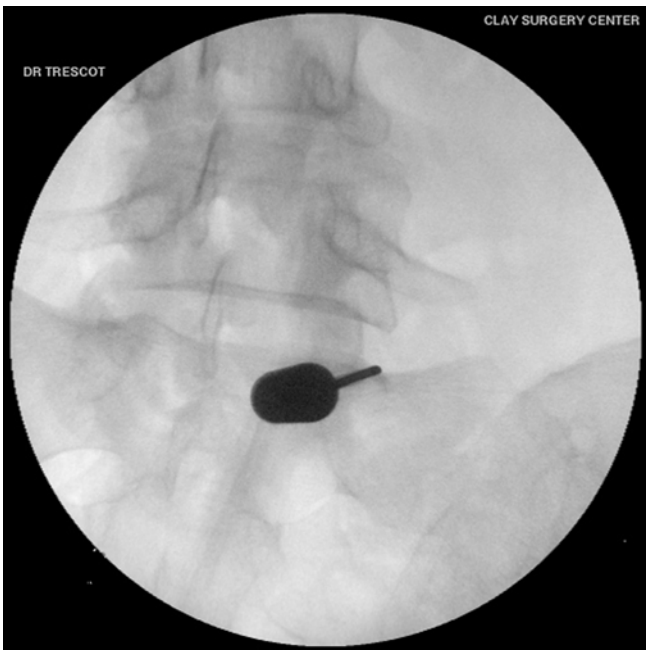


Fig. 2.35 Cryoneuroablation of the medial branches

and 64635/64636) are appropriate to use for cryoneuroablation of the cervical, thoracic, and lumbar facets.

Wolter et al. [79] retrospectively analyzed 117 cryoneurolysis treatments for zygapophyseal joint pain. All the procedures were done under CT visualization after a positive diagnostic block using local anesthetic.

Abdominal/Pelvic Pain

Racz and Hagstron [80] studied 15 patients with chronic abdominal pain treated with cryoneurolysis of the ilioinguinal and iliohypogastric nerves. Seven patients (47 %) reported excellent pain relief. Four of the seven patients experienced pain relief lasting between 4 and 30 months, and the other three had permanent pain relief.

Glynn and Carrie [81] reported two cases of successful cryoneurolysis through the caudal hiatus to provide pain relief from the pain caused by diastasis of the symphysis pubis during pregnancy.

Loev et al. [82] reported one case of cryoneurolysis of the ganglion of impar in a patient with severe anal and perineal pain secondary to surgical resection of rectal carcinoma. The procedure was performed after a diagnostic block through the sacrococcygeal membrane.

Lower Extremity Pain

Hodor et al. [83] reported a successful treatment of the intermetatarsal space neuroma in one patient with a 2-min cryoneurolysis technique. They found a 38 % VAS decrease after 3-month follow-up and even anxiety and depression scale reduction.

Caporusso et al. [84] prospectively evaluated the cryogenic neuroablation of 32 neuromas in 20 patients. All patients were surgical candidates who had failed prior conservative treatment. After 1 year, 38.7 % of patients were pain-free, 45.2 % reported partial pain relief, and 16.1 % returned to the baseline condition.

Allen et al. [85] did a prospective study testing the efficacy of cryosurgery on painful plantar fasciitis in 59 patients (61 heels). The results were impressive with a mean pain rating dropping from 8.38 to 1.26 during a 12-month follow-up period.

Moesker et al. [86] reported the treatment of five phantom limb pain patients with cryoneurolysis of the affected nerve. The nerve was chosen according to the referred pain location described by the patient and confirmed by diagnostic injection using local anesthetic. Cryoneurolysis was performed at the same location using two cycles of 3-min freezing separated by a 2-min defrost. Three of five patients had excellent outcomes, with 90–100 % pain relief. One patient had 40 % pain decrease, and the other one had 20 % pain relief.

Rhame et al. [87] described an ultrasonographic-guided cryoneuroablation of a refractory sural neuroma with long-term relief.

Complications

Cryoneurolysis carries a low probability of complications risk. The most frequent complication is hypoesthesia of the innervated area. Puncture-related complications such bleeding, infection, and pneumothorax can be avoided with a proper technique. Hyperpigmentation or depigmentation is a potential risk as is alopecia at the cryo site (especially the eyebrow).

Conclusion

Cryoneurolysis is an effective interventional pain management technique, providing short- and long-term analgesia for properly selected patients. A positive diagnostic block is mandatory for the technique success.

We have a scarcity of scientific evidence, not only about the cryoneuroablation but also for many of our interventional pain management techniques.

Nonetheless, in this "evidence vacuum," we still have a responsibility to treat. Certainly, we must develop better evidence, but our patients cannot wait for that [88].

References

1. Hippocrates. Heracleitus on the Universe. Aphorisms. 1931. p. 201.
2. Gruner OC. A treatise on the Canon of medicine of Avicenna. London: Luzac; 1930.

3. Evans PJ. Cryoanalgesia. The application of low temperatures to nerves to produce anaesthesia or analgesia. Anaesthesia. 1981;36:1003–13.
4. Trendelenburg W. Über langdauernde nervenausschaltung mit sicherer regenerationsfähigkeit. Z Gesamte Exp Med. 1917;5:371–4. doi:10.1007/BF03011102.
5. Arnott J. Practical illustrations of the remedial efficacy of a very low or anesthetic temperature.?I. In cancer. Lancet. 1850;56:257–9. doi:10.1016/S0140-6736(02)89874-9.
6. MARCUS BIRD H, JAMES ARNOTT MD. Aberdeen. Anaesthesia. 1949;4:10–7. doi:10.1111/j.1365-2044.1949.tb05803.x.
7. COOPER IS, LEE AS. Cryostatic congelation: a system for producing a limited, controlled region of cooling or freezing of biologic tissues. J Nerv Ment Dis. 1961;133:259–63.
8. RAND RW, DASHE AM, PAGLIA DE, et al. Stereotactic cryohypophysectomy. JAMA. 1964;189:255–9.
9. Green NA. Cryosurgery of the prostate gland. Ann R Coll Surg Engl. 1977;59:288–97.
10. Torre D. Cutaneous cryosurgery. J Cryosurg. 1968;1:202–9.
11. House WF. Cryosurgical treatment of Meniere's disease. Arch Otolaryngol. 1966;84:616–29.
12. Lewis MI, de laCruz T, Gazzaniga DA, Ball TL. Cryosurgical hemorrhoidectomy. Dis Colon Rectum. 1969;12:371–8. doi:10.1007/BF02617751.
13. Hill CL. Cryosurgical tonsillectomy. An evaluation. Arch Otolaryngol. 1968;87:434–5.
14. Lincoff HA, Mclean JM. Cryosurgery in treating retinal detachment and other eye disorders. Br J Ophthalmol. 1965;49:337–46.
15. Miyake K, Date H, Miyai Y, et al. Cryoanalgesia--a new approach to pain relief after thoracotomy. Kyobu Geka. 1987;40:731–5.
16. Rewcastle JC, Sandison GA, Saliken JC, et al. Considerations during clinical operation of two commercially available cryomachines. J Surg Oncol. 1999;71:106–11.
17. Chandler JR. Cryosurgery for recurrent carcinoma of the oral cavity. Arch Otolaryngol. 1973;97:319–21.
18. Gill W, Long WB. A critical look at cryosurgery. Int Surg. 1971;56:344–51.
19. Harly S, Aastrup J. Cryosurgery. Principles and application to tonsillectomy. Acta Radiol Suppl. 1972;313:253–9.
20. Miller D. Cryosurgery as a therapeutic modality in treatment of tumours of the head and neck. Proc R Soc Med. 1974;67:69–72.
21. Baust J, Chang Z. Underlying mechanisms of damage and new concepts in cryosurgical instrumentation. Paris, France: Cryosurgery Mech. Appl. International Inst. Refrigeration; 1995. p. 21–36.
22. Taylor MJ. Physico-chemical principles in low temperature biology. In: Arnold E, editor. Effects of Low Temperatures on Biological Systems. London: B.W.W. Grout and G.J. Morris; 1987. p. 3–71.
23. Mazur P. Kinetics of water loss from cells at subzero temperatures and the likelihood of intracellular freezing. J Gen Physiol. 1963;47:347–69.
24. Mazur P. Physical-chemical factors underlying cell injury in cryosurgical freezing physical-chemical factors underlying cell injury in cryosurgical freezing. In: Rand R, Rinfret A, von Leden H, editors. Cryosurgery. Springfield: Thomas; 1968. p. 32–51.
25. Mazur P. The role of intracellular freezing in the death of cells cooled at supraoptimal rates. Cryobiology. 1977;14:251–72. doi:10.1016/0011-2240(77)90175-4.
26. Mazur P. Freezing of living cells: mechanisms and implications. Am J Physiol. 1984;247:C125–42.
27. Sherman JK. Survival of higher animal cells after the formation and dissolution of intracellular ice. Anat Rec. 1962;144:171–89.
28. Mundht ED. Studies on the pathogenesis of cold injury: microcirculatory changes in tissue injured by freezing. Proc Symp Artic Biol Med. 1964;4:51–72.
29. Quintanella R, Krusen F, Essex H. Studies on frostbite with special reference to treatment and the effect on minute blood vessels. Am J Physiol. 1947;149:149–61.
30. Zacarian SA, Stone D, Clater M. Effects of cryogenic temperatures on microcirculation in the golden hamster cheek pouch. Cryobiology. 1970;7:27–39.
31. Tatsutani K, Rubinsky B, Onik G, Dahiya R. Effect of thermal variables on frozen human primary prostatic adenocarcinoma cells. Urology. 1996;48:441–7. doi:10.1016/S0090-4295(96)00199-9.
32. Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. Cryobiology. 1998;37:171–86. doi:10.1006/cryo.1998.2115.
33. Myers RR, Powell HC, Heckman HM, et al. Biophysical and pathological effects of cryogenic nerve lesion. Ann Neurol. 1981;10:478–85.
34. Sunderland S. Nerves and Nerve Injuries. 2nd ed. London: Churchill Livingstone; 1978.
35. Evans PJ, Lloyd JW, Jack TM. Cryoanalgesia for intractable perineal pain. J R Soc Med. 1981;74:804–9.
36. Barnard D, Lloyd J, Evans J. Cryoanalgesia in the management of chronic facial pain. J Maxillofac Surg. 1981;9:101–2.
37. Zakrzewska JM. Cryotherapy in the management of paroxysmal trigeminal neuralgia. J Neurol Neurosurg Psychiatry. 1987;50:485–7.
38. Jeong SM, Park KJ, Kang SH, et al. Anatomical consideration of the anterior and lateral cutaneous nerves in the scalp. J Korean Med Sci. 2010;25:517–22. doi:10.3346/jkms.2010.25.4.517.
39. Fogaça WC, Sturtz GP, Surjan RCT, Ferreira MC. Evaluation of cutaneous sensibility on infraorbital nerve area. J Craniofac Surg. 2005;16:953–6.
40. Kazkayasi M, Ergin A, Ersoy M, et al. Microscopic anatomy of the infraorbital canal, nerve, and foramen. Otolaryngol Head Neck Surg. 2003;129:692–7.
41. Hu K-S, Kwak J, Koh K-S, et al. Topographic distribution area of the infraorbital nerve. Surg Radiol Anat. 2007;29:383–8. doi:10.1007/s00276-007-0227-z.
42. Chan BJ, Koushan K, Liszauer A, Martin J. Iatrogenic globe penetration in a case of infraorbital nerve block. Can J Ophthalmol. 2011;46:290–1. doi:10.1016/j.jcjo.2011.05.012.
43. Piagkou M, Demesticha T, Skandalakis P, Johnson EO. Functional anatomy of the mandibular nerve: consequences of nerve injury and entrapment. Clin Anat. 2011;24:143–50. doi:10.1002/ca.21089.
44. Bagheri SC, Meyer RA. Management of mandibular nerve injuries from dental implants. Atlas Oral Maxillofac Surg Clin North Am. 2011;19:47–61. doi:10.1016/j.cxom.2010.11.004.
45. Somayaji SK, Acharya SR, Mohandas KG, Venkataramana V. Anatomy and clinical applications of the mandibular nerve. Bratisl Lek Listy. 2012;113:431–40.
46. Scott A, Varley I. Mandibular nerve blocks. Anaesthesia. 2012;67:546. doi:10.1111/j.1365-2044.2012.07125.x.
47. Renton T. Prevention of iatrogenic inferior alveolar nerve injuries in relation to dental procedures. Dent Update. 2010;37:350–2. 354–6, 358–60 passim.
48. Kemp WJ, Tubbs RS, Cohen-Gadol AA. The innervation of the scalp: a comprehensive review including anatomy, pathology, and neurosurgical correlates. Surg Neurol Int. 2011;2:178. doi:10.4103/2152-7806.90699.
49. Bovim G, Bonamico L, Fredriksen TA, et al. Topographic variations in the peripheral course of the greater occipital nerve. Autopsy study with clinical correlations. Spine (Phila Pa 1976). 1991;16:475–8.
50. Son B-C, Kim D-R, Lee S-W. Intractable occipital neuralgia caused by an entrapment in the semispinalis capitis. J Korean Neurosurg Soc. 2013;54:268–71. doi:10.3340/jkns.2013.54.3.268.
51. Tom JA, Mesfin A, Shah MP, et al. Anatomical considerations of the suprascapular nerve in rotator cuff repairs. Anat Res Int. 2014;2014:674179. doi:10.1155/2014/674179.
52. Tubbs RS, Nechtman C, D'Antoni AV, et al. Ossification of the suprascapular ligament: a risk factor for suprascapular nerve compression? Int J Shoulder Surg. 2013;7:19–22. doi:10.4103/0973-6042.109882.

53. Wu Y-T, Ho C-W, Chen Y-L, et al. Ultrasound-guided pulsed radiofrequency stimulation of the suprascapular nerve for adhesive capsulitis: a prospective, randomized, controlled trial. Anesth Analg. 2014;119:686–92. doi:10.1213/ANE.0000000000000354.
54. Chatterjee N, Roy C. Pulsed radiofrequency for the suprascapular nerve for patients with chronic headache. J Neurosurg Anesthesiol. 2014;26:267. doi:10.1097/ANA.0000000000000009.
55. Byas-Smith MG, Gulati A. Ultrasound-guided intercostal nerve cryoablation. Anesth Analg. 2006;103:1033–5. doi:10.1213/01.ane.0000237290.68166.c2.
56. Mandelkow H, Loeweneck H. The iliohypogastric and ilioinguinal nerves. Surg Radiol Anat. 1988;10:145–9. doi:10.1007/BF02307823.
57. Loos MJA, Scheltinga MRM, Roumen RMH. Surgical management of inguinal neuralgia after a low transverse Pfannenstiel incision. Ann Surg. 2008;248:880–5. doi:10.1097/SLA.0b013e318185da2e.
58. Campos NA, Chiles JH, Plunkett AR. Ultrasound-guided cryoablation of genitofemoral nerve for chronic inguinal pain. Pain Physician. 2009;12:997–1000.
59. Filler AG. Diagnosis and treatment of pudendal nerve entrapment syndrome subtypes: imaging, injections, and minimal access surgery. Neurosurg Focus. 2009;26,E9. doi:10.3171/FOC.2009.26.2.E9.
60. Labat J-J, Riant T, Robert R, et al. Diagnostic criteria for pudendal neuralgia by pudendal nerve entrapment (Nantes criteria). Neurourol Urodyn. 2008;27:306–10. doi:10.1002/nau.20505.
61. Choi S-S, Lee P-B, Kim Y-C, et al. C-arm-guided pudendal nerve block: a new technique. Int J Clin Pract. 2006;60:553–6. doi:10.1111/j.1742-1241.2006.00836.x.
62. Maigne JY, Lazareth JP, Guérin Surville H, Maigne R. The lateral cutaneous branches of the dorsal rami of the thoraco-lumbar junction. An anatomical study on 37 dissections. Surg Radiol Anat. 1989;11:289–93.
63. Kuniya H, Aota Y, Saito T, et al. Anatomical study of superior cluneal nerve entrapment. J Neurosurg Spine. 2013;19:76–80. doi:10.3171/2013.4.SPINE12683.
64. Horner G, Dellon AL (1994) Innervation of the human knee joint and implications for surgery. Clin Orthop Relat Res. (301):221–6.
65. Toms AD, Mandalia V, Haigh R, Hopwood B. The management of patients with painful total knee replacement. J Bone Joint Surg Br. 2009;91:143–50. doi:10.1302/0301-620X.91B2.20995.
66. Papastergiou SG, Voulgaropoulos H, Mikalef P, et al. Injuries to the infrapatellar branch(es) of the saphenous nerve in anterior cruciate ligament reconstruction with four-strand hamstring tendon autograft: vertical versus horizontal incision for harvest. Knee Surg Sports Traumatol Arthrosc. 2006;14:789–93. doi:10.1007/s00167-005-0008-3.
67. Detenbeck LC. Infrapatellar traumatic neuroma resulting from dashboard injury. J Bone Joint Surg Am. 1972;54:170–2.
68. Apaydin N, Basarir K, Loukas M, et al. Compartmental anatomy of the superficial fibular nerve with an emphasis on fascial release operations of the leg. Surg Radiol Anat. 2008;30:47–52. doi:10.1007/s00276-007-0284-3.
69. Louisia S, Masquelet AC. The medial and inferior calcaneal nerves: an anatomic study. Surg Radiol Anat. 1999;21:169–73.
70. Liden B, Simmons M, Landsman AS. A retrospective analysis of 22 patients treated with percutaneous radiofrequency nerve ablation for prolonged moderate to severe heel pain associated with plantar fasciitis. J Foot Ankle Surg. 2009;48:642–7. doi:10.1053/j.jfas.2009.05.013.
71. Cione JA, Cozzarelli J, Mullin CJ. A retrospective study of radiofrequency thermal lesioning for the treatment of neuritis of the medial calcaneal nerve and its terminal branches in chronic heel pain. J Foot Ankle Surg. 2009;48:142–7. doi:10.1053/j.jfas.2008.11.007.
72. Dirim B, Resnick D, Ozenler NK. Bilateral Baxter's neuropathy secondary to plantar fasciitis. Med Sci Monit. 2010;16:CS50–3.
73. Zakrzewska JM. Cryotherapy for trigeminal neuralgia: a 10 year audit. Br J Oral Maxillofac Surg. 1991;29:1–4.
74. Sidebottom AJ, Carey EC, Madahar AK. Cryoanalgesia in the management of intractable pain in the temporomandibular joint: a five-year retrospective review. Br J Oral Maxillofac Surg. 2011;49:653–6. doi:10.1016/j.bjoms.2010.11.007.
75. Momenzadeh S, Elyasi H, Valaie N, et al. Effect of cryoanalgesia on post-thoracotomy pain. Acta Med Iran. 2011;49:241–5.
76. Ju H, Feng Y, Yang B-X, Wang J. Comparison of epidural analgesia and intercostal nerve cryoanalgesia for post-thoracotomy pain control. Eur J Pain. 2008;12:378–84. doi:10.1016/j.ejpain.2007.07.011.
77. Green CR, de Rosayro AM, Tait AR. The role of cryoanalgesia for chronic thoracic pain: results of a long-term follow up. J Natl Med Assoc. 2002;94:716–20.
78. Birkenmaier C, Veihelmann A, Trouillier HH, et al. Medial branch blocks versus pericapsular blocks in selecting patients for percutaneous cryodenervation of lumbar facet joints. Reg Anesth Pain Med. 2007;32(1):27–33.
79. Wolter T, Deininger M, Hubbe U, et al. Cryoneurolysis for zygapophyseal joint pain: a retrospective analysis of 117 interventions. Acta Neurochir (Wien). 2011;153:1011–9. doi:10.1007/s00701-011-0966-9.
80. Racz G, Hagstrom D. Iliohypogastric and ilioinguinal nerve entrapment: diagnosis and treatment. Pain Dig. 1992;2:43–8.
81. Glynn CJ, Carrie LE. Cryoanalgesia to relieve pain in diastasis of the symphysis pubis during pregnancy. Br Med J (Clin Res Ed). 1985;290:1946–7.
82. Loev MA, Varklet VL, Wilsey BL, Ferrante FM. Cryoablation: a novel approach to neurolysis of the ganglion impar. Anesthesiology. 1998;88:1391–3.
83. Hodor L, Barkal K, Hatch-Fox LD. Cryogenic denervation of the intermetatarsal space neuroma. J Foot Ankle Surg. 1997;36:311–4.
84. Caporusso EF, Fallat LM, Savoy-Moore R. Cryogenic neuroablation for the treatment of lower extremity neuromas. J Foot Ankle Surg. 2002;41:286–90.
85. Allen BH, Fallat LM, Schwartz SM. Cryosurgery: an innovative technique for the treatment of plantar fasciitis. J Foot Ankle Surg. 2007;46:75–9. doi:10.1053/j.jfas.2007.01.0062007.
86. Moesker AA, Karl HW, Trescot AM. Treatment of phantom limb pain by cryoneurolysis of the amputated nerve. Pain Pract. 2014;14:52–6. doi:10.1111/papr.12020.
87. Rhame EE, DeBonet AF, Simopoulos TT. Ultrasonographic guidance and characterization of cryoanalgesic lesions in treating a case of refractory sural neuroma. Case Rep Anesthesiol. 2011. doi:10.1155/2011/691478.
88. Harden RN, Oaklander AL, Burton AW, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. Pain Med. 2013;14:180–229. doi:10.1111/pme.12033.
89. Peng PW, Tumber PS. Ultrasound-guided interventional procedures for patients with chronic pelvic pain – a description of techniques and review of literature. Pain Physician. 2008;11(2):215–24.

Targeted Radiofrequency Techniques

3

Aaron Calodney, Richard Rosenthal, Abigail Gordon, and Robert E. Wright

Introduction

Most often in pain medicine, radiofrequency (RF) current is used throughout the nervous system to make discrete therapeutic lesions in various targets to prevent nociceptive signals from reaching the central nervous system [1–6]. While RF current does not treat the root cause of pain, it serves to anesthetize the source of a patient's pain. It can thus produce lasting analgesia sufficient to reverse the deleterious effects of chronic pain including mood disturbance, sleeplessness, social isolation, and occasionally loss of life. When correctly applied to indicated patients, RF current allows the patient to return to normal activities and functions. Various techniques (e.g., cryosurgery and chemical neurolysis) were used in an attempt to produce localized nervous system lesions before the introduction of modern day RF equipment; however, none have been as widely used or are as effective as RF. Today, RF is implemented percutaneously by means of an insulated needle with a metal active tip that is placed in the appropriate nerve pathway. Applied current then serves to alter the function of the nerve and blocks transmission of the painful signal [1]. Newer ablation techniques, including magnetic resonance-guided focused ultrasound (MRgFUS), are being developed and will have direct application in the treatment of spinal pain [6–9].

The first use of electricity to manage pain was described in 1931 when direct current was applied to the gasserian ganglion for the treatment of trigeminal neuralgia [4, 10]. Due to its production of inconsistent lesions and complications, though, use of direct current was soon abandoned and replaced with high-frequency alternating current. This method was then introduced to produce lesions of a predictable size [11]. Temperature monitoring was found to further enhance the ability of a physician to make consistent, dependable lesions shortly after. The method was termed radiofrequency because the frequencies used (350–500 kHz) were also used in radio transmitters [5]. Today, the Federal Communications Commission assigns the frequency used by modern RF machines (right below the AM band) to prevent interference with radio transmissions.

Radiofrequency current for pain management was first focused on percutaneous lateral cordotomy to treat malignant pain [11]. The first use for nonmalignant pain began in the 1970s for treatment of trigeminal neuralgia [3, 12]. Cosman and Cosman introduced an RF machine with voltage and time settings that was capable of monitoring temperature, impedance, and current near the same time [13, 14]. The first use of RF current for the treatment of spinal pain consisted of a method for treating pain from the zygapophyseal joints (commonly referred to as facet joints) by targeting the medial branch described by Shealy [15]. When it was discovered from anatomic dissections that the electrode placements from this original paper were not actually on the medial branch, Bogduk published a modified technique [2, 16]. In another study, Uematsu targeted the dorsal root ganglion (DRG) using RF to treat radicular pain [13]. His use of a large (14-gauge) electrode to heat the DRG to 75 °C (167 °F) resulted in nearly complete destruction of the ganglion and severe deafferent pain sequela [5]. With poor outcomes in these early uses of RF for pain treatment, the method failed to gain acceptance [3].

Technological constraints limited RF therapy until 1980, when Sluijter and Metha introduced a 22-gauge cannula through which a thermocouple probe could be inserted and widespread use of RF current for the treatment of spinal pain began [3, 5]. The smaller electrode meant that the procedure could be performed percutaneously without causing too

A. Calodney, MD, FIPP, ABIPP (✉)
Texas Spine & Joint Hospital, Tyler, TX, United States
e-mail: aaroncalodney@me.com

R. Rosenthal, MD, DABPM, FIPP
Utah Center for Pain Medicine and Research, Provo, Utah, USA

A. Gordon, BA
Baylor College of Medicine, Houston, Texas, USA

R.E. Wright, MD, DABPM, FIPP
Denver Pain Management, Greenwood Village, CO, USA

Nimbus Concepts, LLC, Denver, CO, USA

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_3

much discomfort on a conscious patient. This important development allowed the patient to be monitored for complications. Shortly after the introduction of the Sluijter-Metha cannula (SMK) needle, a series of studies were published on the use of RF current for the treatment of facet joint pain, discogenic pain, sacroiliac (SI) joint pain, and sympathetically mediated pain [3, 17–25]. RF lesioning has since been found to be safe, target specific, and effective for the treatment of pain. Due to the highly focused nature of RF lesions, it has largely supplanted the use of other neurolytics (particularly chemical neurolytics).

Up until the late 1990s, only continuous RF was utilized, which heats the tissue surrounding the electrode and lyses the targeted nerve. On a pathologic level, continuous RF current heats nerve fibers and results in Wallerian degeneration [26–29]. On a physiologic level, continuous RF current destroys all fiber types within a nerve and is not selective for any one fiber type [2, 30, 31]. Pulsed RF (PRF) was then introduced, partially developed as a less destructive alternative. This method delivers RF current in small bursts and thus prevents the accumulation of heat around the electrode, though the exact mechanism of action remains elusive [1, 3]. One of the prevailing theories postulates that the electrical field generated during a PRF procedure reversibly disrupts the transmission of impulses across small unmyelinated fibers, causing a blockade of pain signals [1, 32–34]. Today pulsed RF is often considered safer than continuous RF as there have been no case reports of neurological side effects.

This chapter is clinically focused to provide an overview of the radiofrequency lesion generator and both types of radiofrequency lesions—continuous and pulsed. It describes RF lesioning for the most well-studied and common procedures and describes best practices based on the current scientific literature and clinical experience. The history, anatomy, patient indications, technique, and possible complications are explained to provide the pain practitioner the means to treat patients. For example, it presents new methods of performing RF for older procedures, such as the lumbar RF procedure and presents data to support the use of PRF in clinical practice.

Radiofrequency Lesion Generator (Fig. 3.1)

A radiofrequency lesion generator is a device used to produce lesions in the nervous system or other tissue by the direct application of high-frequency current to targeted sites. The following systems are typically present in an RF lesion generator: continuous impedance monitoring, monitoring of voltage, current, and temperature, nerve stimulation, and pulsed current delivery mode [5, 6]. At approximately 500 kHz, radiofrequency current alternates at a high frequency. The current flows from the electrode tip through the body to a dispersive grounding electrode. Focused around the active tip of the electrode, the energy activates charged molecules (mainly proteins) to oscillate with the rapid changes in alternating current, thereby producing friction in the tissue. Heat will then form directly around the active tip as a consequence of ionic oscillations of the charged molecules in the tissue, rather than direct heating of the electrode element itself. The generation of heat is greatest around the active tip, where the current density is largest. The grounding electrode serves to complete the circuit and disperse heat buildup, preventing a burn of the skin (Fig. 3.2a, b) [2].

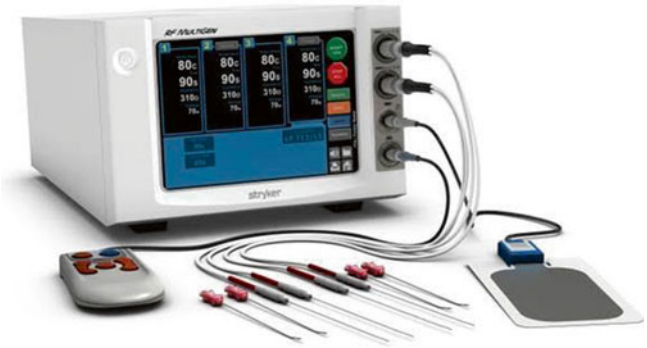


Fig. 3.1 Image of a radiofrequency generator (Courtesy of Stryker Interventional Spine: Kalamazoo, MI)

The RF ablation procedure utilizes a basic resistor circuit. Current can be expressed by Ohm's law: $I = V/R$, where I is current in amperes, V is voltage in volts, and R is impedance in ohms (defined as the electrical resistance in an AC circuit). As tissue impedance rises, the power output tends to decrease and the final lesion size is smaller. If tissue impedance can be lowered, the current density will decrease and power output increase, delivering more energy to the tissues and allowing the lesion to expand. Power, P, can be defined as the product of current and voltage: $P = \mathrm{VI} = V^2/R = \mathrm{I}^2\mathrm{R}$ [36].

Impedance Monitoring

When heat lesions are made in the continuous mode, impedance monitoring is primarily used to confirm continuity of the electrical circuit. During an RF lesion, impedance typically varies from 200 to 800 Ω and is greatly affected by density of the tissues in which the active tip is placed. For example, impedance is high when an electrode is placed in densely packed tissue (e.g., scar tissue), whereas it is low when an electrode is placed inside a blood vessel. In the pulsed mode, impedance monitoring is more crucial because the strength of the electrical field decreases when the impedance is high. Thus, high impedance can reduce the efficacy of the procedure and may be a cause of treatment failure. Both impedance and current should be noted and monitored during the creation of PRF lesions.

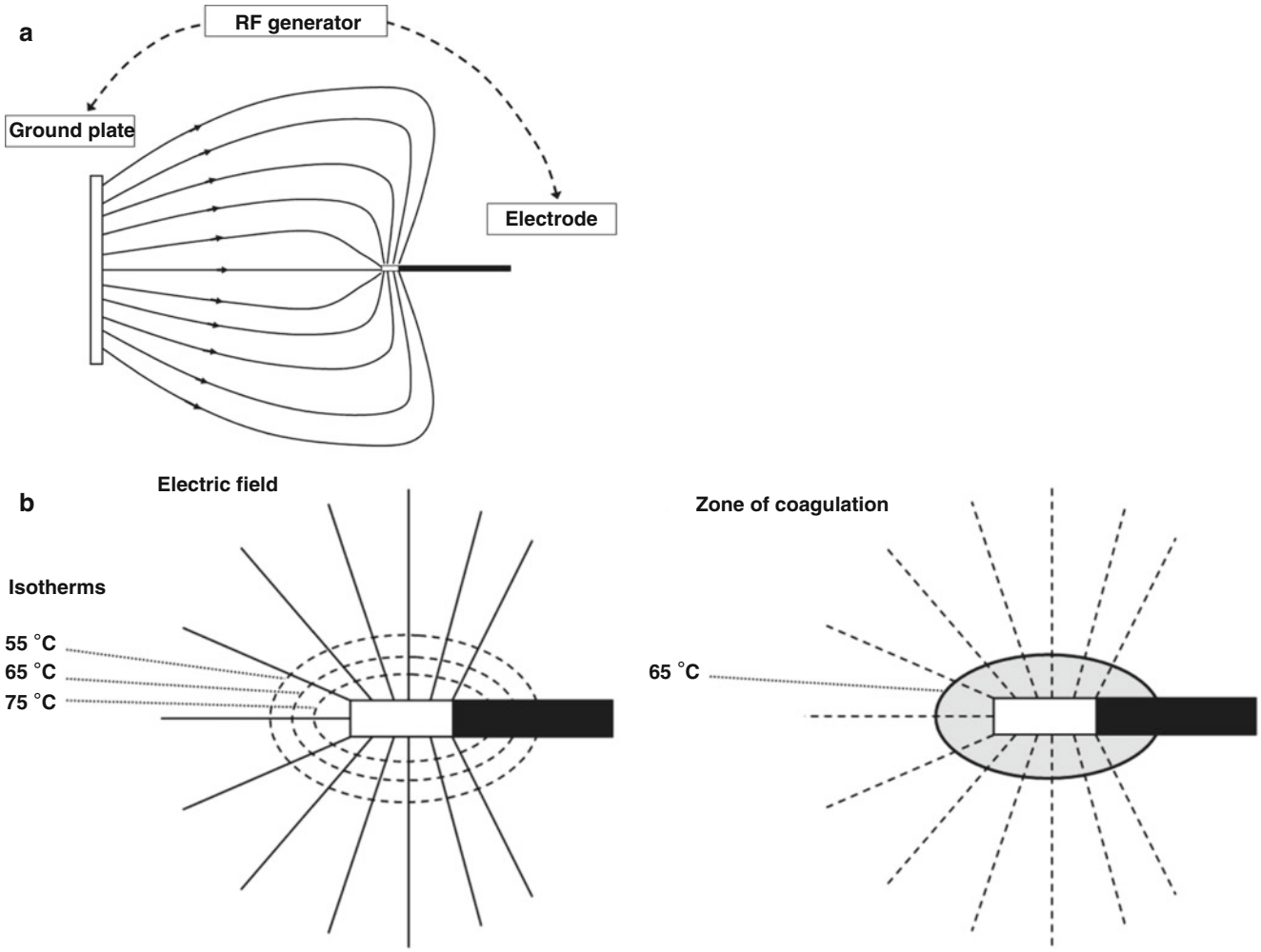


Fig. 3.2 (**a**) Thermal radiofrequency neurotomy current flow. The radiofrequency current generator produces an alternating current, which oscillates between the electrode and the ground plate. At any point in time, the current is just as likely to be flowing from ground plate to electrode as from electrode to the grounding plate. The electrical field is widely dispersed at the ground plate (decreased current density), which prevents the formation of heat in this area. Approaching the uninsulated electrode tip, the current density is concentrated and tissue heating occurs (From Bogduk [35]). (**b**) Isotherms and lesions. As the current density increases toward the electrode, surrounding oscillating molecules create increasingly higher temperatures. Temperature gradients can be plotted in the form of isotherms. Within an isotherm, tissues are heated to the corresponding temperature. Higher current density and thus higher temperatures are found closer to the electrode; proteins are coagulated at and within the 65° isotherm, forming a lesion in the shape of a prolate spheroid around the long axis of the electrode. Coagulation is unlikely to occur, and thus, no lesion is produced outside of the 65° isotherm (From Bogduk [35])

Temperature, Voltage, and Current Monitoring

Temperature monitoring facilitates generation of a discrete, controlled lesion of predictable sized. Because voltage and current are automatically adjusted in accordance with the temperature setting, monitoring them is of secondary importance when producing a heat lesion using the continuous mode.

However, in the pulsed mode, both impedance and current are important, as it is thought that the strength of the electrical field is critical to producing the desired effect. Recall that Voltage, impedance and current output are related as described in the equation $V = IR$, where V is voltage, I is current, and R is impedance (defined as the electrical resistance in an AC circuit). Both voltage and impedance can be regulated during the generation of a pulsed lesion: voltage output is adjusted using the generator, and impedance can be decreased by injection of saline. The goal is to adjust these variables to produce a current of about 200 milliamps. Temperature is of secondary importance, as long as it remains below neurolytic levels (45 °C) [37].

Motor and Sensory Stimulation

Nerve stimulation may be utilized in both the continuous and pulsed radiofrequency modes. There are two types of

Table 3.1 Stimulation voltage vs. duration of effect based on studies

Author	Sensory stimulation (V)	Duration (months)
Simopoulos et al. [40]	0.6	3.18
Teixeira et al. [41]	0.22	15.8
Chao et al. [42]	<0.5	3
Van Zundert et al. [43]	<0.5	3

stimulation: motor and sensory. Motor stimulation is used to determine if a needle is located near motor fibers, most commonly the ventral rami of the spinal root nerve, and it occurs at 2 Hz. The use of motor stimulation is intended to avoid accidental damage to neural structures. However, as these procedures are done under careful fluoroscopic guidance, it is often felt to be superfluous.

Sensory stimulation occurs at 50 Hz and is used to determine the distance between the electrode and the targeted nerve fiber. The minimum sensory threshold (i.e., the minimum voltage required to produce an electrical discharge of the nerve) is directly related to distance from the nerve fiber [5, 38]. Although sensory stimulation has been used to determine the accuracy of needle placement, there has been no meaningful correlation demonstrated between sensory stimulation threshold and the outcomes of lumbar facet radiofrequency denervation [39]. This is more important in the pulsed mode than in the continuous mode and is considered superfluous during radiofrequency ablation of the medial or lateral branches. Sensory stimulation is helpful in pulse radiofrequency lesioning for two reasons. First, there is limited evidence that increasing the proximity between the electrode and the targeted nerve can increase the duration of the effect. Second, sensory stimulation levels of less than 0.05 V are thought to indicate intraneural placement (Table 3.1).

Continuous and Pulsed Radiofrequency Lesioning

Figure 3.3a–c shows images of monopolar and bipolar lesions.

Continuous RF Lesioning

In the continuous mode, the heat generated causes tissue coagulation in a small, discrete oval surrounding the active tip of the electrode. Very little energy extends distal to the tip, so the largest area of damage is around the long axis of the electrode. Therefore, the pain practitioner should position the electrode parallel to the nerve to reliably coagulate the largest area of nerve fibers. Heat diminishes rapidly as the distance from the electrode tip increases and the area of coagulation is rather small, so the electrode must be placed directly on the nerve to guarantee neurolysis. If the electrode is as much as one electrode width away from the nerve, it will fail to completely coagulate the nerve [2, 3].

Continuous radiofrequency energy causes non-selective thermal damage to the offending nerve. The size of the lesion depends on several factors:

- Tissue temperature: The volume of the lesion expands in direct proportion to the temperature surrounding the electrode, up to a maximum temperature of 90 °C [2]. Temperatures beyond 90 °C risk charring of tissues, which can cause cavitation and possible sterile abscess formation [45]. In an ex-vivo animal tissue model, one can observe the increased lesion size as temperatures are increased (Fig. 3.4) [30], [44, 46].
- Duration of coagulation: The volume of the lesion grows over time, most rapidly over the first minute. Beyond 1 min the lesion continues to grow. Average lesion width increases by 11–20 % by 2 min and is 23–32 % larger at 3 min compared to 1 min [2, 44]. Lesion times of 2–3 min are logical methods of increasing lesion size for standard monopolar, dual-monopolar, bipolar, and cooled RF (Figs. 3.5 and 3.6).
- Gauge of electrode and length and gauge of active electrode tip: Larger gauge electrodes and longer active tips produce a larger lesion (Fig. 3.7a, b) [5, 47].
- Tissue Impedance: Injection of local anesthetic or saline solution prior to lesioning can decrease local tissue impedance and allow for more energy to be transferred to the tissue and thus increase lesion size. Increasing the NaCl concentration of the injected fluid significantly increased the final lesion size and allowed for the RF generator to maintain a higher power output throughout the lesion cycle (Figs. 3.8 and 3.9) [48–50]. There is one report suggesting that the injection of particulate methylprednisolone acetate prior to RF ablation has a negative impact on lesion size [51]. The presence of bone adjacent to RF lesions is common for many spinal applications covered in this chapter including cervical and lumbar medial branch radiofrequency ablation. When an RF lesion is made adjacent to bone, the maximum effective vertical radius from the outer wall of the needle (Mer_v) was nearly doubled compared to a lesion made in muscle only (Fig. 3.10) [52].
- Altering the current density by changing the surface area of the active tip: Several needle designs which increase the active tip emitting surface by using multiple tines are available including Venom by Stryker, and Nimbus by Nimbus Concepts (Fig. 3.11a, b). These designs allow for a larger lesion without the need for a larger cannula gauge size. Increasing the surface area of the emitter decreases the density of the radiofrequency current. Therefore, a

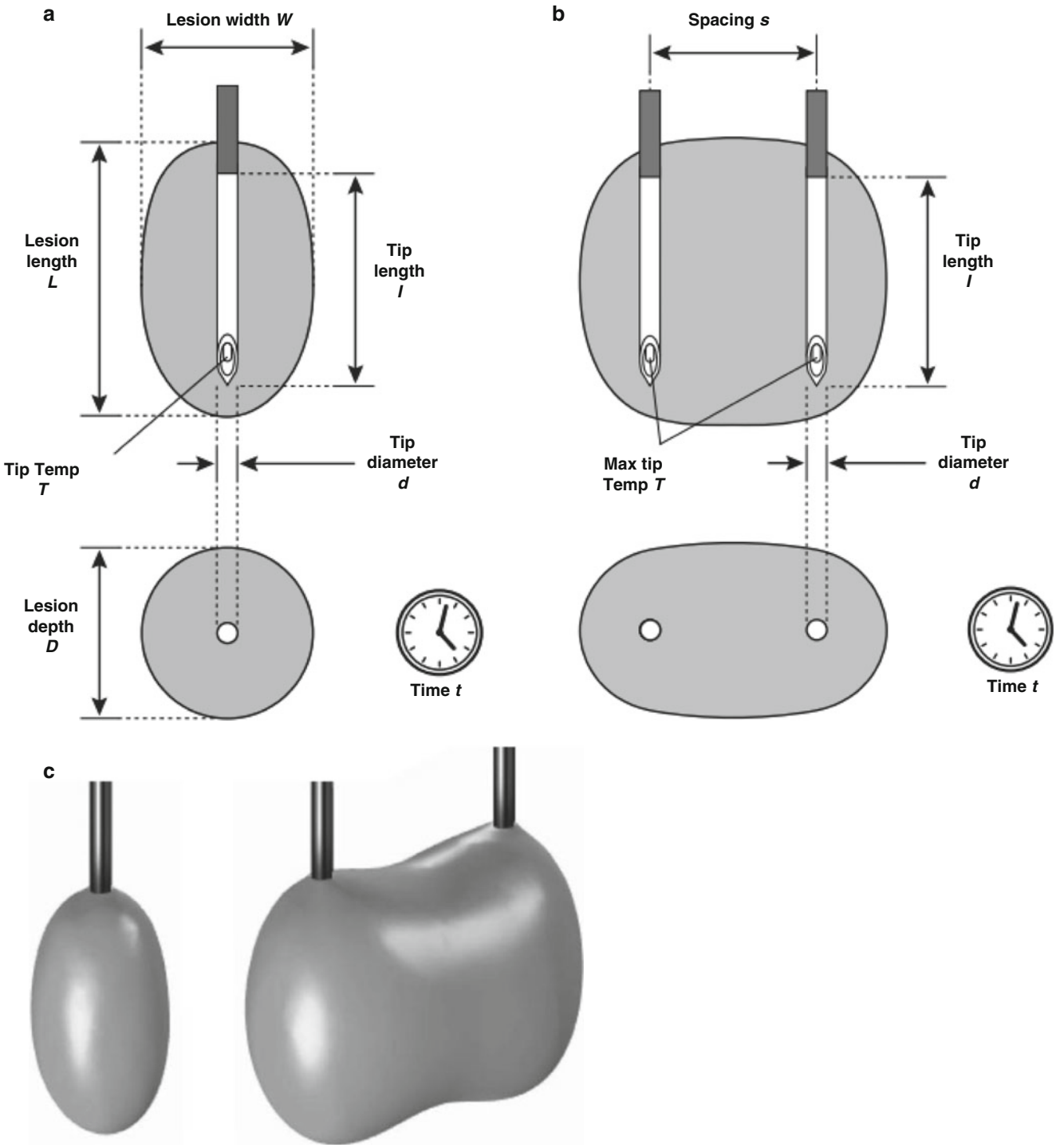


Fig. 3.3 (**a**) Monopolar lesions are prolate spheroidal. Lesion size depends on tip diameter *d*, tip length *l*, tip temperature *T*, and lesion time *t*. (**b**) Bipolar lesion size depends upon the same factors as monopolar but is additionally influenced by the spacing between the tips *s*. (**c**) Finite element modeling of the 55° isotherm of a monopolar 18 ga/10 mm/80°/2 min (*left*) and bipolar 18 ga/10 mm/90°/3 min with 12 mm spacing (*right*) (From Cosman et al. [44])

cannula with a larger conducting surface area requires greater RF energy in order to elicit an equivalent thermal response from the surrounding tissue. A larger conductive surface area requires that the temperature controlled RF generator increase power output to maintain a similar thermal profile, thus creating a larger lesion.

- Cooled RF: Cooled RF increases the volume of coagulated tissue and can create very large lesions. The elec-

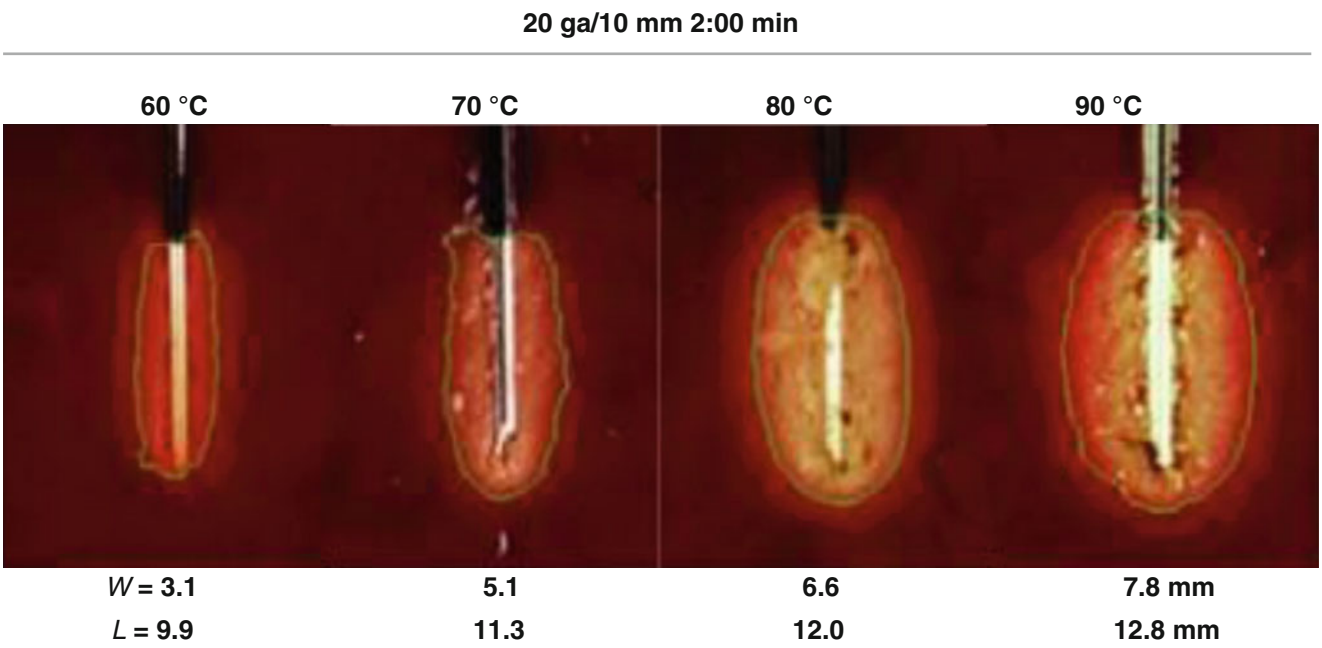


Fig. 3.4 The effect of temperature (From Cosman et al. [44]). Average midline width *W* and length *L* of RF heat lesions created by sharp-tip RF cannula/electrodes due to cannula temperature

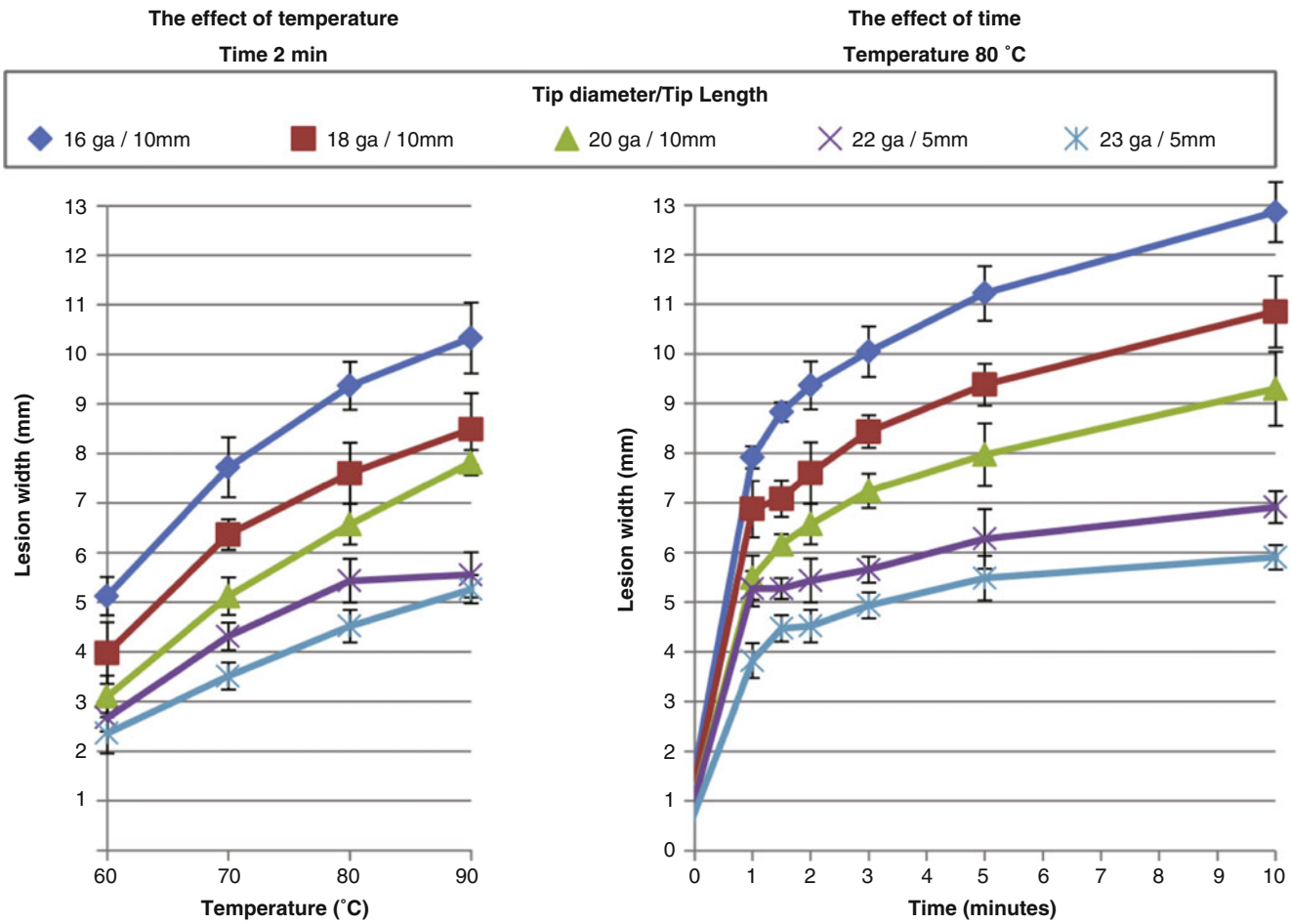


Fig. 3.5 The effect of temperature and the effect of time (From Cosman et al. [44]). Average monopolar RF heat lesion width *W* plotted as a function of set temperature and set time for sharp RF cannulae/electrodes and the RRE "Ray" electrode. Error bars plot the standard deviation about the average dimension

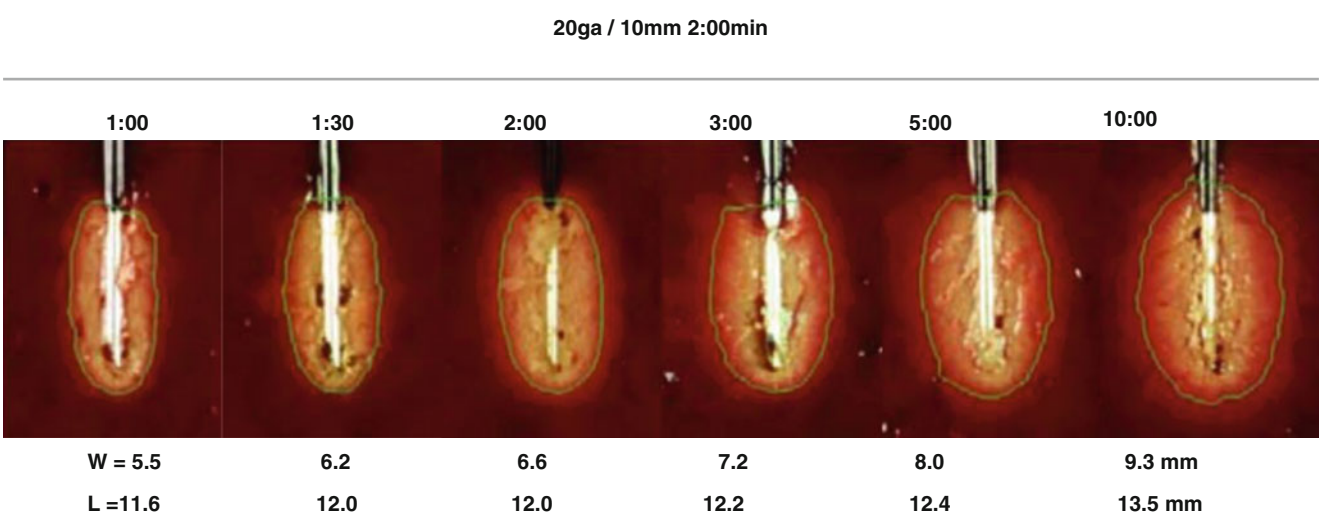


Fig. 3.6 The effect of time (From Cosman et al. [44]) Average midline width *W* and length *L* of RF heat lesions created by sharp-tip RF cannula/electrodes due to time

trode is cooled by passing water through a channel in the electrode. Heat is drawn away from the electrode slowing the coagulation of tissue around the electrode surface. This keeps the impedance low which allows current to continue to pass through the tissue. The total thermal energy delivered to the tissue is increased and a large volume of tissue can be coagulated (Fig. 3.12) [35].

The clinical relevance of the above discussion is important to note. According to ISIS guidelines, efficacy is maximized when needle placement is anatomically precise, larger needles are utilized (e.g., 18–20 g), and multiple parallel lesions are generated (within one needle width from each other) to account for the variable nerve topography [2]. Larger lesions are created using higher temperatures, larger gauge needles, multitined needles, cooled radiofrequency probes, and longer lesion times (i.e., up to 3 min) [30]. Heat decreases rapidly as the distance from the electrode tip increases. The ISIS Practice Guidelines 2nd Edition recommends a minimum 90 s lesion time at a temperature of 85–90 °C. If a larger lesion is desired, increasing lesion times from 90 s to 120–180 s is logical based upon the work of Eric Cosman Jr, PhD. [35, 44, 46].

The average size of a lesion is no more than 1.6–2.3 electrode widths [2]. Two lesions should be made one electrode width from each other to maximize effectiveness. If electrodes are positioned as little as two electrode widths away from each other or from the targeted nerve, therapeutic failure may occur from incomplete lesioning [2]. For that reason, larger 18 g electrodes were developed to improve the chance of incorporating the nerve in the lesion and are recommended for use when making heat lesions [2, 53]. Electrodes placed perpendicular rather than parallel to the nerve may succeed in coagulating the nerve if placed directly on the target, but also may also result in incomplete coagulation and shorter duration of relief due to the shorter length of the lesion produced [2, 30].

Pulsed RF Lesioning

The current from radiofrequency energy produces an intense electrical field in addition to generating heat. The therapeutic effect of pulsed radiofrequency lesioning is thought to be the result of the electrical field, rather than the thermal effects, though the mechanism of action is not understood [1, 3].

Convention holds that the word "lesion" should not be used when referring to a pulsed RF procedure. The word "lesion" is defined as "a localized pathological change in a bodily organ or tissue," and Sluijter suggests that a pulsed RF procedure clearly meets this criterion [54]. Additionally, heat bursts with temperatures in the neurodestructive range in a thin layer of tissue immediately surrounding the electrode have been observed [55]. Experimental evidence also suggests that PRF results in cellular damage that appears to be more pronounced for c fibers [56, 57]. Electron microscopy in a study by Erdine et al. demonstrated physical evidence of ultrastructural damage following exposure to PRF. This evidence would dispute the currently held belief that pulsed RF does not cause a lesion, though the clinical significance of these findings is still unknown. In this chapter, the word lesion will be used when referring to a pulsed RF procedure.

Historically, many thought that tissue destruction was the method through which RF current produced its effect; however, this theory was reevaluated in light of certain findings that were inconsistent with this explanation [3–5, 26, 33, 34, 40, 43, 55, 58–67]. First, Sluijter noticed that electrodes placed distally to the nociceptive focus seemed to produce a therapeutic effect, though it was known that heat produced

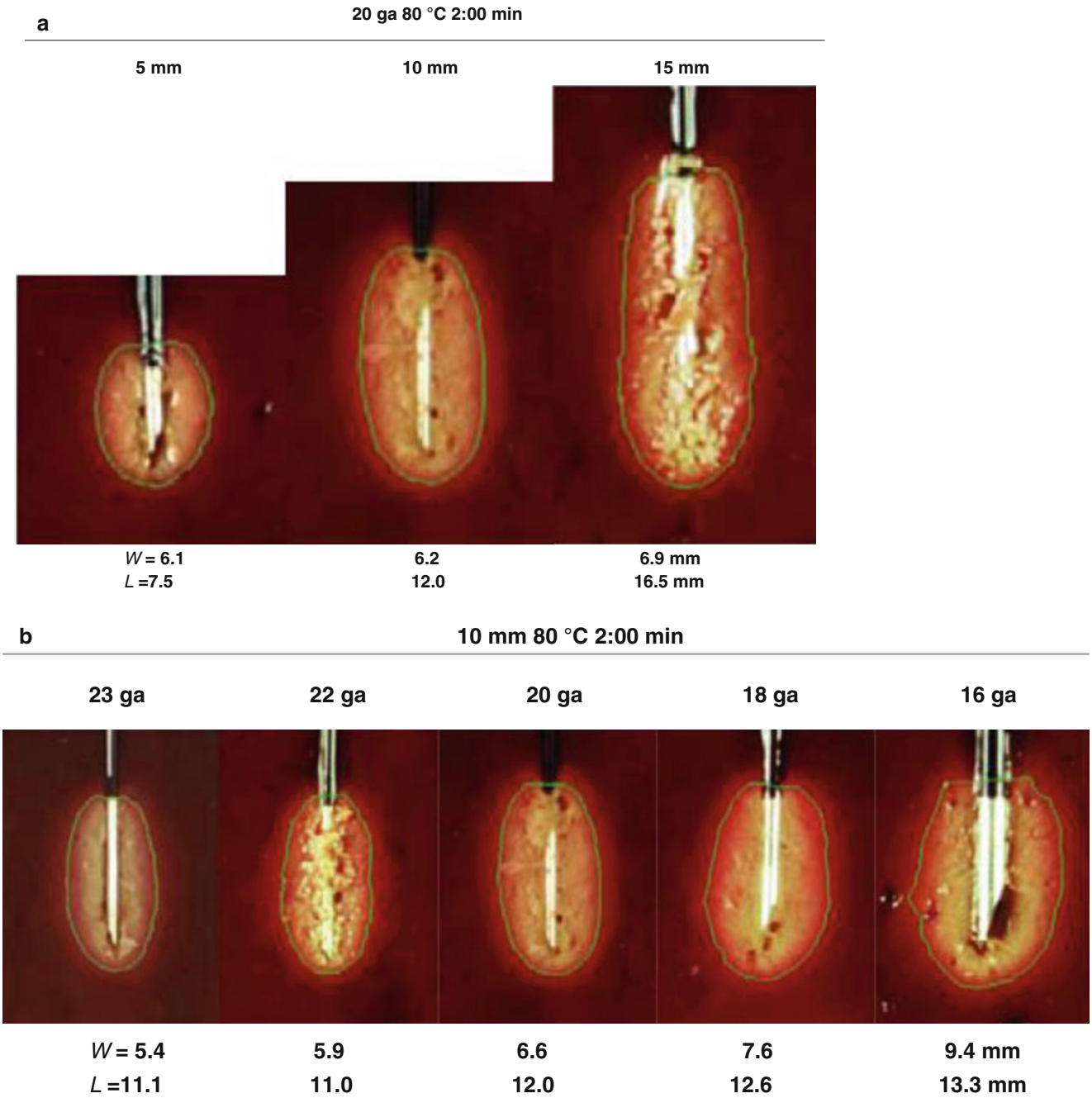


Fig. 3.7 (**a**) Average midline width *W* and length *L* of RF heat lesions created by sharp-tip RF cannula/electrodes due to cannula tip length. (**b**) Average midline width *W* and length *L* of RF heat lesions created by sharp-tip RF cannula/electrodes due to diameter/gauge (From Cosman et al. [44])

its effect by causing a lesion between the nociceptive focus and the central nervous system [68]. For example, despite the fact that heat is applied distal to the nociceptive focus, the spinal root nerve, treatment of radicular pain by heating the dorsal root ganglion seemed to produce a therapeutic effect. Secondly, Sluijter observed that heat lesioning of the dorsal root ganglion produced only transient sensory loss, whereas the pain relief lasted a much longer duration. Lastly, Slappendel et al. published a paper that showed there were no differences in outcome, when two different tip temperatures (40 and 67 °C) were applied to the cervical dorsal root ganglion for chronic cervical radicular pain [59]. The role of heat was thus considered uncertain, though each of these arguments has since been brought into question. At the time, though, it seemed reasonable to attempt to deliver radiofrequency energy in a manner that did not result in the

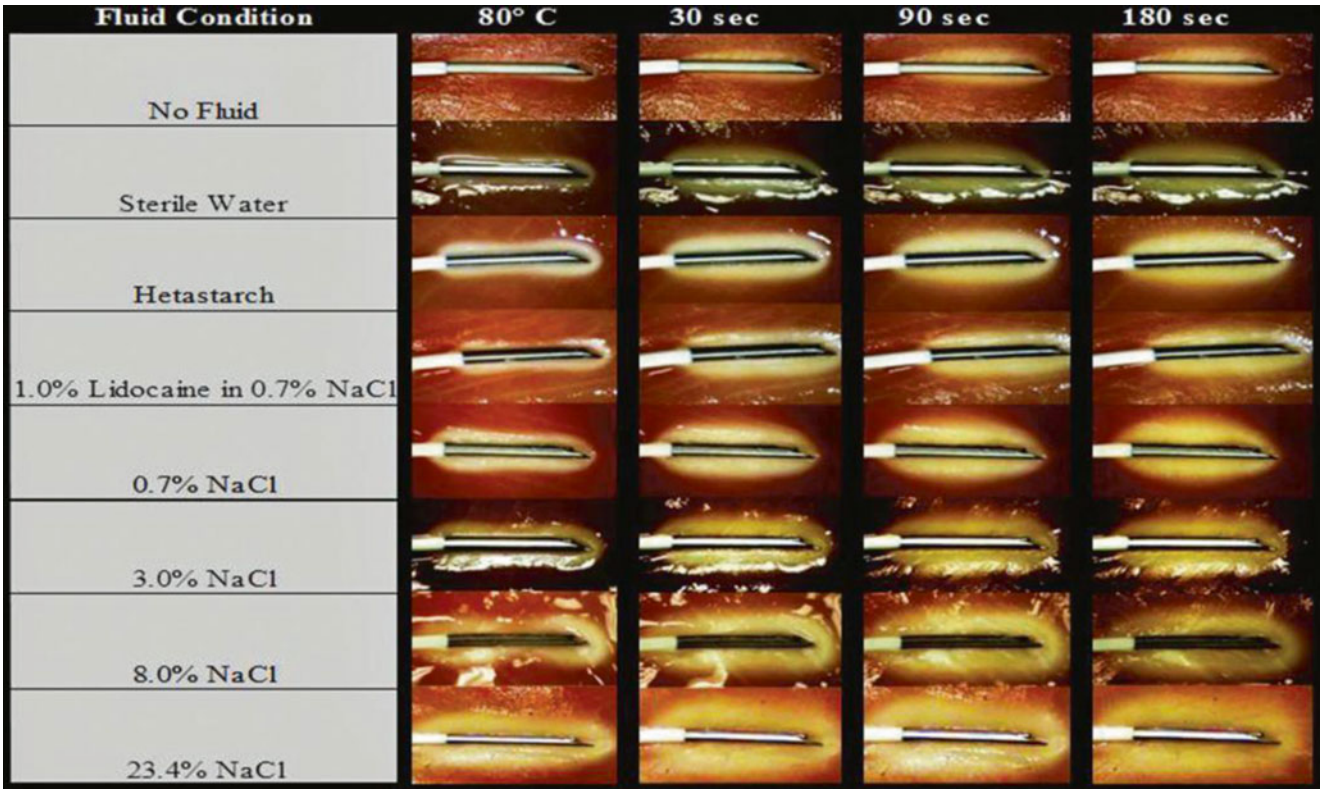


Fig. 3.8 Lesion size enlarges with increased NaCl concentrations. (From Provenzano et al. [50])

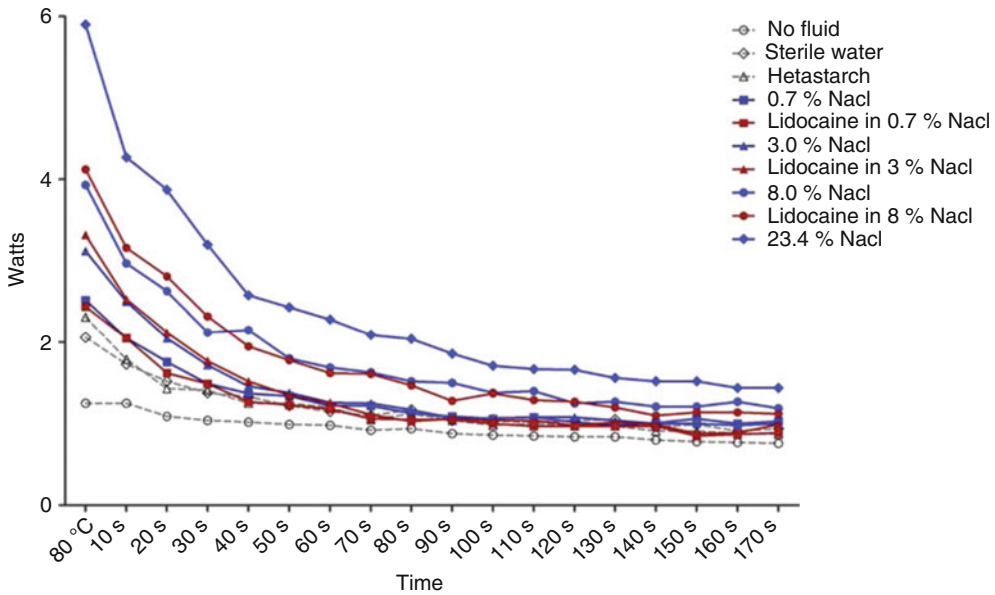


Fig. 3.9 Increasing the NaCl concentration extends the amount of time in the lesion cycle that the power output is significantly larger than the nonionic fluids (From Provenzano et al. [50])

production of heat. These observations provided supporting evidence that led to the development of the pulsed radiofrequency procedure in the early 1990s.

Pulsed radiofrequency seeks to generate intense electrical fields while keeping the temperature below neurolytic levels. This is accomplished by delivering quick, 20 ms bursts of energy twice per second, followed by a quiet phase lasting 480 ms during which no current is applied. This allows for heat dissipation by keeping tissue temperature below 45 °C, the neurodestructive threshold [3]. Studies in homogeneous

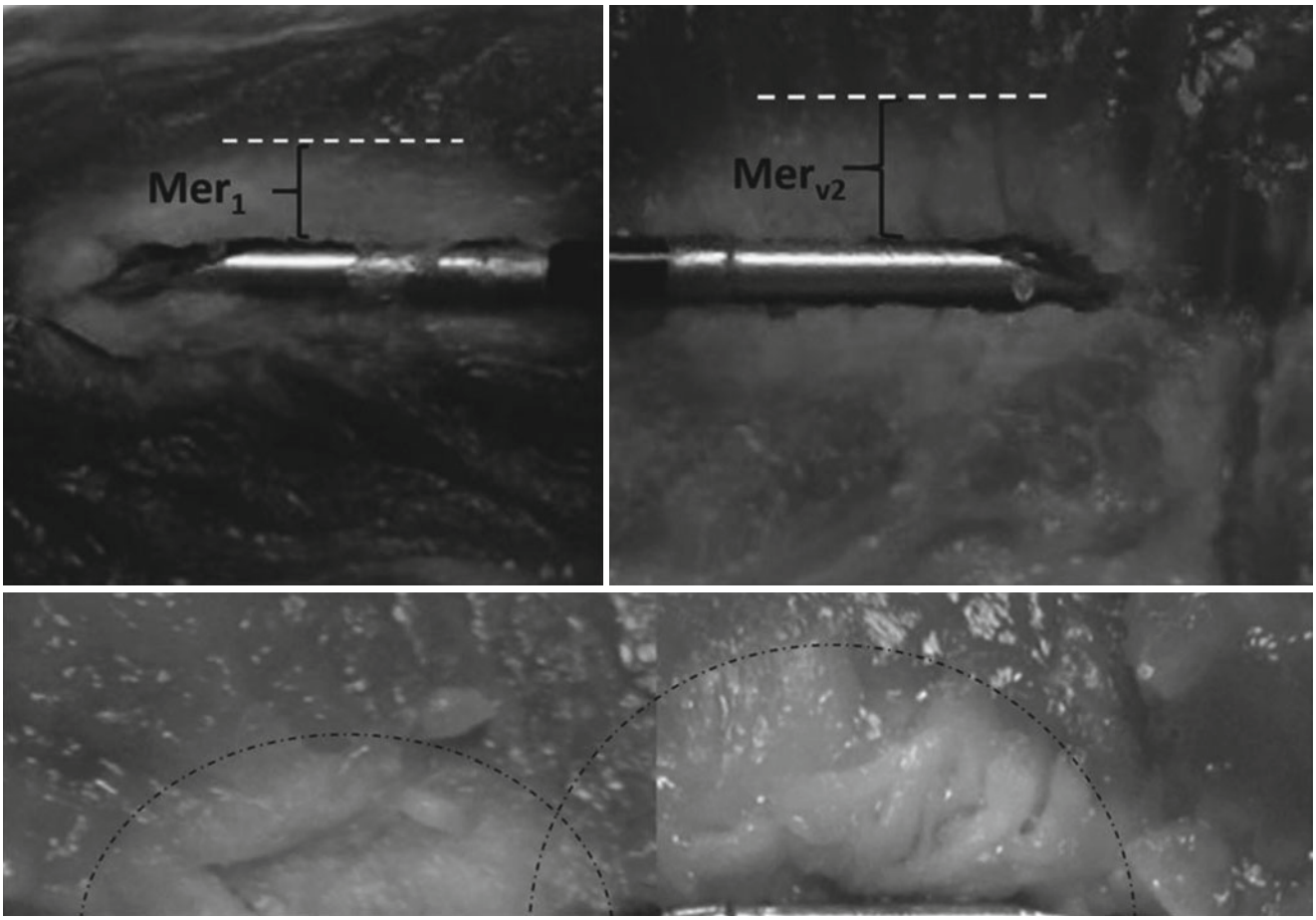


Fig. 3.10 Mer_v is the maximum effective vertical radius of the lesion from the outer wall of the needle. The needle in the top left is in muscle. The size of the lesion made, measured as Mer_{v1}, is shown in the upper frame and outlined with a black dotted line in the photo below. The vertical radius of this lesion away from the outer wall of the needle is smaller than in the picture on the right. On the right, the lesion is made with a needle against bone. This lesion is larger as measured by Mer_{v2} and outlined in the image below on the right (From Eckmann et al. [52])

nerve tissue suggest that irreversible conduction block occurs at temperatures greater than 45–50 °C [69–71].

Substantial increase in the power output of the generator results from pulsing the current. Voltage in the continuous mode is 15–25 V compared to 45 V in the pulsed mode [5]. It is recommended that the electrodes be placed perpendicular, rather than parallel, to the targeted nerve when performing a pulsed radiofrequency lesion because the electric field is strongest at the tip of the electrode. Note that the recommendation given for continuous radiofrequency lesioning, where the electrodes should be placed parallel, is opposite the suggestion for pulsed radiofrequency lesioning.

Originally pulsed RF was thought to be a totally nondestructive procedure, but further research suggests that this may not be the case [55–57, 72]. It appears there are both thermal and nonthermal effects of pulsed radiofrequency current. Cosman and Cosman first elucidated the thermal effects of pulsed radiofrequency when they noticed heat spikes produced during the 20 ms active phase of a pulsed radiofrequency current. It is not known whether these brief elevations in temperature have a biological effect. A mild ablative effect in an in vitro model has also been described, but its significance in a biological system is unknown [55–57, 72]. The nonthermal effects may be attributed to an effect on the function of voltage-gated ion channels. Additionally, there appears to be central nervous system effects as a direct result of the radiofrequency current [62, 73].

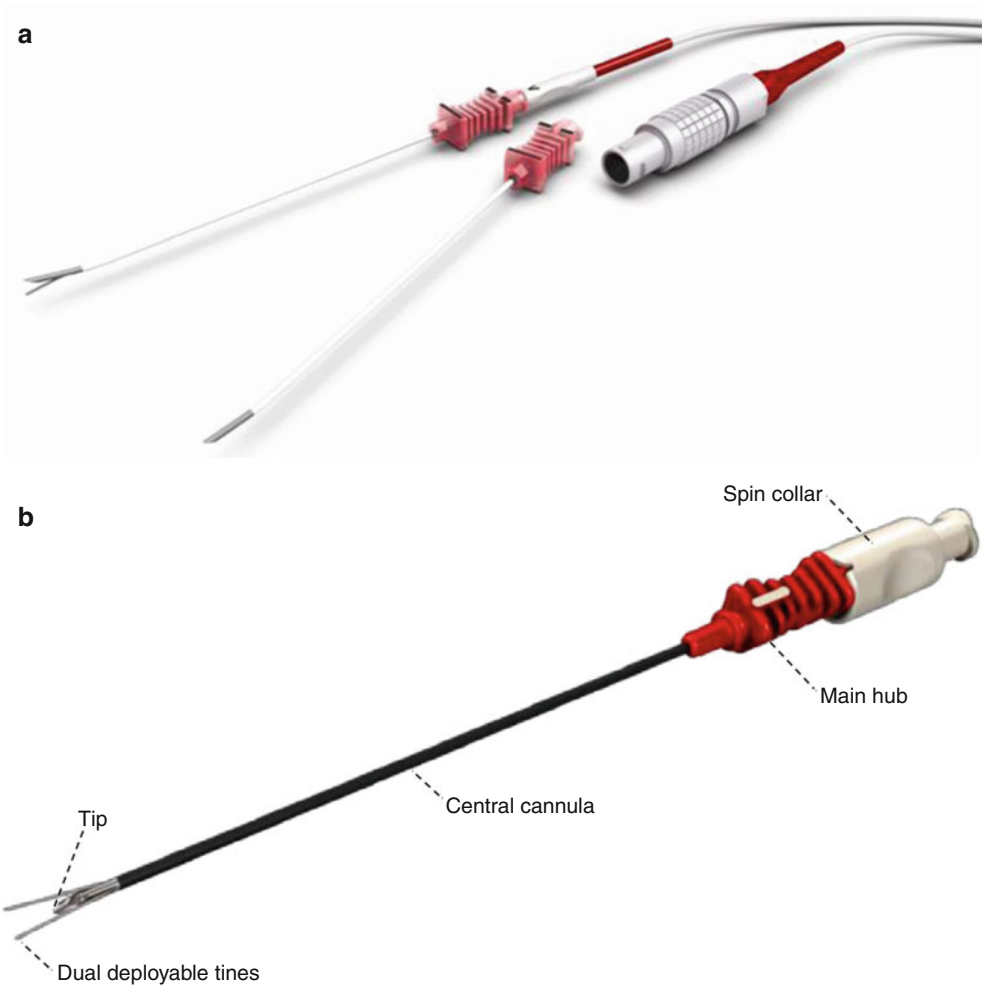


Fig. 3.11 (**a**) Stryker Venom needle (Courtesy of Stryker Interventional Spine: Kalamazoo, MI). (**b**) Nimbus Needle (Courtesy of Nimbus Concepts, LLC: Denver, CO)

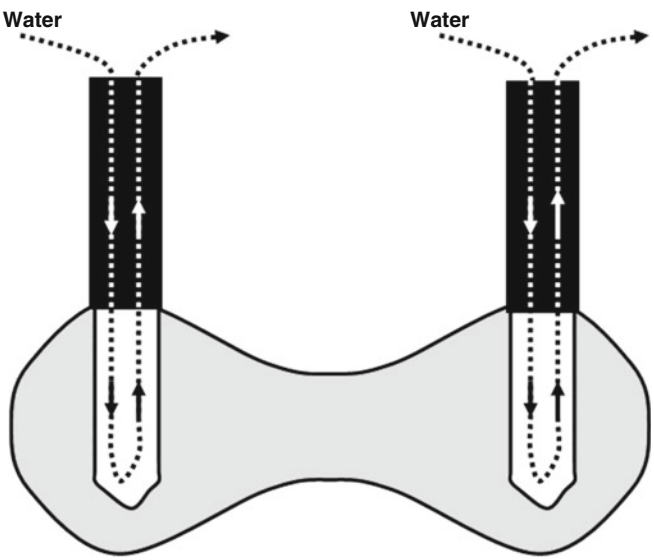


Fig. 3.12 A coronal section of a cooled RF lesion. The RF probes are actively cooled by passing water through them. In this illustration, each probe produces a lesion, but the area of coagulation is elongated and creates a continuous bow-tie or dumbbell-shaped lesion incorporating both probes and the intervening tissue (From Bogduk [35])

Even though pulsed RF creates a small lesion around the active tip, that alone cannot completely account for the clinical effects observed. Unfortunately, though, no single theory fully explains the observed effects. Current belief is that the electric field is responsible for the clinical effect, despite evidence of a mild ablative effect. Pulsed RF appears to produce its effect proximal to the point where energy is applied, rather than producing local effects surrounding the electrode, as with continuous RF. Indeed, changes within the central nervous system have been observed in response to pulsed RF energy.

When the operator applies pulsed RF energy to the dorsal root ganglion (DRG), changes in gene expression within the dorsal horn of the spinal cord occur. The rapidly alternating current activates a protein called C-Fos, which alters pain transmission. On a cellular level, animal studies have shown that exposure of the dorsal root ganglion to pulsed RF current causes both early and late bilateral induction of the protein C-Fos in layers 1 and 2 of the dorsal horn. These effects seem to occur as a result of current fluctuations, rather than tissue heating, as they are not temperature dependent [3, 4, 26, 33, 55, 61, 62, 65, 66, 68, 73]. Other proteins are also produced in response to pulsed RF current, though it remains unclear whether any of these changes are responsible for the observed therapeutic effect [65, 66]. In addition, it is believed that strong electrical fields alter the nerve cell membranes, so as to affect nerve transmission. This theory is supported by evidence showing that pulsed RF induces changes in synaptic transmission and causes electroporation [66, 68].

The use of the pulsed mode in clinical practice has been slow to gain wide spread acceptance. This may be due to the paucity of evidence showing a clear therapeutic advantage over placebo during the early years of its use. However, over the past 5 years, there have been several studies that demonstrate an advantage over placebo. Pulsed radiofrequency lesioning is traditionally considered safer than continuous RF because there have been no reports of neurological side effects. However, the author has direct knowledge of a case in which vocal cord paralysis lasting approximately 6 months was induced by a brief delivery of pulsed RF current during a C3 DRG procedure. This suggests that pulsed mode RF may indeed cause temporary nerve damage and supports the contention that pulsed RF does in fact produce a lesion. However, for the majority of cases, pulsed RF current delivery is a safe method of creating nervous system lesions as there are no similar published case reports.

Still, the role of pulsed RF in clinical practice has been an issue of debate. Some have argued that it is unnecessary because of the availability of continuous RF, which appears to be effective according to well-designed studies. This argument, while true for treatment of medial branches, is not relevant when considering the use of RF current for the treatment of radiculopathies and painful peripheral neuropathies. For both of these chronic and painful conditions, there is currently little to offer these patients. Pulsed RF of the dorsal root ganglion in cervical radicular pain and pulsed RF of the suprascapular nerve in chronic shoulder pain have been demonstrated efficacious in RCTs [64, 74, 75]. When one considers the benign nature of this treatment and its possibility of real relief, there is little reason not to offer it as a therapeutic option. It would appear that the best use for this modality is in the treatment of these two conditions.

Clinical Applications

Lumbar Medial Branch Radiofrequency

Background

The facet joint was first characterized as a source of pain as early as 1911, and in 1933 Ghormley coined the term facet syndrome [76–78]. Rees was the first to suggest a treatment almost 40 years later [77, 79]. He used a special scalpel to make longitudinal incisions through the back muscles hoping to sever what he thought were the articular branches of the nerves. The procedure as proposed was later proved invalid by anatomic studies showing the correct location of the articular branches [16, 77, 80]. The nerves were not located where he depicted them, were too deep to be cut by a scalpel, and ran longitudinally rather than transversely. Shealy was the first to attempt what became known as facet denervation by using radiofrequency electrodes [15, 77, 81]. Unfortunately, his novel idea ultimately failed as it exceeded the current knowledge of the ideal method to denervate the joints—no nerves were located where Shealy described placing his electrodes. Finally Bogduk elucidated an accurate description of the anatomy, and he devised a technique for denervating the facet joints by placing electrodes against the medial branch of the dorsal ramus (rather than the articular branches which are less accessible) [16].

Initially the procedure consisted of placing electrodes perpendicular to the medial branches in order to coagulate them; however, this resulted in only short-term relief [30, 82]. To better understand the area of coagulation surrounding the active tip of a RF electrode, investigators performed RF lesions in experimental media [30]. They found that larger size electrodes created a larger area of coagulation and that the largest area of coagulation was around the long axis of the electrode with very little heat extending distal to the tip [30, 53]. These facts suggested that electrodes should be oriented parallel rather than perpendicular to the nerve in order to coagulate that longest segment of nerve. In addition, to account for minor variations in the location of the nerves, they recommended larger gauge electrodes (16–18 g) and multiple lesions [2, 82, 83]. Finally, an anatomic study by Lau recommended a technique to better align electrodes to lie parallel to the targeted nerve in order to achieve maxi-

mum contact along the length of nerve [83]. All of these recommendations were incorporated into guidelines produced by the International Spinal Intervention Society [2]. A summary of their recommendations includes the following:

1. Electrodes should be placed parallel to the targeted nerve in order to coagulate the longest segment of nerve.
2. Using standard 18 or 20 gauge electrodes, at least two lesions should be made, one electrode width, apart in order to insure that the nerve is incorporated within the area of coagulation.
3. Lesions could be made based on accurate anatomic placement alone without the need to verify electrode placement with sensory stimulation.
4. Lesion times of 90 s at 85 °C produced a large volume of coagulation without risking boiling of tissues.

Anatomy (Fig. 3.13)

The medial branches in the lumbar spine are located at the base of the SAP at their respective vertebral levels. The target is not only at the junction of the SAP and TP as originally described but also slightly up the wall of the SAP at its neck (these points are about 1–2 needle widths apart) [83].

The nerves curve around the lateral aspect of the neck of the SAP and then give off articular branches to the z-joints at the level of origin and the level below it. The nerves at the L1–L4 levels are consistently located as a result of two anatomic features. First, the nerve passes through a small foramen in the posterior leaflet of the intertransverse ligament just superior to the transverse process/superior articular process junction. It then runs along the lateral aspect of the neck of the SAP in what is often described as the groove. Second, the nerve passes deep to the mamillo-accessory ligament (MAL) [16, 84]. These ligaments fix the nerve in place allowing correct anatomic positioning of an RF electrode to consistently locate and ablate the nerve [2]. The L1–L4 medial branch nerves are only accessible for coagulation for a limited length. Lesions made too distal fail to coagulate the nerve as it lies underneath the mamillo-accessory ligament (a thick fibrous band of tissue that protects the nerves from coagulation), while lesions made too proximal risk coagulation of the dorsal ramus [85]. The nerve targeted for coagulation at the L5 level is the dorsal ramus and is longer than the medial branch nerves. It follows a rostral course from the sacral ala [84].

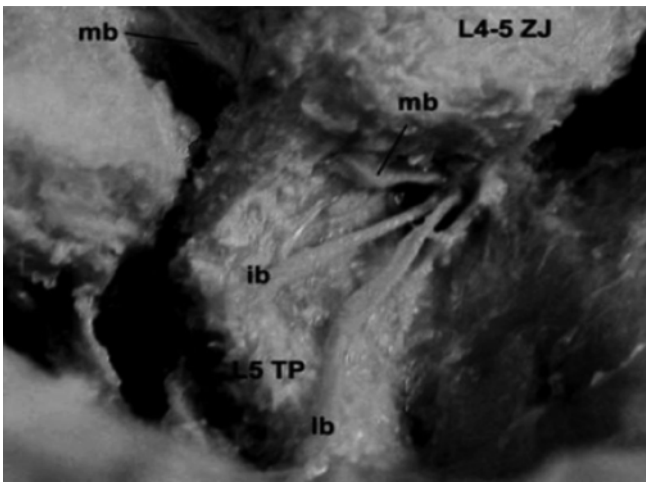


Fig. 3.13 The position of the medial branches and the mamillo-accessory ligament. *Mb* medial branch, *Ib* intermediate branch, *L5 TP* lumbar 5th vertebra transverse process, *L45 ZJ* lumbar 4-5 zygohypophaseal joint (From Lau et al. [83])

The medial nerve branches that innervate the facet joint must be anesthetized in order to anesthetize a given facet joint. In order to do this, the operator must locate the nerves, which can be confusing due to the numbering. The vertebral segment and numbering of the medial branch do not coincide. Two medial branches innervate each facet or z-joint, one from the vertebral level of origin and one from the vertebral level above. For example, the L5–S1 level is innervated by a branch arising from the L4 and L5 vertebral levels; the L4–L5 joint is innervated by medial branches from the L3 and L4 levels.

Patient Selection

Patients with facet joint pain commonly present with a deep, aching sensation in the low back that refers in a non-dermatomal pattern to the buttocks, the posterior or anterior thigh above the knee, the groin, and the hip. Older patients may report insidious onset, while younger patients more often report that the pain followed some type of trauma. Both groups often report morning stiffness. The diagnosis is more common in patients older than 65 years and cannot be made solely on the basis of history, physical examination, or laboratory studies, such as x-ray. On physical examination, there may be focal tenderness over the facet joints, and extension or lateral side bending may increase the pain [2, 6, 7, 86–88]. Patients with only facet joint pain will have a normal neurological examination. Imaging studies may show a normal-looking facet joint; however, some patients show degenerative changes of the discs and facet hypertrophy [2, 6, 87, 88].

There are no specific physical exam findings that are pathognomonic for lumbar facet arthropathy. Pain referral patterns from the lumbar facet joints overlap with those of other lumbar structures. Correlation between CT and MRI evidence of facet arthropathy and response to lumbar facet injection or medial branch block is poor [2, 5, 89–91]. Persistent pain following vertebral compression fractures may be posterior element in origin. Vertebral body fractures create biomechanical pain due to compromise of the biomechanics in the affected area. Both anterior wedge fractures and vertical compression fractures change the articulation of the adjacent facet joints. With an anterior wedge fracture, the super-adjacent joint is affected. In the case of a vertical fracture, it is the sub-adjacent joint. Diagnostic medial

branch block should be considered in patients with continued pain following vertebral compression fracture (Fig. 3.14) [92, 93].

Mechanical pain should be distinguished from radicular pain. Lower extremity pain associated with a mechanical cause is never independent of back pain—it is only severe when the back pain is severe. Radicular pain travels in a narrow band in the affected extremity. The pain is typically described as shooting or lancinating in nature, rather than dull or aching. It has both a deep and superficial quality, i.e., the patient feels both a deep and cutaneous sensation in the affected extremity. It is more often felt below rather than above the knee [94]. When attempting to distinguish these two causes for pain, it is helpful to quantify the percentage of pain in the back versus the lower extremity. Of the pain in the lower extremity, one must distinguish between the percentages of pain above the knee versus below it.

There is no direct correlation between response to medial branch block and clinical findings, which complicates diagnosis [89, 90, 95, 96]. A correctly performed series of two medial branch blocks determines the outcome of a radiofrequency procedure. The procedure involves quantifying the amount of pain relief reported by a patient after placing a small amount (0.3 cc) of local anesthetic on the targeted nerves [2, 82]. If the patient reports greater than 70–80 % relief after each of two medial branch procedures and the pain is solely emanating from the facet joint, a radiofrequency procedure is indicated. However, because there may be more than one cause of back pain in a given patient, some investigators have suggested that greater than 50 % pain relief is an adequate criterion [97–99]. Others have suggested that complete pain relief in a distinct topographical area is adequate to constitute a positive response [2]. Diagnoses based on single medial branch block are not considered valid due to the high false-positive response rate, up to 40 %; diagnoses based on a single medial branch block are considered invalid [2]. The target specificity of the medial branch procedure has been established by Dreyfuss, who showed that, with properly placed needles, injected contrast dye incorporated the medial branch nerves without spread to

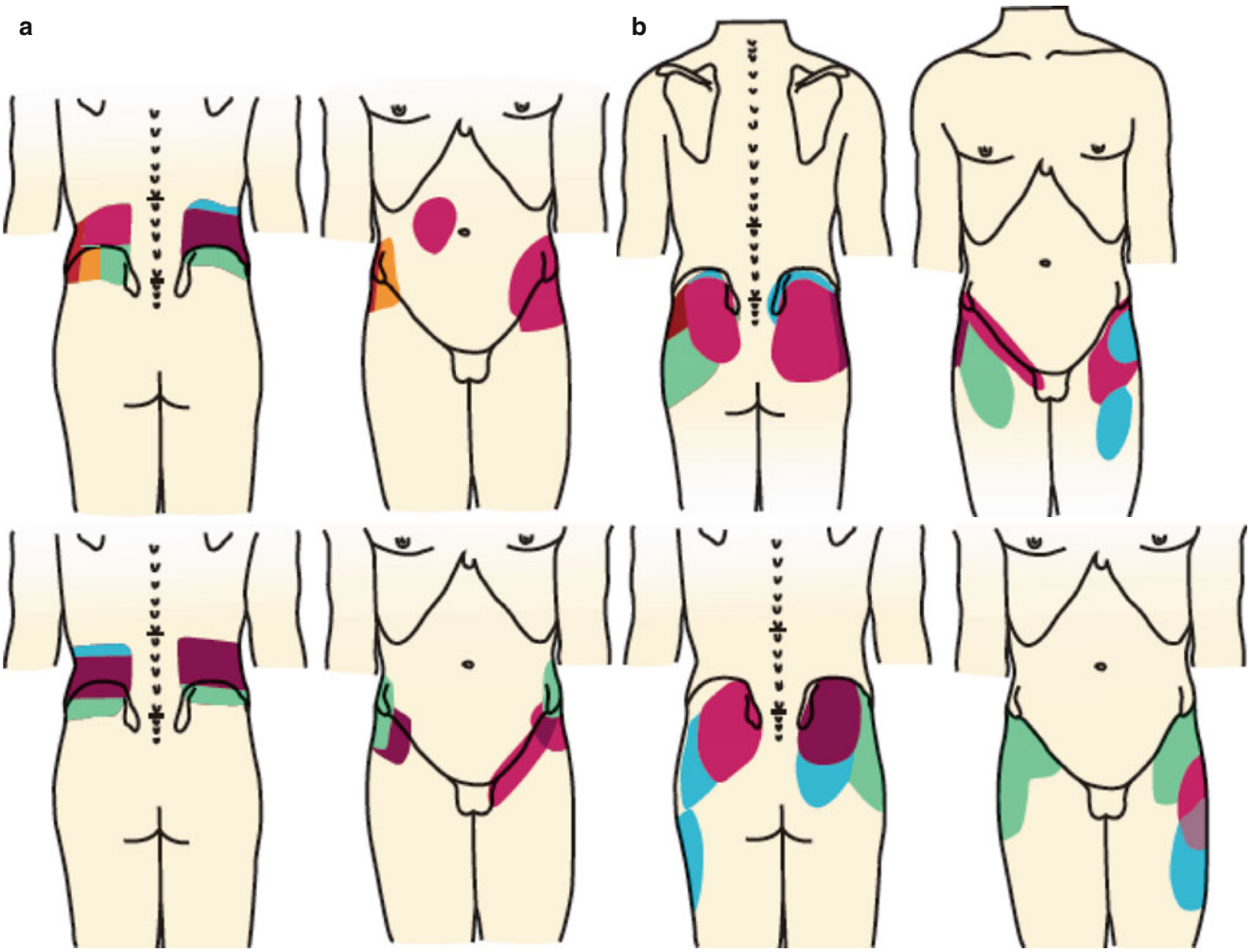


Fig. 3.14 Lumbar zygapophyseal joint (z-joint) referral maps. (**a**) Upper lumbar level referred pain pattern, (**b**) lower lumbar referred pain pattern

the adjacent spinal nerve [100]. The blocks have also been shown to have both face validity and construct validity and are therefore predictive of a positive outcome for a properly performed radiofrequency procedure. There is significant discussion as to the proper diagnostic workup. The necessity of a second, confirmatory block has been questioned. Four of the RCTs evaluating lumbar medial branch RF ablation used single blocks as the diagnostic tool. Cohen has suggested that proceeding to RF denervation without any diagnostic blockade may be the most cost-effective paradigm. The cost per successful treatment was significantly lower in the 0-block paradigm as opposed to the single- or double-block paradigm based upon Medicare reimbursement payments at the time of his study. Denervation success was 33 % in the 0-block group and 39 % and 64 % in the 1- and 2-block groups, respectively [101]. Derby found that a more stringent requirement of 70 % or greater relief from the medial branch block prior to RF ablation resulted in the lowest cost per patient. Similar to Cohen, he found an increased success rate of RFA in the two-block protocol by excluding false-positive responders [102]. But unlike Cohen, he found that the double-block protocol resulted in the lowest total cost. The false-positive rate decreases with a second block; however, the false-negative rate increases, increasing the risk of withholding an effective treatment from patients [103]. Derby has suggested consideration of a confirmatory block in patients reporting 50–69 % relief after the first injection as he found these patients to have a false-negative rate of up to 47 % [104].

Indications

Indications for this procedure are pain that has persisted for more than 3 months and has not responded to conservative therapy. Additionally, the patient must not be abusing analgesics. The patient must have responded positively on two separate occasions to medial branch blocks with 70–80 % relief; though, as noted above some suggest that only 50 % is necessary [2, 97–99].

Procedure

The patient is placed prone on the fluoroscopy table, and the back is sterilely prepped and draped in sterile fashion. Generally, intravenous or oral sedation is administered. The amount of sedation utilized is variable, from none to deep sedation with propofol. This is based upon patient and physician preference. If the patient is awake enough to communicate during the procedure, he or she can report any discomfort felt. An electrode misplaced onto the spinal nerve can cause coagulation of the major motor and sensory nerve to the lower extremity. A deeply sedated patient may not be able to provide feedback to the physician during lesioning.

The target for the L1–L4 medial branches can be found distal to the dorsal ramus, but proximal to the mamillo-accessory ligament (MAL). The classically described location of the nerve is at the junction of the superior articular process (SAP) and the transverse process, though the nerve is sometimes located at the lateral surface of the neck of the SAP [83].

A lesion is made to the dorsal ramus, instead of the medial branch, at the L5 level. It is located at the junction of the S1 SAP and the sacral ala, and not slightly up the wall of the SAP, as at the L1–L4 levels. Recommendations from Lau et al. have altered how the procedure is performed. First, they recommended that multiple parallel lesions be made one needle width apart (the first at the base of the SAP and the second slightly "up the wall"), to account for the variable topography of the nerve. Second, they recommended that the practitioner use larger gauge needles (i.e., 16 or 18 g). Third, they recommended that the electrode be inserted from an oblique, cephalocaudad trajectory, in order to lie parallel to the nerve. This has been referred to as a pillar view. The trajectory maximizes the length of the active tip that is in contact with the nerve and places the electrode parallel to the nerve, which has been shown to increase the duration of effect [30, 53, 82]. Finally, they recommended that needle placements be assessed in multiple views. In a "pillar" view, the target area is located against the lateral neck of the SAP. In an AP view, the needle should be well applied to the SAP. However, for the L1–L4 levels, the needle must be passed at an angle from the sagittal plane in order to avoid the tip of the electrode being deflected laterally by the MAL. In a lateral view, the middle two-quarters ($^2/_4$–$^3/_4$) of the SAP are targeted. For the L5 dorsal ramus, the target zone is the middle and posterior one-third of the neck of the SAP at S1.

To obtain a pillar view, visualize the disc space at the targeted level in an anterior-posterior (AP) view. Then, rotate the image intensifier obliquely approximately 30° to the ipsilateral side or until the SAP is projected a generous one-third of the way across the image of the vertebral body. Next, place a pointer approximately one vertebral level below the targeted nerve. Decline the image caudally, approximately 30°, until the pointer is projected directly over the SAP at the targeted nerve level. Finally, make any small adjustments both obliquely and cephalocaudally, until the lateral cortical margin of the SAP is clearly defined [83]. In this view, the nerve lies against the lateral aspect of the SAP. As an example, to target the L3 medial branch, the superior endplate of L4 is squared in order to open the disc space between the L3 and L4 vertebral bodies. The C-arm is then rotated obliquely as described above. A pointer is placed over the SAP of L4 (which is the level below the targeted level), and the C-arm is moved caudally until the image of the groove between the SAP and transverse process (TP) at the L3 level comes into view overlaying the pointer. Then, final adjustments are made until the lateral margin of the L3 SAP is "crisp." The

needle is passed "down the beam," until the base of the SAP is contacted at its lateral margin. The needle is then viewed in an additional three views (AP, steep oblique, and lateral), and small adjustments are made in each view. In the AP view, the needle should be seen resting tightly against the SAP and above the TP. In a steep oblique view (at least 45°), the needle should be seen across the "ear" of the Scotty dog, with the tip resting at the leading edge of the SAP. In the lateral view, the needle should cover the middle two-fourths of the SAP at the L1–L4 levels, while at the L5 level, it should cover the middle and posterior one-third of the SAP. It should also be resting on the TP, which is located posterior to the inferior aspect of the foramen. If the needle is seen above the TP (above the inferior aspect of the foramen), it is too high (cephalad) and should be adjusted inferiorly. The needle should never be located anterior to the posterior aspect of the vertebral foramen when viewed in a lateral view. The needle is too posterior if it lies posterior to the image of the SAP. In this position, the nerve lies under the mamillo-accessory ligament and is not accessible for coagulation. If the needle is seen to be anterior to the posterior aspect of the foramen, it is too ventral and the neural foramen can be inadvertently entered.

Once the needle position is established, it is wise to check the electrical impedance to assure the overall integrity of the RF system [6]. Traditionally, location of the targeted nerves is based on radiographic landmarks, as well as sensory and motor stimulation. There are, however, no comparative studies documenting the benefit of sensory stimulation over radiographic landmarks alone to determine optimal needle placement.

Motor stimulation at 1.0 V can be used to confirm needle placement posterior to the dorsal root ganglion. Multifidus muscle contraction may be noted during this procedure and is consider normal [6]. Sensory and even motor stimulation are no longer considered necessary according to the ISIS guidelines for the following reasons [2]:

1. Dreyfuss et al. showed that sensory stimulation thresholds did not correlate with improved outcome. They found that correct anatomical placement of the electrode produced reliable nerve coagulation [105].
2. Evoked sensations may be falsely positive.
3. Electrical stimulation may cause an evoked sensation, but not necessarily close enough to coagulate the nerve.
4. Rigorous sensory testing requires testing at three different locations: at the location where the lowest sensory threshold is obtained, at a location both cephalad and caudad to the first location showing higher sensory thresholds, and at each location compared to the original location. The ISIS guidelines argue that just as many electrode placements are required in making subsequent lesions after making the initial lesion. Thus, radiographic landmarks are the primary tool to localize final needle position prior to lesioning.

After confirmation of correct placement with fluoroscopy and motor stimulation, 1 mL of 2 % lidocaine is injected through each of the cannulas and 30–60 s are allowed to pass while waiting for production of anesthesia. Then, the generator is turned on in the automatic mode, and lesions are created at a temperature of 85 °C applied for 60–90 s. After completion of the first lesion, a second lesion is performed one needle width cephalad to the first lesion, slightly up the wall of the SAP. The position of the second lesion is established in the same pillar view used for the initial placement of the needle (Fig. 3.15a–f).

These needle positions described above apply only to the lumbar medial branches from L1 to L4. At the L5 level, the anatomy is slightly different, in that the L5 dorsal ramus is much longer and more easily accessible than at typical lumbar levels. Therefore, at the L5 level, the dorsal ramus, and not the medial branch, is lesioned. It runs along a groove formed between the ala of the sacrum and the base of the S1 SAP. The area exposed for lesioning is much longer than that of a typical medial branch; therefore, once the first lesion is completed, the needle is repositioned caudally for a second lesion (rather than "up the wall" of the SAP). This allows a longer length of nerve to be coagulated, thus increasing the period of time before nerve regrowth (Fig. 3.16a–d-flouro images of L5 dorsal ramus RF).

In the lumbar spine, patients who fail to obtain relief after medial branch RF lesioning can be assessed by segmental multifidi electromyography (EMG) to evaluate the technical success of the procedure [105]. For patients who obtain good relief, but in whom the pain recurs, the effects of the procedure can be successfully reinstated 85 % of the time [106].

Postprocedure Advice

The patient should be advised that it could take up to 3 or 4 weeks before the full effect of the procedure is experienced. During the first week following the procedure, the patient should treat any increased pain with analgesics. During subsequent weeks, the physician may refer the patient to physical therapy for a deep muscle relaxation technique, such as deep tissue massage or "augmented soft tissue manipulation" (ASTYM), which should relieve any muscle tightness or trigger points that may have been caused by chronic inflammation associated with the facet joint syndrome. Physical therapy also facilitates healing of any small, procedure-related hematoma.

Complications

The expected procedure-related side effects from this procedure are minor and self-limited. In a patient rendered unconscious from general anesthesia or intravenous sedation, needle placement that is inadvertently too close to the spinal nerves could result in severe injury and even permanent motor and sensory deficits. The ISIS guidelines report just such a case, in which a patient under general anesthesia had

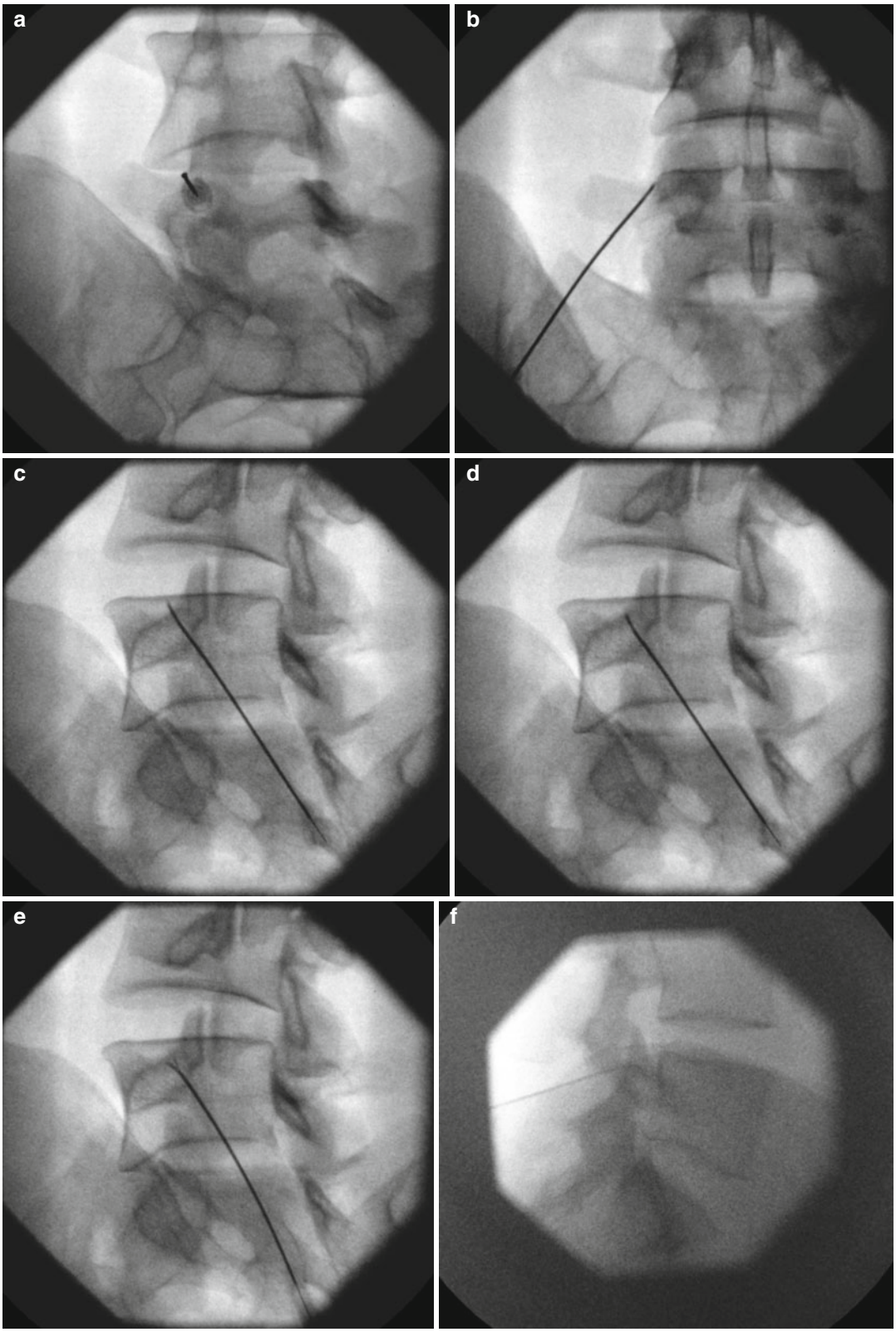


Fig. 3.15 (**a**–**f**) Fluoroscopic images of medial branch (MB) radiofrequency lesioning at the L4 level (Courtesy of Aaron Calodney). (**a**) Pillar view showing correct placement at the L4 medial branch. (**b**) Anterior-posterior view of correct needle position. The needle is coming from below-up and from lateral to medial. The tip is over the transverse process and inside the lateral silhouette of the superior articular process (SAP). (**c**) Steep oblique view showing improper tip location beyond the leading edge of the SAP putting the intermediate and lateral branches and the contents of the neuroforamen at risk. (**d**) Steep oblique view with proper tip location at the leading edge of the SAP. (**e**) Steep oblique showing Stryker Venom probe with tine deployed to create large radiofrequency lesion. (**f**) Lateral view showing needle with proper trajectory and placement. The needle is coming from below-up. It is crossing the lateral aspect of the neck of the SAP with the active tip covering the middle third of the SAP

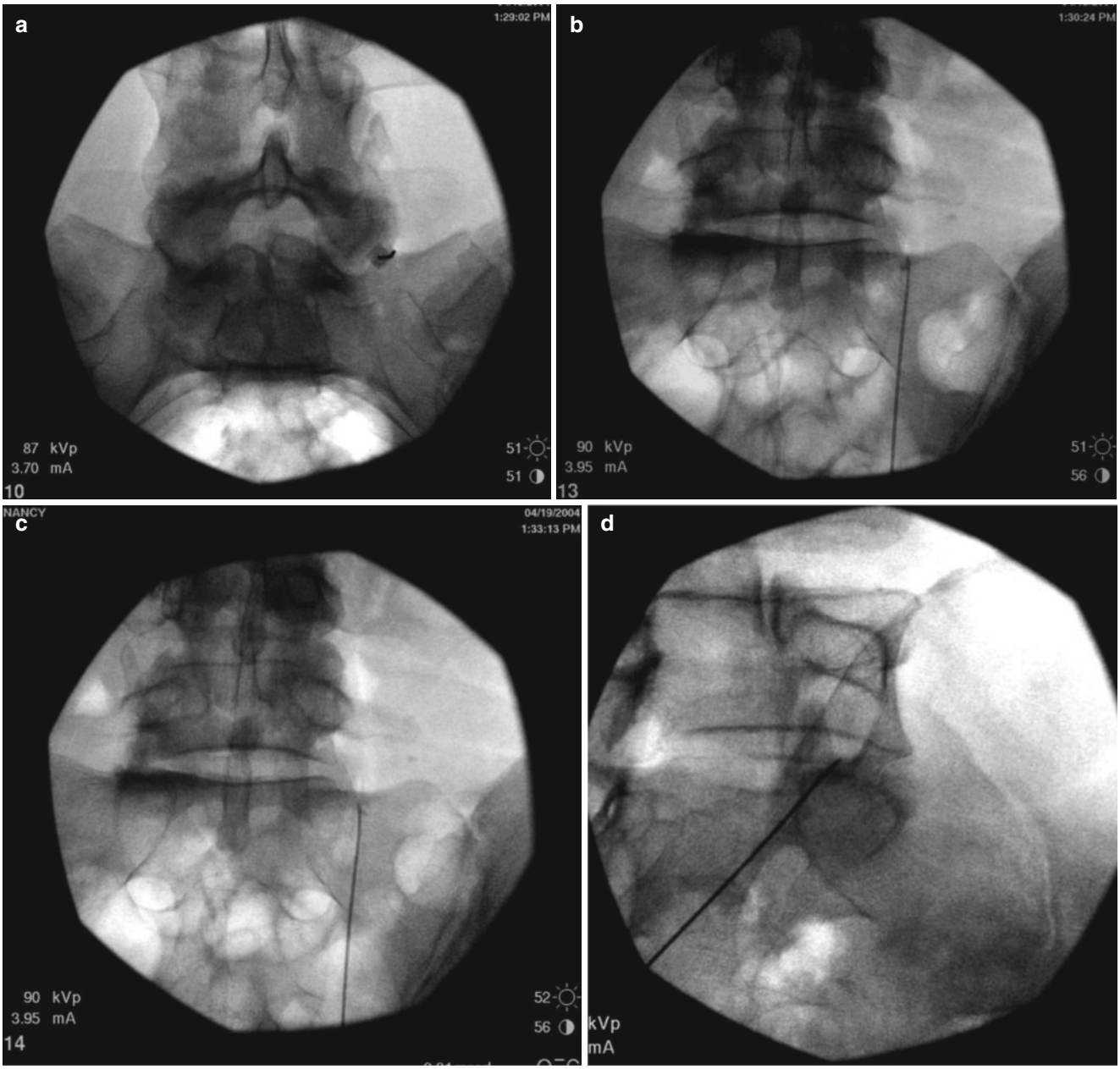


Fig. 3.16 (**a**–**d**) Lumbar L5 dorsal ramus RF. (**a**) L5, pillar view (Courtesy Paul Dreyfuss). (**b**) L5, AP view, lesion point one (Courtesy Paul Dreyfuss). (**c**) L5, AP view, lesion point two (Courtesy Paul Dreyfuss). (**d**) L5, steep oblique view (Courtesy Paul Dreyfuss)

the ventral ramus of the spinal nerve coagulated during the procedure. The ISIS guidelines also describe a case in which a patient suffered full thickness burns when a spinal needle was used to ground the patient instead of the usual dispersive grounding electrode.

Additionally, some patients may experience back pain that usually resolves within 1–2 weeks and neuritic pain lasting less than 2 weeks. In a review of 92 patients who received 616 lesions, neither complication had an incidence higher than 0.5 %. There were no cases of infection or new motor or sensory deficits reported [107].

Efficacy

Bogduk, Dreyfuss, and Govind have written an excellent review on the lumbar medial branch neurotomy procedure [82]. In that review, they point out that to evaluate the outcome of any procedure, one must first assess if the procedure was performed properly. This would mean that the procedure was performed in a manner expected to produce the desired result. They then state that three of the six randomized controlled trials performed to date should not be consider as evidence based on improper patient selection (patients not selected based on positive response to two correctly per-

formed medial branch blocks) or improper surgical technique (electrodes not correctly aligned parallel to nerve). While the remaining three were suboptimal in terms of proper anatomic technique or patient selection, they all showed positive results when compared with placebo. An additional three published descriptive studies that utilized proper patient selection and anatomic technique all showed positive outcomes, as well. The authors feel that when these results are examined together, they present strong evidence supporting efficacy of the procedure. The table below summarizes the results of the best studies performed to date (Table 3.2).

Five additional randomized controlled trials (Gallagher et al. [155]; van Kleef et al. [109]; Leclaire et al. [156]; van Wijk et al. [25]; Tekin et al. [32]) had significant methodological problems and were excluded from the table. More specifically, the studies were flawed as a result of improperly selected patients based on the results of two medial branch blocks or appropriate positioning of the electrodes to fully lesion the medial branch nerves.

Lumbar DRG Procedure

Background

Uematsu first attempted at dorsal root ganglion lesioning for the treatment of radicular pain resulted by heating the DRG using a large 14-g cannula. As expected, it caused damage to the pain fibers. It additionally damaged the sensory and motor fibers, which resulted in near destruction of the spinal nerve. The procedure was quickly abandoned. In 1980 Sluijter developed small electrodes that could fit inside of a 22-g needle, and dorsal root ganglion lesioning was reintroduced [3]. This permitted both smaller lesion size and less pain during the procedure. At that time, the recommended tip temperature for treatment of the DRG was 67 °C. The lower temperatures prevented the complications associated with the Uematsu procedure and resulted in smaller lesions [13]. However, many patients still developed complication including neuroma formation, allodynia, and dysesthesias as a result of heating the DRG [58]. Geurts et al. studied the heat procedure in a double-blind randomized controlled trial [113]. He concluded that "lumbosacral radiofrequency lesioning of the dorsal root ganglion failed to show advantage over treatment with local anesthetics." Thus, its use in treatment of radicular pain was not recommended.

In 1998, pulsed mode radiofrequency, which allows for the delivery of high-frequency electric current without the development of heat, was introduced. Due to this lack of heat, pulsed RF had the potential for therapeutic efficacy without the potential of nerve damage from the heating of the dorsal root ganglion. In clinical studies to date, the pulsed treatment of the dorsal root ganglion has shown increasing evidence of efficacy. For these reasons, only pulsed RF treatment of the DRG will be presented here.

Anatomy

There are five paired nerves that exit their respective intervertebral foramina from L1–L2 to the L5–S1 levels. Just as the orientation of the lumbar zygapophyseal joint differs from L1–L2 to L5–S1, the lumbar nerves exit their respective foramina at different angles from L1 through L5. At

Table 3.2 Radiofrequency of the lumbar medial branch

Author	Study design	*N*	Efficacy
Randomized controlled trial			
Tekin et al. (2007) [32]	Randomized controlled trial	60	Effect of RF maintained at 6 months and 1 year. Only 40 % of patients using analgesics at 1 year follow-up
Nath et al. (2008) [108]	Randomized controlled trial	40	Patients in the treatment group and significant short-term improvements in pain and quality of life
van Kleef et al. (1999) [109]	Randomized controlled trial	31	At 6 and 12 months post treatment, there were significantly more successful outcomes in the RF group compared to the placebo group
Prospective uncontrolled trials			
Dreyfus et al. (2000) [105]	Prospective audit	15	12 months post procedure, 60 % of patients experienced 90 % relief of pain; 87 % had at least 60 % relief
Gofeld et al. (2007) [110]	Prospective audit	174	68.4 % had good to excellent pain relief lasting from 6 to 24 months
Burnham et al. (2009) [111]	Prospective cohort	44	Patients reported significant improvements in pain, disability, analgesic requirement, and satisfaction. These effects peaked at 6 months post procedure
MacVicar et al. (2013) [112]	Prospective audit	106	58 and 53 % of patients in two practices reported complete pain relief for 15 months from the first RF and 13 months for repeat treatments

RF radiofrequency

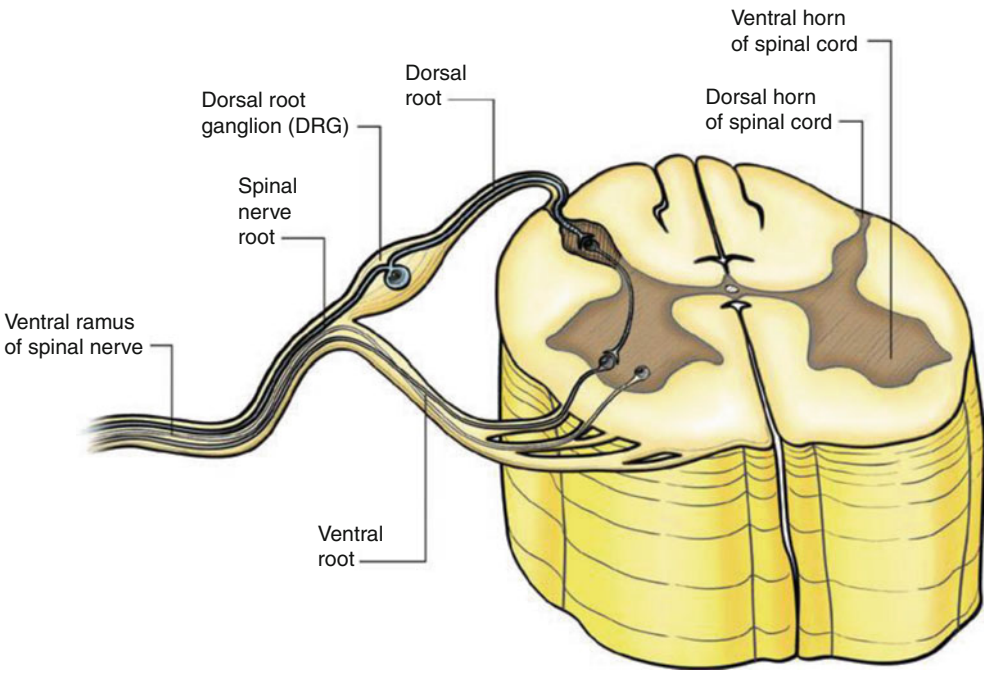


Fig. 3.17 Cross-sectional anatomy of spinal cord (From Mathis and Golovac [115])

L1, the nerves exit downward and forward at an acute angle, whereas at L5, the nerves exit more horizontally and at a more obtuse angle [3, 63, 94]. This has important corollaries for positioning of the fluoroscope. For example, imaging the L5–S1 foramen requires a great deal more obliquity than when imaging the L1–L2 foramen. In addition, the C-arm must be tiled in a caudad direction to square the endplate at L1, while in a cephalad direction for L5. The lumbar ventral roots find their cell bodies of origin within the spinal cord at the T9–T11 vertebral level [114]. Rootlets come off the dorsal and ventral surface of the spinal cord to form the dorsal and ventral roots. The dorsal and ventral roots then join to form the spinal nerve root. The dorsal root ganglion contains cell bodies that provide sensation, proprioception, and pain [63].

The spinal nerve root immediately divides to form the dorsal and ventral rami. The ventral ramus is the larger branch and travels to the lower extremity. The dorsal ramus divides into three branches; medial, lateral, and intermediate. The lateral and intermediate branches supply sensation and motor function to the skin and muscles of the back, while the medial branch provides sensation to the z-joint and motor function to the multifidi muscles (Fig. 3.17) [16].

Indications

Neuropathic pain that is confined to the distribution of a known nerve is the general indication for PRF [3, 58, 61, 68]. The specific indication for pulsed radiofrequency treatment of the dorsal root ganglion is radicular pain or radiculopathy that is completely but temporarily relieved by transforaminal injection of local anesthetic done on two separate occasions. To identify the location of the origin of the pain and confirm the nerve levels involved, local anesthetic injections are done diagnostically. The procedure has been used for both acute and chronic radicular pain and radiculopathy [3–5, 40, 41, 61, 64, 66–68, 116–119].

Procedure

Figure 3.18a–c

Introduction

Extremely careful and precise placement of the electrode is required for pulsed radiofrequency lesioning (PRF) of the dorsal root ganglion (DRG). The pain practitioner should have soft hands and hone excellent needle handling skills before attempting this procedure. This discussion will be limited to the PRF procedure in the lumbar spine, since continuous RF current applied to the DRG was found to be no more effective than control treatment with local anesthetics [113]. However, PRF of the DRG is possible at all spinal levels.

The retroneural approach is the best method of needle placement to reach the DRG, as described in the ISIS guidelines presented in the chapter on lumbar spinal nerve block [2]. The target lies at the intersection of two lines in this approach. In a lateral view, the first line runs longitudinally between the posterior and anterior half of the foramen, bisecting the foramen into two equal halves. The second line runs in a transverse direction between the superior one-third and the inferior two-thirds of the foramen. The intersection

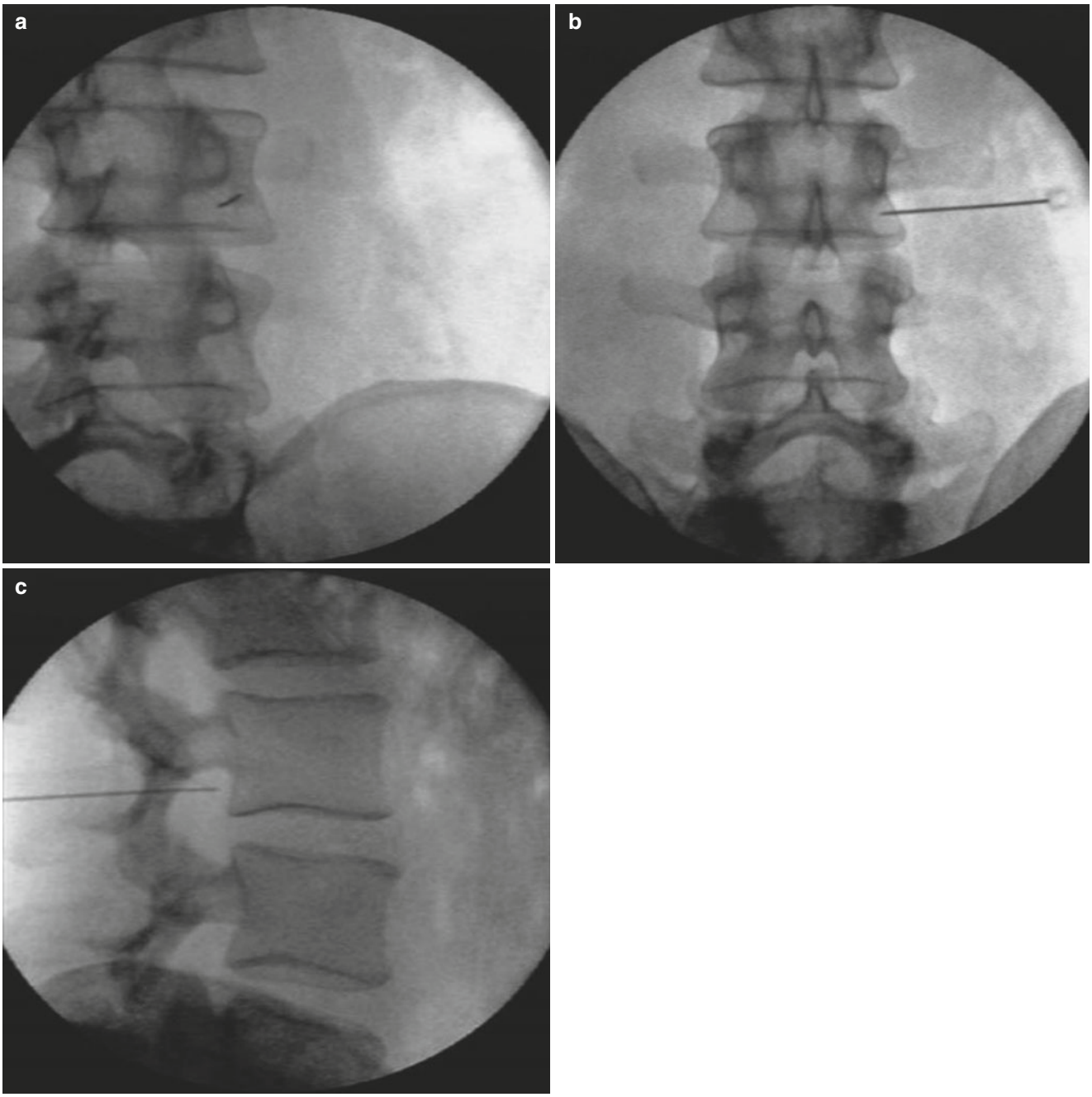


Fig. 3.18 (**a**–**c**) Fluoroscopic images of dorsal root ganglion RF (Courtesy Richard Rosenthal). (**a**) Oblique view. (**b**) AP view. (**c**) Lateral view

serves as a starting point for locating the DRG; however, it can lie anywhere between the mid aspect to the most anterior aspect of the foramen in the anterior-posterior plane.

Target Identification

The electrode must be pointing directly perpendicular and very close to the targeted nerve for PRF to be effective. Similar to that used for a transforaminal procedure, one should obtain an oblique view to identify the target. After squaring the superior endplate at the involved level, rotate the image intensifier into an oblique view until the superior articular process is projected one-third of the distance across the image of the vertebral body (approximately 25°). The starting point for the needle in this view is slightly inferior and lateral to that used for a transforaminal injection. The target lies at a point just beneath the pedicle, one-third of the way down the foramen. As the operator advances the needle, he/she should rotate into an AP projection to assess the depth of insertion. If further insertion is required, rotate back to an oblique view and continue to advance. When the needle tip

approaches the lateral aspect of the vertebral body, it is best to advance further in an AP view. When advancing the needle, be sure to do so very slowly (only 1 mm at a time) in order to avoid damage to the nerve. This can be achieved by pinching the needle shaft at the point of skin entry. When one encounters difficulty in locating the nerve, the needle tip is usually too medial and should be corrected in an oblique view so that the tip is located directly beneath the pedicle on a line that bisects it. Since there is evidence that a small lesion does occur around the electrode tip, it may be unwise to allow the electrode to penetrate neural tissue. Warn patients that they will feel a paresthesia and should not make any sudden movements. Because the greatest current density is projected from the tip of the needle, it is best to point the needle tip directly toward nerve tissue and not against the vertebral body, i.e., the needle tip rather than the shaft should be perpendicular to the targeted nerve. Once a paresthesia is felt, place the electrode into the needle and begin testing. Be very careful when handling the needle at this time, as any movement risks spearing and damaging the nerve.

A modification of the above technique is required to perform the procedure at the S1 nerve level. In the case of the S1 nerve, the procedure is performed at the level of the ventral ramus, rather than directly at the DRG, since the former is located more proximally within the spine. The procedure is performed differently than a typical S1 transforaminal injection. First, adjust the cephalocaudal tilt in a cephalad direction to optimize the view of the foramen. Note that the C-arm should remain in an AP view (rather than in the ipsilateral oblique position recommended for a transforaminal injection). The needle entry site is at the inferior and lateral quadrant of the foramen with the trajectory superior and medial. This follows the course of the nerve. The needle should first touch the posterior shelf of the sacrum before entering the foramen. This gives a sense of depth and provides a warning before the needle enters the foramen. Once inside the foramen, advance the needle very slowly (1 mm at a time) toward the nerve. When contact is established, perform sensory testing and proceed as usual. If you are unable to locate the nerve after three or four attempts, withdraw the needle and find a new starting place. This is necessary due to the limitation in needle adjustments imposed by the foramen (i.e., the foramen confines the needle such that only a limited territory of space can be searched).

Needle Tip and Nerve Proximity

Electrical stimulation tests can be used to determine proximity between the nerve and the needle tip. The patient should feel reproducible stimulation (tingling in the distribution of the stimulated dermatome) at less than 0.2 V with adequate needle placement. Conduct two stimulation tests. The first test should determine the minimum sensory threshold—the lowest voltage at which the patient can still perceive a sensation. The second test is used to time and to determine reproducibility. In this test, slowly increase the voltage by 0.05 V until the patient reports perceiving a stimulus (this should be within 0.05 V of the first stimulation test). If the patient does not feel the current at the required level of less than 0.2 V, advance the needle slightly (no more than 1 mm) or reposition the needle altogether and retest. If the patient feels the current at a level lower than 0.05 V, the needle should be retracted slightly due to possible intraneural placement [5]. Since the modality does not damage motor fibers, there is no need for motor stimulation when performing PRF.

Impedance

Next, the operator should lower the impedance sufficiently to produce a current of 150–200 mA during the procedure. The maximum impedance should be less than 400 Ω and ideally less than 250 Ω. To achieve this, inject a small amount (1 mL) of local anesthetic (1–2 % Xylocaine) or saline through the needle. When injecting fluid through the needle, a practitioner should secure the position by using one hand at the skin to prohibit movement, which could cause a severe pain and possible needle trauma to the nerve. If there is any resistance during injection, stop, retract the needle slightly, and inject again; then replace the needle to its original position. Resistance can indicate the axon bundle, and injection could leave the patient with persistent motor and/or sensory deficits. Liquid should flow easily through a 20-g needle. Prior to treatment, the practitioner should record the minimal stimulation threshold and impedance prior to treatment.

Pulsed Radiofrequency Treatment

At this point, turn on the power in the PRF mode and slowly increase the voltage to 45 V. Verify that the patient feels pulsing. In this author's opinion, the needle must be close enough to the target nerve to produce a perceptible electrical discharge in the treated extremity with each pulse. If the patient does not feel pulsing, this may indicate that the needle is not close enough to the targeted nerve tissue to produce an effect. If this is the case, reposition the needle and begin treatment again. If desired, this step can be performed prior to lesioning the nerve, as it is unlikely that the patient will feel pulsing once the nerve has been anesthetized. No study has demonstrated this step to be necessary; however, it can be another useful test to verify proximity to the targeted neural tissue.

The standard protocol is to proceed with PRF treatment for 3–4 min at 45 V (as long as the temperature does not exceed 42 °C), two pulses per second, with current applied for 20 ms during each pulse. However, an alternative protocol is to increase the voltage as high as necessary to produce a current of at least 150 mA, which may cause additional heating around the needle. If it is necessary to produce the higher current (of at least 150 mA), the temperature can be

allowed to rise as high as 45 °C. Because treatment protocols may vary among operators, consult the literature for other examples of lesion parameters.

Postprocedure Advice

Typically after the completion of the procedure, the patient usually feels immediate relief due to the injection of local anesthetic onto the affected nerve. When the effect wears off, the patient may begin to feel sore. Advise that he/she may continue to feel sore for the first week and better the second week and that the full effect can take 3–4 weeks to develop. The patient does not need to restrict activities during this time, except as needed due to pain. Deep tissue massage once a week for the first 3 weeks following the procedure may relieve soreness due to the procedure, as well as chronic trigger points which may have developed over the course of the disease.

Complications

Vasovagal syncope is the most common risk incurred during any spinal procedure and is eight times more common during a cervical procedure than a lumbar procedure (8 % vs. 1 %) [120, 121]. Other risks include transient non-positional headache, increased back pain, facial flushing (if steroids are used), increased leg pain, ischemia of the anterior spinal artery if particulate steroid is injected, infection (epidural abscess, meningitis, discitis), and other complications related to injected medications [4, 122, 123].

Potentially, neural trauma associated with this procedure can occur, but this has not been studied specifically. In the authors' experience, after performance of over 1000 procedures, no incidence of neural trauma has occurred. Certainly, with proper needle handling techniques, the complication should be rare. During injection of local anesthetic to anesthetize the nerve, fluid can be inadvertently injected into the axon bundle, leaving the patient with persistent motor and/or sensory deficits. This complication should never occur in a properly performed procedure and can be detected by resistance to flow of fluid upon injection. If any resistance is encountered during injection, especially if accompanied by pain, stop injecting and retract the needle slightly before continuing. Hematoma may occur just under the skin or in the deeper muscle layers as a result of the procedure. The majority of patients report mild discomfort in the treated extremity that spontaneously resolves within about 3 weeks [124]. All risks have a low incidence of occurrence.

Efficacy

Much research has been done regarding the efficacy of pulsed RF lesioning of the DRL. Martin et al. have proposed that the efficacy of pulsed radiofrequency lesioning of the dorsal root ganglia is directly related to the proximity of the radiofrequency electrode to the targeted neural structure and the amount of delivered current [125]. They recommend using a stimulation voltage between 0.1 and 0.3 V in order to properly position the electrode. They also suggest that higher current delivery (150–200 m amps) improves outcomes.

Additional studies have been done investigating the efficacy of pulsed RF lesioning of dorsal root ganglia by targeting either the lumbar, thoracic, or cervical spine. One was a randomized controlled trial and the majority were prospective uncontrolled trials or retrospective studies. The four prospective uncontrolled trials each concluded that pulsed radiofrequency lesioning of dorsal root ganglia was a safe and effective treatment for pain relief, and each of the five retrospective studies reported similarly positive results. These data are summarized in Table 3.3.

The above studies appear promising; however, most reported only relatively short-term efficacy (typically 3 months) and none included a control group. To date there has been only one double-blind randomized placebo-controlled trial of pulsed radiofrequency lesioning, which studied patients with chronic cervicobrachial pain for 6 months [64]. Twenty-three patients underwent either pulsed radiofrequency lesioning ($n=11$) or received a sham lesion ($n=12$) at the C5–C7 nerve levels. At 3 months, significantly more treatment group patients (83 %) than control group patients (33 %) reported at least 50 % improvement in global perceived effect, an effect that was also maintained at 6 months. Similarly, at 3 months, significantly more treatment group patients (82 %) than control group patients (25 %) reported at least a 20-point decrease in VAS; however, the effect was not maintained. However, this study has been criticized for a few reasons. First, it was fraught with recruitment challenges that limited its statistical power. Additionally, the two study groups were not comparable in terms of baseline VAS scores as well as average age. Finally, the effect was not maintained at 6 months, again showing short-term efficacy. Despite the shortcomings described above, this study is important, because it is the first prospective controlled trial to show a treatment effect.

Examining the preponderance of the evidence presented above, it appears that pulsed RF does indeed have a clinical effect for the treatment of radicular pain. Further research is required to bolster the data presented here and to prove the long-term utility of the procedure. However, it is this author's opinion that there is currently enough evidence to support the use of pulsed radiofrequency lesioning in clinical practice for the treatment of radicular pain.

Cervical Medial Branch Radiofrequency

Background

Lord et al. published the first double-blind randomized placebo-controlled trial. This study illustrated that cervical

Table 3.3 Radiofrequency of the dorsal root ganglia

Study	*N*	Type of pain	Efficacy
Randomized controlled trial			
Van Zundert et al. [64]	23	Cervical radicular	82 % achieved at least 50 % improvement in global perceived effect and at least a 2-point reduction of VAS at 3 months
Prospective uncontrolled trials			
Sluijter et al. (1998) [33]	15	Lumbar radicular	53 % achieved at least a 2-point reduction of VAS at 6 months, and 40 % did so at 1 year
Pevzner et al. (2005) [126]	28	Lumbar radicular cervicobrachial	2 patients had "excellent" pain relief, 12 had "good" pain relief, and 9 had "fair" pain relief at 3 months
Shabat et al. (2006) [124]	28	Spinal neuropathic	82 % achieved at least a 30 % reduction of VAS at 3 months, and 68 % did so at 1 year
Simopoulos (2008) [40]	76	Lumbar radicular	Patients reported an average 4.3-point decrease in pain scores, with a 3.18-month average duration of success
Retrospective studies			
Van Zundert et al. (2003) [43]	18	Cervicobrachial	72 % achieved at least 50 % pain relief at 2 months, 56 % did so at 3–11 months, and 33 % did so for greater than 1 year
Teixeira et al. (2005) [41]	13	Lumbar radicular	92 % achieved at least a 5-point improvement in NRS at 1 year
Cohen et al. (2006) [127]	13	Thoracic segmental	62 % achieved at least a 50 % pain relief at 6 weeks and that 54 % did so at 3 months
Abejón et al. (2007) [116]	54	Herniated disc Spinal stenosis FBSS	40 % of patients with herniated discs ($n=29$) and 40 % of patients with spinal stenosis ($n=12$) achieved "successful treatment" at 180 days post treatment Treatment not as successful in patients with failed back surgery syndrome ($n=13$)
Chao et al. (2008) [42]	154	Lumbar radicular Cervical radicular	45 % of patients with lumbar pain ($n=116$) and 55 % of patients with cervical pain ($n=49$) achieved at least 50 % relief at 3 months

FBSS failed back surgery syndrome, *NRS* numerical rating scale, *VAS* visual analog scale

medial branch radiofrequency lesioning was clearly efficacious when performed accurately (i.e., based on results of anatomic studies). This research was followed by subsequent studies reporting that coagulation of the third occipital nerve could serve to relieve cervicogenic headache and that long-term relief of neck pain was possible [128–130].

Anatomy

Bogduk and Lord dissected multiple cadavers to locate and map the positions of the cervical medial branches in each cadaver prior to the publishing of the Lord et al. study [2, 31, 131]. They found that the location of the cervical medical branches was not consistent from one cadaver to the next, unlike the nerves in the lumbar spine. Thus, a region of the articular pillar (superior to inferior), rather than a specific location, must be coagulated to completely block sensation from a particular joint (Fig. 3.19a, b). The region must be covered with radiofrequency lesions to successfully destroy the innervation to a particular nerve level, and it can be considered to have a volume consisting of a height, length, and width [2].

Lord et al. also found that the location of the medial branch nerves varied, depending on the vertebral level. In general, they assume a curved course around the "waist" of the articular pillar. This archetypical course is exhibited at the C5 level, where nerves run in the center of the articular pillar on a lateral view and in the "waist" of the articular pillar in an AP view. At the C3 level, there are two medial branches, one of which is superficial and one of which is deep. The superficial medial branch is also referred to as the third occipital nerve (TON) and provides sensory innervation to the C2–C3 joint. Its location potentially extends from the top of the superior articular process of C3 to the bottom of the C2–C3 intervertebral foramen. The TON is 1.5 mm in diameter, whereas the other medial branches are less than 1.0 mm, making it all the more difficult to destroy by radiofrequency coagulation. The deep medial branch innervates the C3–C4 joint, and it is located from the joint line to the mid aspect of the C3 articular pillar. The C4 and C6 medial branches are found in the upper half of the articular pillar. The location of the C7 medial branch is different, in that the nerves are "pushed up" by the C7 transverse process. Therefore, the medial branch is located significantly higher on the articular pillar than are the other nerves. It can be found on the corner formed by the junction of the C7 SAP and the root of the transverse process in an AP view. The anatomy of the articular pillars and their joints must be considered when performing a radiofrequency procedure. Because the articular pillars slope caudally, the electrodes must be inserted from an inferior position heading superiorly in order for the electrode to lie parallel to the nerves (Fig. 3.20) [2, 31].

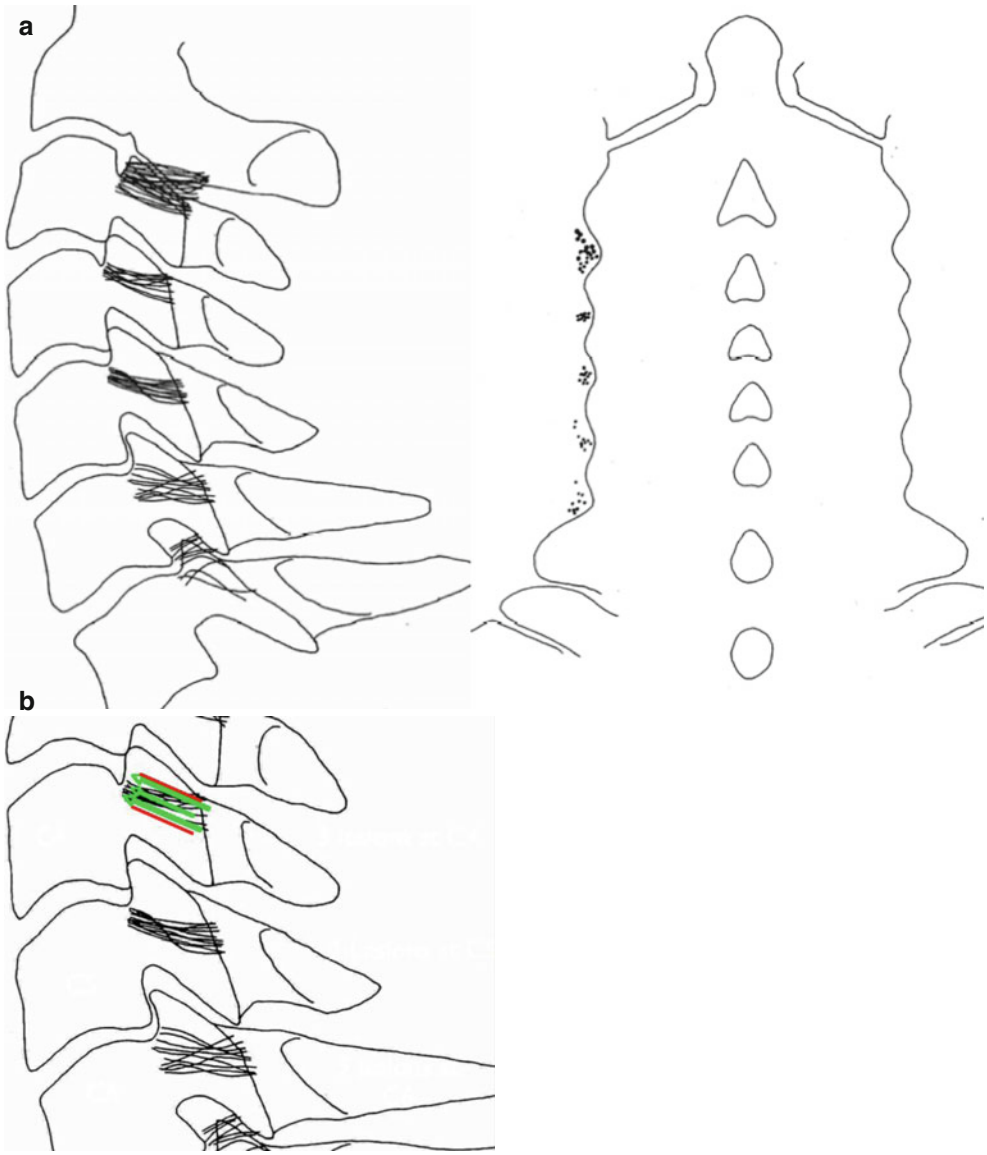


Fig. 3.19 (**a**, **b**) Location of cervical medial branches. (**a**) Images of location of medial branches of multiple cadaveric specimens (Modified from Lord et al. [128]; and McDonald et al. [129]). (**b**) Location of lesions required to coagulate C3 medial branches (Modified from Lord et al. [128]; and McDonald et al. [129])

It is important to note that the articular branches, which innervate the joints, divide off the medial branch at the mid-to-posterior aspect of the articular pillar. This has clinical significance in that if a radiofrequency lesion is performed posterior to the location where the articular branches divide, neurotomy of the joint has not occurred. In effect, the anterior two-thirds of the articular branches must be lesioned to coagulate the nerves to the facet joints.

In the cervical spine, two nerves innervate each facet joint: one from the vertebral level above the joint and one from the vertebral level below the joint. For example, the C5 and C6 medial branches innervate the C5–C6 facet joint. Because of the inconsistent and varying locations of the medial branches, Lord et al. concluded that to coagulate the nerve, multiple lesions were required at each level. To do this successfully, each lesion should be located one electrode width from the last, so that no "gaps" remain between the lesioned areas. In addition, careful attention must be paid to electrode placement to assure that the most anterior aspect of the nerve is coagulated.

Patient Selection

Cervical facet joint pain is thought to occur as a result of tearing of the joint capsule, which allows microscopic movement of the joint surfaces, causing inflammation and pain [132]. The two most commonly injured joints are the C2–C3 joint and the C5–C6 joint [133]. Pain emanating from the C2–C3 facet joint is often described as a unilateral headache located at the base of the skull and sometimes radiating to the forehead and commonly causes posterior occipital headaches. Pain in the C5–C6 facet joint often radiates to the inferior aspect of the trapezius muscle and scapular area.

The goal of radiofrequency neurotomy of the cervical medial branches is to reduce afferent nociceptive signals

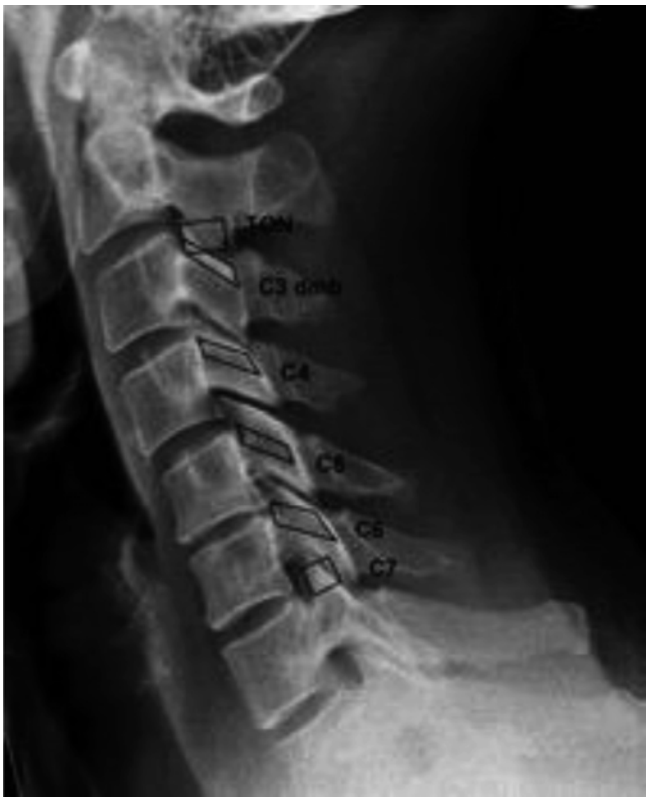


Fig. 3.20 Target zones for cervical medial branch neurotomy plotted on a lateral radiograph of the cervical spine (From Bogduk [35])

from the facet joints and provide palliative relief. Because pain emanating from a specific facet joint is difficult to localize, treatment is usually performed on three medial branches or two facet joints.

Patients with facet joint pain commonly present with a deep, aching sensation in the neck, punctuated by sharp shooting sensations with certain types of movements. They may complain of increased pain with flexion, extension, rotation, or lateral side bending of the head. The pain is most often bilateral, exacerbated by movement, and relieved by rest. Younger patients may report a traumatic event causing a whiplash injury, but older patients more often report an insidious onset of the pain. The pain refers in a non-dermatomal pattern into the occipital area and/or forehead, shoulder, and upper back. Physical exam may reveal focal tenderness or spasm, with no sensory or motor deficits [7, 134].

Cervical facet joint pain cannot be definitively diagnosed by history, physical exam, or the results of imaging studies nor is a single medial branch block considered to be a valid method of confirming the diagnosis [2, 135–137].

Dwyer et al. mapped pain referral patterns by injecting saline into the joints of normal volunteers. Aprill et al. used this data to predict the segmental location of the pain (Fig. 3.21) [138, 139].

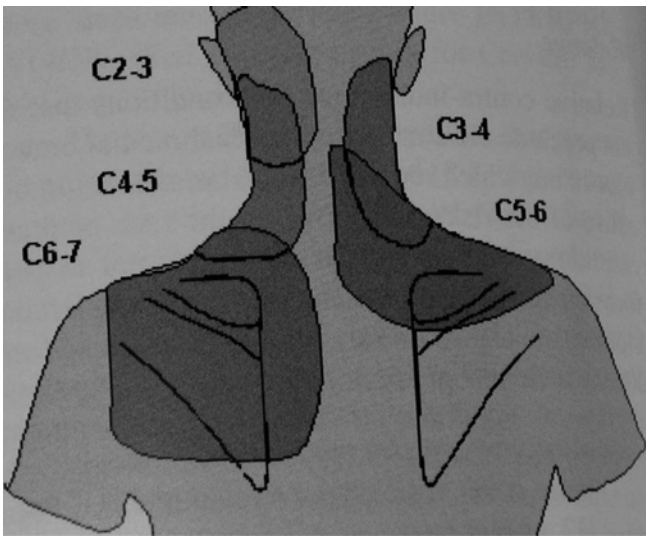


Fig. 3.21 Images of facet joint referral maps (From Bogduk [35])

Indications

Indications for this procedure include pain that has persisted for more than 3 months and has not responded to conservative therapy. The patient must report relief after diagnostic cervical medial branch blocks under fluoroscopic guidance, but the amount of relief is controversial. Traditionally, patients must report greater than 80 % pain relief on two separate occasions in response to medial branch blocks [2]. However, a study on patients with cervical facet pain showed no difference in outcome of the RF procedure in patients reporting 50 % relief and those reporting 80 % [140]. Based on this study, for patient with cervical facet joint pain, 50 % reduction in pain after MBB may be adequate.

Procedure (Figs. 3.21, 3.22, 3.23, 3.24, 3.25, and 3.26)

Prone Approach

The patient is positioned prone on a fluoroscopy table. It is wise to position the patient on a bolster in order to drop the shoulders down and away from the cervical spine, thus facilitating lateral imaging. To do this, multiple pads are placed under the chest such that the area is built up enough to allow the shoulders to drop down and away from the neck. The skin is sterilely prepped and draped in the usual fashion, and monitors are placed if IV sedation is planned. It is important that the patient remains awake and alert during the entire procedure such that if there is any discomfort, it can be evaluated by the operator. A fluoroscopic image is then obtained of the targeted vertebral level. The superior endplate is squared to open the disc space. Next, the C-arm is obliquely 10–15° to the ipsilateral side in order to target the anterior and mid aspect of the articular pillar. A pointer is placed over the articular pillar one level inferior to the targeted medial branch, and the C-arm is declined (image intensifier moved toward feet),

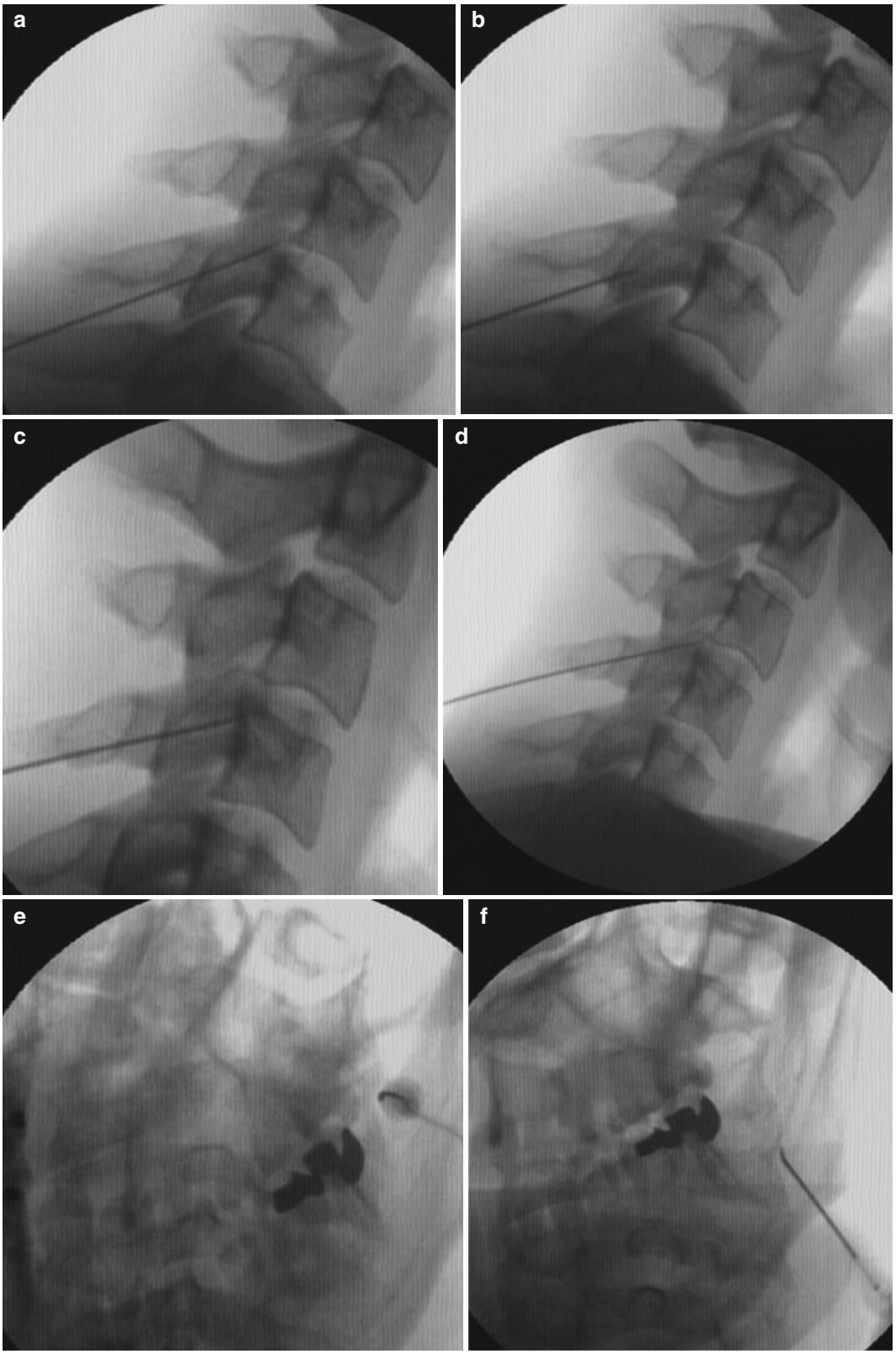


Fig. 3.22 (**a**–**f**) Fluoroscopic cervical medial branch radiofrequency lesioning: prone C3–C6 (Courtesy Richard Rosenthal). (**a**) Lateral view of placement at C5 level. (**b**) Retracting needle no further than posterior articular pillar for placement at second lesion point. (**c**) Second lesion at C5 level. (**d**) Lateral view showing third lesion point for C5 level. (**e**) Placement of needle in "pillar" view. (**f**) AP view of needle showing placement in superior half of the "waist" of the articular pillar at the C3 level

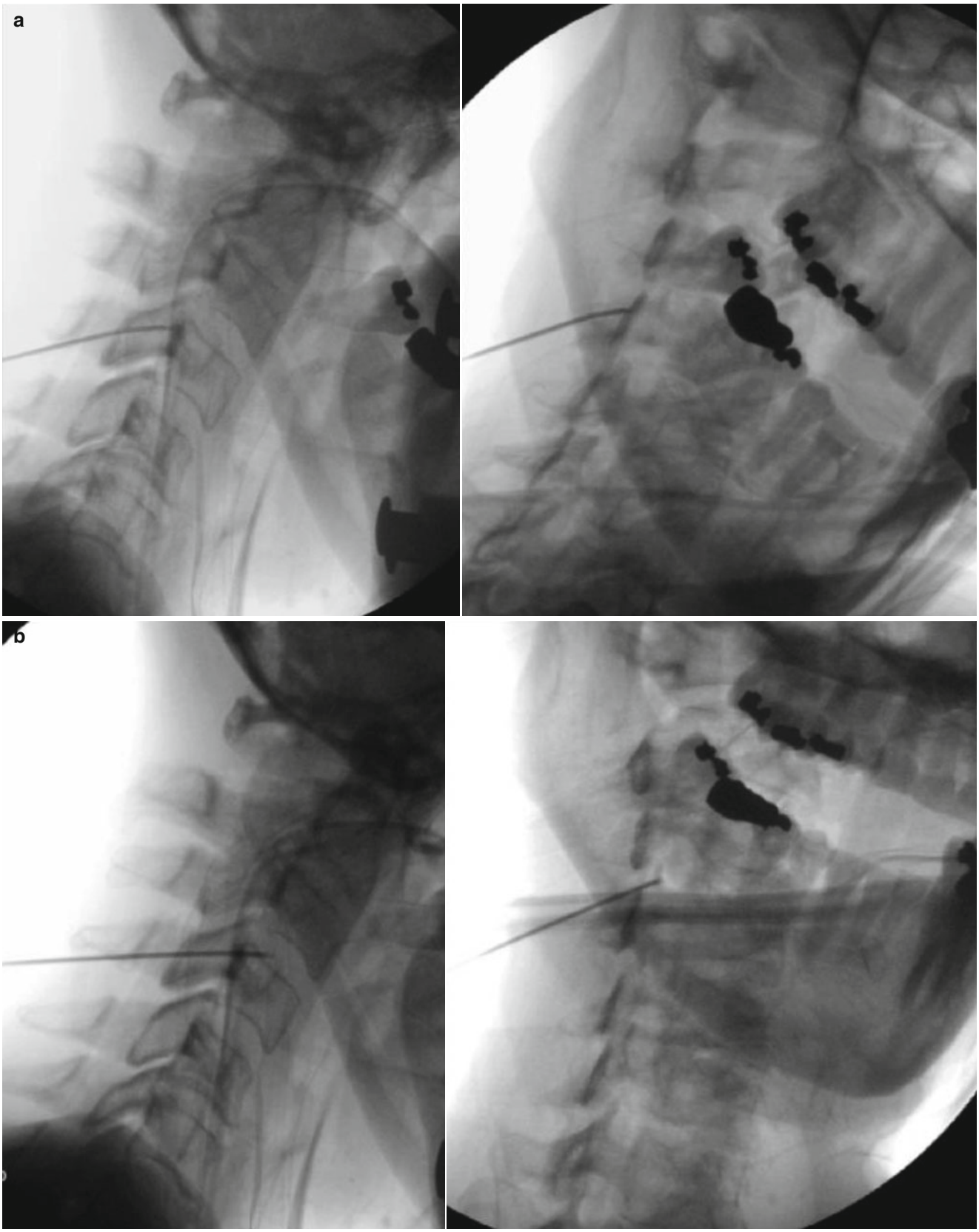


Fig. 3.23 (**a**, **b**) Safety view showing location of needle in lateral view relative to the foramen. (**a**) Lateral view with needle correctly positioned. Note location of needle relative to foramen in image on the right (Images courtesy of Aaron Calodney). (**b**) Lateral view with needle advanced past correct position. Note location of needle in posterior aspect of foramen (Images courtesy of Aaron Calodney)

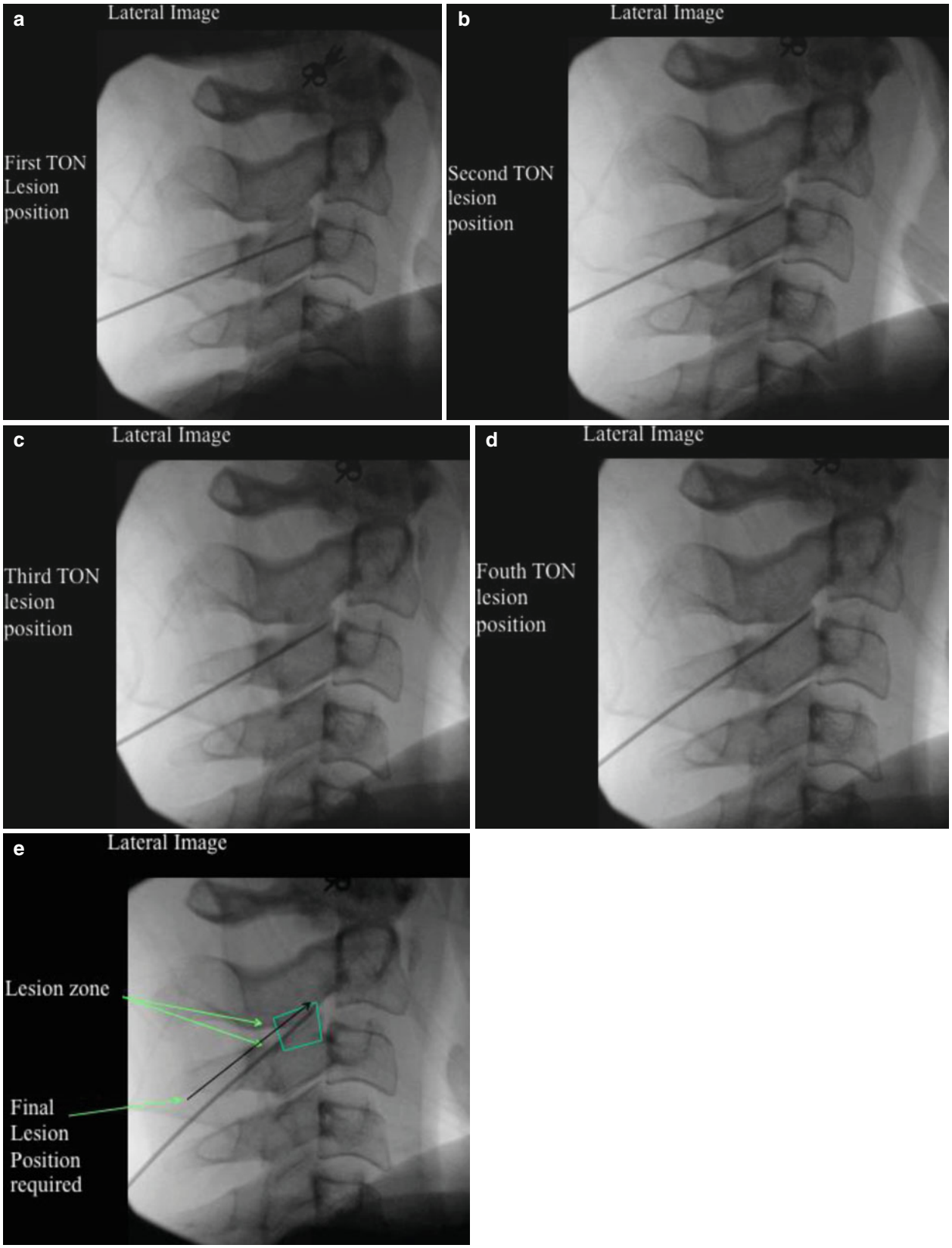


Fig. 3.24 (**a**–**e**) C3 medial branch radiofrequency lesioning showing sweeping of needle for coagulation of multiple possible locations of C3 third occipital nerve (TON) (Courtesy Paul Dreyfuss)

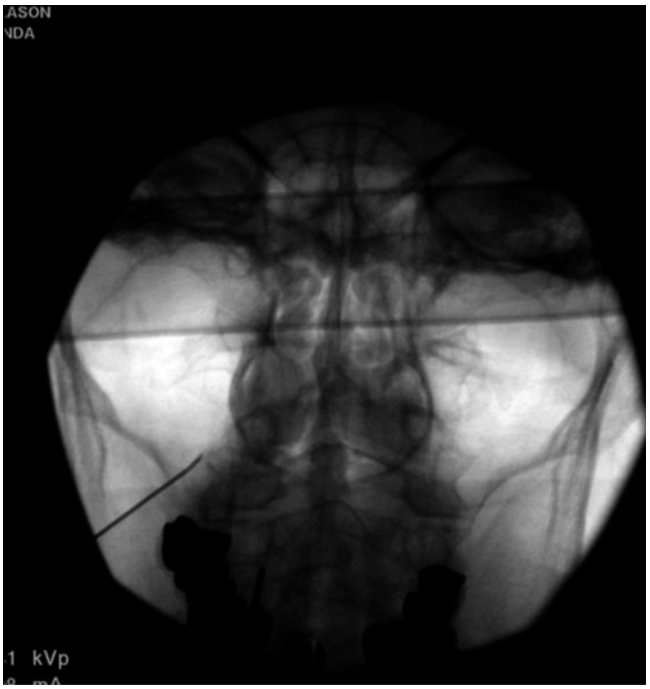


Fig. 3.25 C3 medial branch RF, AP view (Courtesy of Paul Dreyfuss).

until the targeted nerve level is directly beneath the pointer. This is referred to as a pillar view. Its purpose is to allow needle placement using a "down-the-beam" approach (needle parallel to x-ray beams). It also serves to align the active tip of the electrode parallel to the medial branch. A skin wheal is made slightly lateral to the targeted level at about the mid aspect of the articular pillar. A 20-g needle with a 10-mm active tip is then advanced down the beam until contact with the posterior aspect of the articular pillar is made. At this point a lateral view is obtained, and the needle is carefully advanced to the most anterior aspect of the articular pillar. It is important to obtain a true lateral view in order to accurately locate the tip of the needle at the most anterior aspect of the articular pillar. A steep contralateral oblique view (safety view) is then obtained to confirm that the needle tip is well behind (dorsal to) the intervertebral foramen. An AP view is obtained to confirm needle placement against the articular pillar (at or slightly above the waist depending on the level targeted). It is important that the needle is directed in a slight lateral to medial direction rather than medial to lateral. The lateral and anterior portion of the articular pillar is most crucial to lesion and may be missed if the starting place on the skin is positioned too far medially. Once the correct position is established, motor testing can be carried out to establish that the active tip of the electrode is far from the ventral ramus. Contraction of the paraspinal muscles of the neck is a normal finding, whereas contraction of the muscles of the arm indicates a need to reposition the needle more posteriorly. The position for needle passage for the TON is slightly different. There is no need to obtain a pillar view for the approach as the flange of the SAP is not present as it is at other levels. Using this approach, the starting point is at the C2–C3 joint line with the initial target the superior aspect of the SAP of C3 (as seen in a lateral view) [141].

After confirmation of correct placement with fluoroscopy and stimulation, 1 mL of 2 % lidocaine is injected through each of the cannulas, and 30–60 s is allowed to pass while waiting for production of anesthesia. Then the generator is turned on in the automatic mode, and lesions are created at a temperature of 85 °C applied for 60–90 s or longer if a larger lesion is desired. After completion of the first lesion, a series of subsequent lesions are performed to completely cover the volume of space were the nerves could potentially be located. This is done by retracting the needle back (while in a lateral view) no further than the posterior aspect of the articular pillar (warning—retracting the needle more than this risks misplacement to the inside of the articular pillar and coagulation of the spinal cord or rootlets). The number of lesions needed to completely cover the prescribed volume varies at each level. At the C3 level, the lesion area must extend from the superior aspect of the C3 SAP to the mid aspect of the C3 articular pillar in order to coagulate both the superficial (TON) and deep (C3 MB) medial branches. This requires five lesions spaced one needle width apart. At the C4–C6 levels, three lesions are recommended; at C7, four lesions must be done (Fig. 3.27a–f).

A modification of the technique described above is one in which a bipolar lesion is made at each nerve level. The technique has yet to be validated but seems reasonable and provides a method of coagulating a large volume of tissue with fewer lesions [142]. In addition, because a bipolar lesion is significantly larger than a monopolar lesion, it may be more likely to incorporate the medial branch within the lesion [142]. The concept is identical to that described above, but instead of performing multiple lesions at each level, only one or two bipolar lesions are required per nerve level. The technique involves placing two 10-cm needles with a 10-mm active tip at the superior and inferior aspect of the prescribed lesion zone and a bipolar lesion made between them. Bipolar lesions must be made no more than 6 mm apart (which is approximately three needle widths). Therefore, a single bipolar lesion would theoretically cover the lesion zone at C4–C6. It is recommended that two bipolar lesions be performed at the C3 and C7 levels.

Posterolateral Approach

Figure 3.28

Rationale for the Procedure

As recommended by Sluijter, Van Kleef, Van Zundert, and others, the posterolateral approach serves as a second method of performing the cervical medial branch procedure. It is

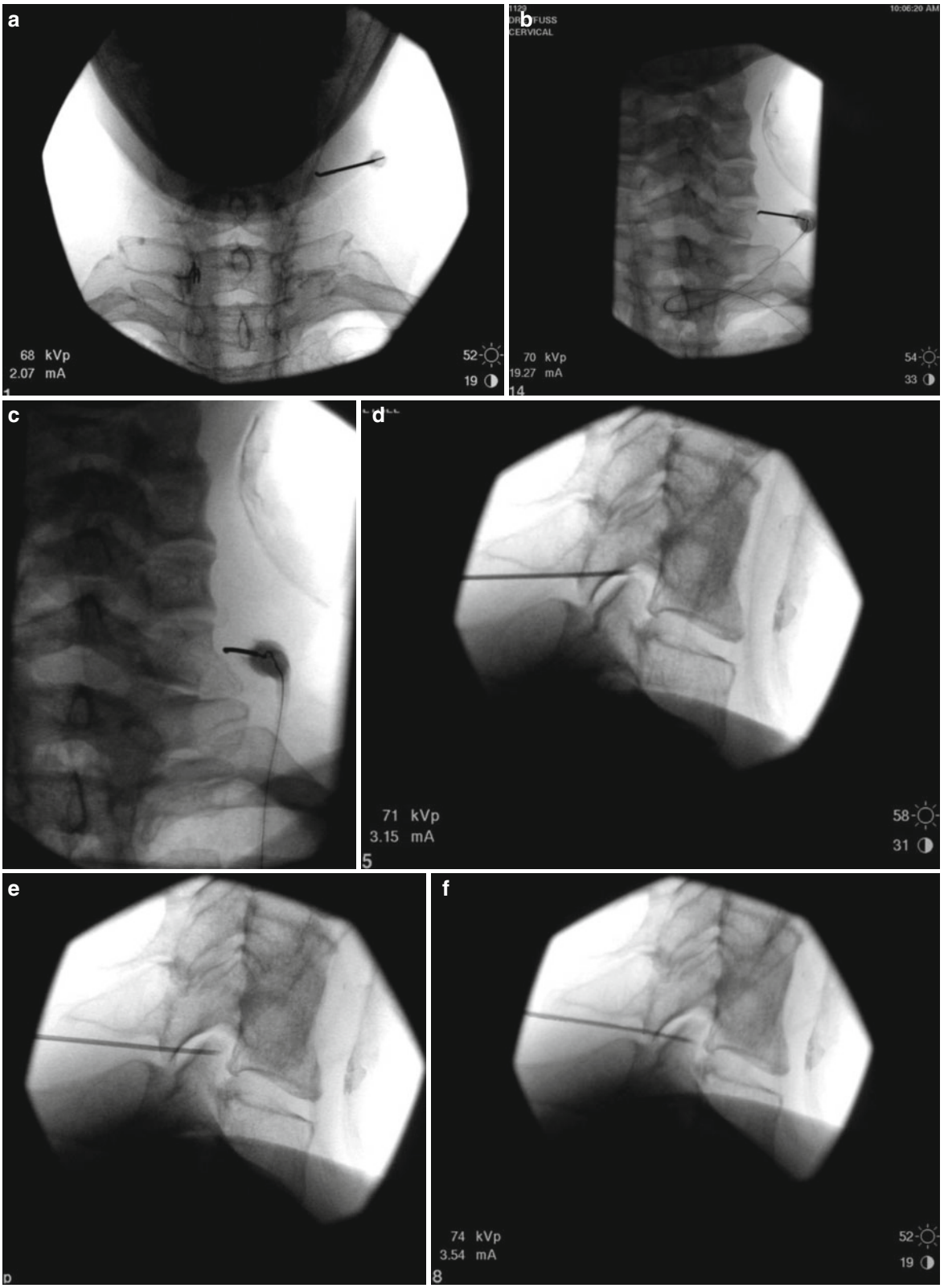


Fig. 3.26 (**a**–**f**) C7 technique. (**b**) AP view lesion point 1 (Image courtesy of Paul Dreyfuss). (**b**) AP view C7 lesion point 2 (Image courtesy Paul Dreyfuss). (**c**) AP view lesion point 3 (Image courtesy Paul Dreyfuss). (**d**) Lateral view, C7 medial branch RF, lesion point 1 (Image courtesy of Paul Dreyfuss). (**e**) Lateral view C7, lesion point 2 (Image courtesy of Paul Dreyfuss). (**f**) Lateral view C7, lesion point 3 (Image courtesy of Paul Dreyfuss)

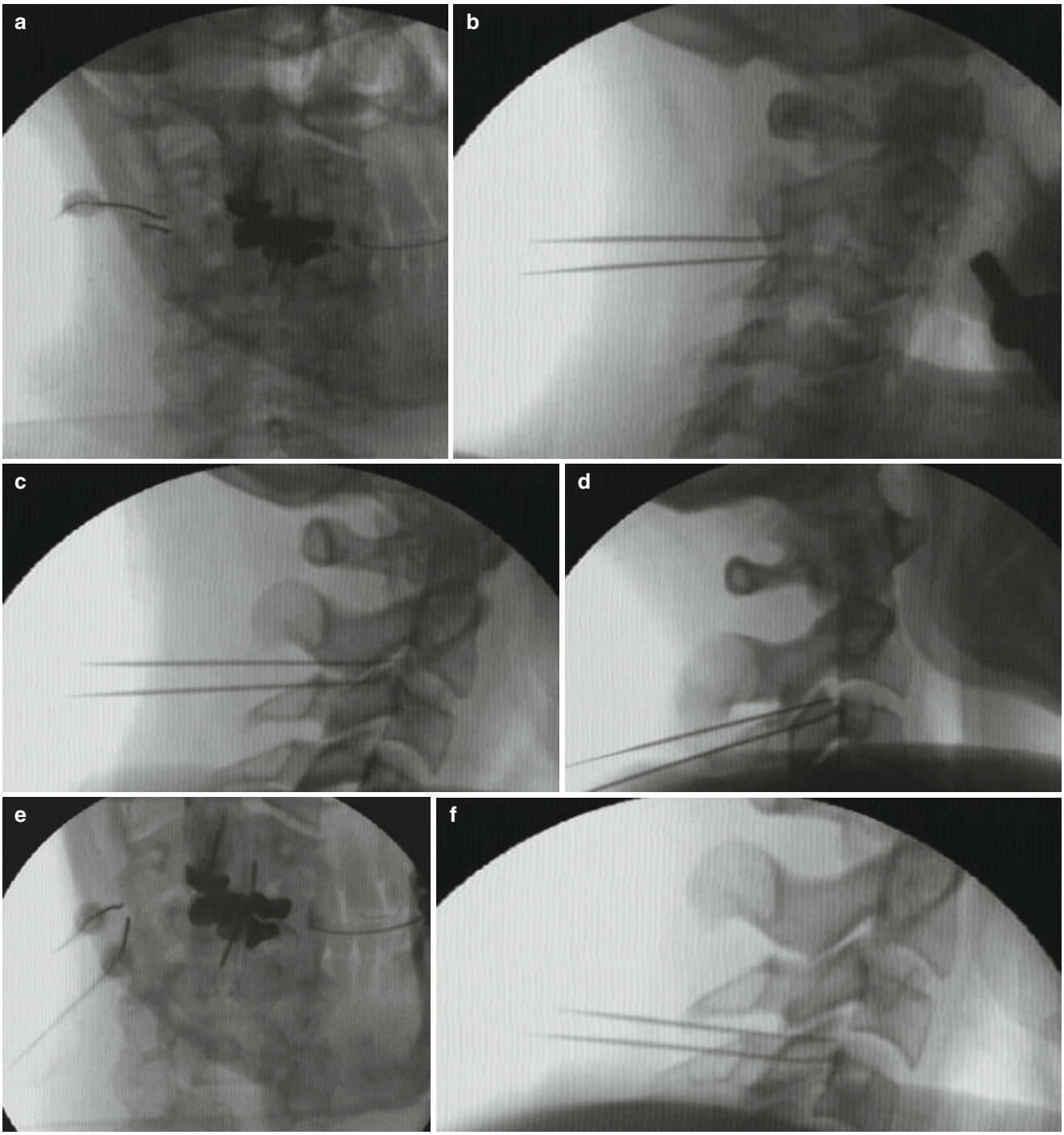


Fig. 3.27 (**a**–**f**) Cervical MB RF bipolar technique (Courtesy of Richard Rosenthal). (**a**) AP view C3 bipolar RF. (**b**) Oblique "safety" view C3. (**c**) Needle positions for lesioning 3 TON, lateral view. (**d**) Needle position C 3 TON, position two. (**e**) AP view, C4 medial branch RF bipolar. (**f**) Lateral view, C4 RF bipolar

performed with the patient in a supine position, which is sometimes better tolerated than the prone position. Though this approach has not been as well studied as the prone approach, it can be useful in some situations. For example, the prone approach may be difficult when patients have severe degenerative disease and arthritic spurring, because bony wings or flanges can prevent passage of the needle to the targeted nerve. Additionally, target visualization in the lateral view may be difficult using the prone approach when a patient has a short and stout neck. Finally, it is always wise to have more than one method of accomplishing the same task [4, 5, 129, 143].

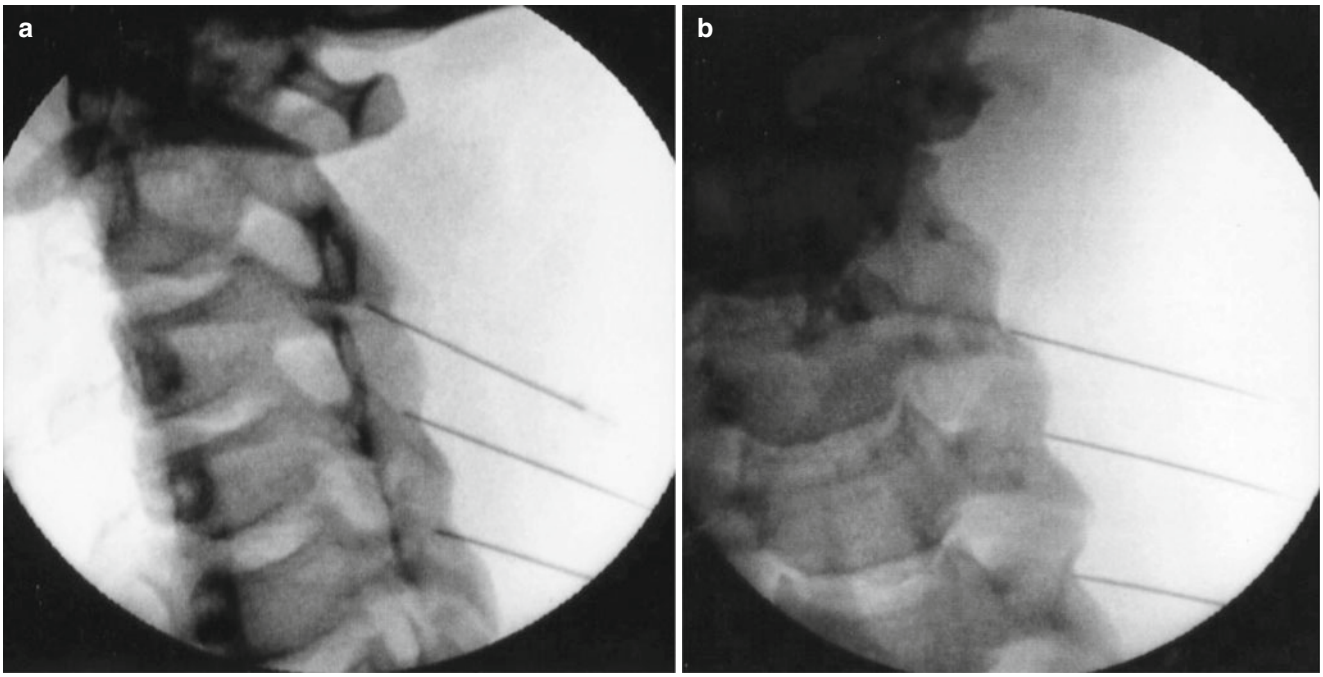


Fig. 3.28 (**a**, **b**) Cervical MB RF posterolateral approach (Courtesy Richard Rosenthal). (**a**) Cervical medial branch RF from posterolateral approach, oblique view. (**b**) AP view of cervical medial branch RF from posterolateral approach

For the posterolateral approach, the patient is placed supine on the operating room table with the head turned to the contralateral side. The skin is sterilely prepped and draped in the usual fashion, and monitors are placed if intravenous sedation is planned. It is important that the patient be awake and alert during the entire procedure, so that any discomfort can be evaluated. A fluoroscopic image is then obtained of the target vertebral level. The C-arm is tilted slightly caudally in order to square the vertebral endplates and open the disc space at the targeted level. Next, the C-arm is rotated into the oblique position on the ipsilateral side in order to visualize the cervical foramen at the level of interest. Observation that the pedicles on the contralateral side are projected approximately 50 % of the way across the vertebral body can be used as a visual reference regarding the degree of obliquity required [144].

The target point is the base of the SAP at or just below the most inferior aspect of the intervertebral foramen (IVF). A lesion performed at this location (just distal to the dorsal ramus) is felt to provide a similar effect to a lesion performed over the entire length of the nerve although no studies comparing both techniques have been performed [145]. The needles are not passed in a tunnel vision view. Instead, the entry point is slightly posterior and caudal to the target. The skin overlaying the target is anesthetized, and a 20-g needle with a 10-mm active tip is advanced to the target point in the oblique or foraminal view. The needle tip must be projected over the image of the articular pillar to prevent passage posterior to the column of bone. Once bone is contacted, care must be taken to assure the needle tip remains behind a line created by the posterior aspect of the IVF. The needle should touch bone at a superficial depth. If bone is not immediately contacted, one should reevaluate placement in both the foraminal view and an AP view. In the latter view, the tip of the needle should be seen resting against the mid aspect of the articular pillar. If it is medial to the edge of the articular pillar, one should suspect needle placement into the foramen (confirmed in an oblique view) or posterior to the articular pillar.

Once correct position is established, motor testing can be carried out at 1.0 V to demonstrate proper distance from the exiting ventral ramus. Contraction of the paraspinal neck muscles is a normal finding, whereas contraction of the arm muscles indicates a need to reposition the needle. After confirmation of correct placement with fluoroscopy, 1 mL of 2 % lidocaine is injected through each of the cannulas, and 30–60 s is allowed to pass while waiting for production of anesthesia. Then, the radiofrequency generator is turned on in the automatic mode and lesions are created at a temperature of 85 °C applied for 60–90 s. After completion of the first lesion, repeat lesions are performed both cephalad and caudad to the original needle position (as noted above), in order to coagulate the volume of space sin which the medial branches may be found.

Complications

In general, complications associated with this procedure are rare. Postprocedure pain generally lasts up to 2 weeks. Approximately 30 % of patients report numbness in the

Table 3.4 Radiofrequency of the cervical medial branch

Author	Study design	*N*	Efficacy
Lord et al. (1996) [128]	Double-blind randomized trial	24	Median time to return of 50 % of pre-op pain was 263 days
McDonald et al. (1999) [129]	Observational	28	71 % had complete pain relief; median duration of relief was 422 days
Govind et al. (2003) [130]	Observational	49	88 % achieved a successful outcome; median duration of pain relief was 297 days

cutaneous distribution of the coagulated nerves, but this is usually not disturbing to patients and does not require treatment. Twenty percent of patients may experience dysesthesias in the cutaneous distribution of the coagulated nerves lasting 2–3 weeks. This usually resolves spontaneously without treatment [2, 128]. Complications associated with coagulation of the third occipital nerve (TON) require special mention. This nerve plays a role in proprioception such that when coagulated, most patients experience mild transient ataxia lasing 2–3 weeks [2, 4, 130]. The symptom may be more severe if both nerves are coagulated at the same time. Patient should be cautioned not to drive or operate heavy machinery until the symptom resolves. Another almost universal symptom of coagulation of the TON is hypersensitivity and dysesthesias in the cutaneous distribution of the nerve. These symptoms usually last for 1–4 weeks and resolve without treatment [2, 130]. If treatment is required, a Medrol dose pack or anticonvulsants are helpful. If these prove ineffective, an epidural steroid injection may help to resolve the symptoms. There have been two published reports of "dropped head syndrome" or progressive severe kyphosis following multilevel cervical radiofrequency ablation. Both required instrumented fusion to repair the deformity [146, 147]. Finally, the ISIS guidelines report a case of spinal cord injury in a patient under general anesthesia when an electrode was passed medial to the targeted joint, through the interlaminar space, and directly onto the spinal cord and exiting nerve roots [2]. This is prevented by never retracting the electrode further than the posterior aspect of the articular pillar when performing multiple lesions on a single nerve level in a lateral view. It can also be easily avoided by simply checking an AP view whenever the electrode is repositioned.

Efficacy: Prone Approach

In a double-blind randomized controlled study comparing cervical medial branch radiofrequency lesioning to a sham treatment, Lord et al. found that patients in the treatment group experienced statistically significant improvement in pain when compared to the control group (median time to recurrence of pain was 263 days vs. 8 days, respectively) [128]. Patients with C2–C3 joint pain were excluded from the study, because preliminary data indicated that radiofrequency treatment was difficult at that level. However, subsequent research demonstrated that C2–C3 joint pain could be successfully treated by radiofrequency neurotomy of the third occipital nerve [130]. In a follow-up to the Lord study, 63 % of patients reported complete pain relief for an average of 421 days [129]. Finally, a study by Schofferman demonstrated that when pain recurred following radiofrequency neurotomy, repeat treatment was an effective, long-term solution (Table 3.4) [106].

C2 Radiofrequency Treatment for Cervicogenic Headache

Background

Cervicogenic headache of spinal origin is most commonly caused from injury to the C2–C3 joint. Occasionally, the C1–C2 and C0–C1 joints can be involved. In the early 1990s, some researchers first began to suspect that the upper cervical joints might be responsible for headache [2, 148]. However, it remained largely unrecognized for many years that the upper cervical joints served as a primary cause of headaches in whiplash victims [5]. A study by Lord in whiplash victims reporting headache as the primary symptom revealed that the prevalence of C2–C3 joint pain was 53 % [5, 149]. In an attempt to prove the C2–C3 joint as a source of headache, Dwyer injected contrast dye into the C2–C3 joint of normal volunteers and was able to induce a characteristic headache in the occipital area [2, 138]. Bogduk and Marsland later showed that anesthetizing the TON could relieve pain emanating from the joint [150, 151]. Dreyfuss performed a similar study of the A-A joint and was able to induce pain at the base of the skull [152]. Bogduk then described a technique of anesthetizing the C2 spinal nerve as a means of diagnosis [2, 153]. Finally, the idea of anesthetizing the joint directly as a means of diagnosis was proposed (Fig. 3.29).

Anatomy

The anatomy of the upper cervical spine is complex because there are several communicating branches between the C1, C2, and C3 dorsal rami [5]. The confusion is compounded by the trigeminal cervical system. The trigeminal nucleus descends into the upper cervical segments of the spinal cord possibly as far down as C3 [143].

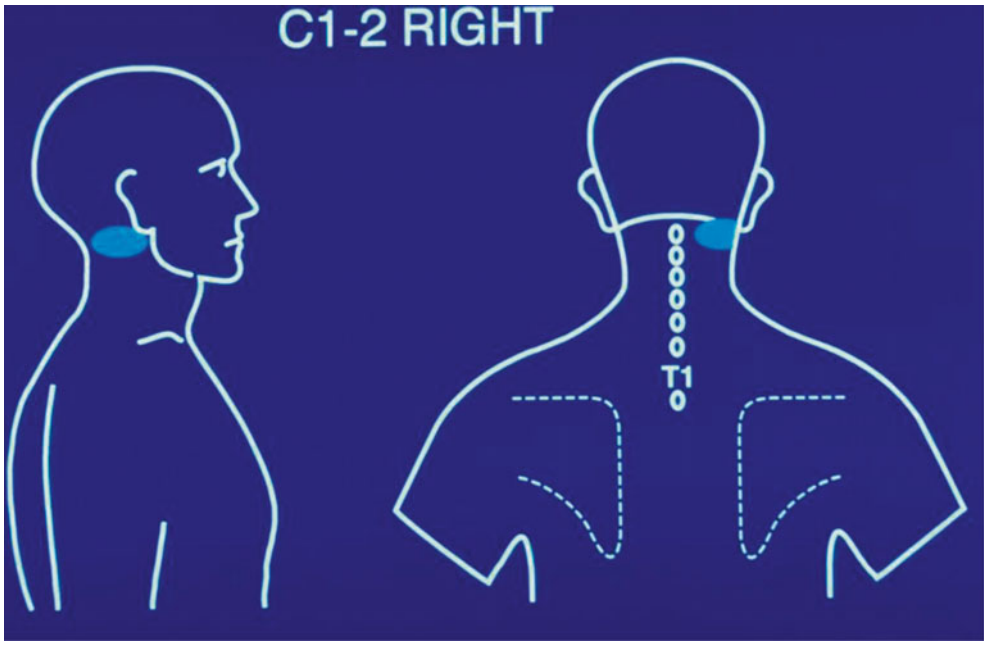


Fig. 3.29 C1–C2 cervical facet joint referral map

There is a facilitatory influence from stimulation of the occipital nerves on input from the dura. Furthermore, stimulation of muscle afferents produced more input than skin afferents suggesting that increases in cervical muscle tone may increase input into the cervicotrigeminal system. This may explain why anesthetizing the occipital nerves relieves tension-type headache. For this group of patients, it may make sense to perform a pulsed RF lesion of the C2 DRG as this is the sensory nucleus of the occipital nerve.

For those patients with headache of spinal origin, it most commonly emanates from the C1–C2 or C2–C3 joint. The third occipital nerve innervates the C2–C3 joint, while C1–C2 innervation comes from the C2 dorsal ramus. Finally for patients with pain from occipital neuralgia due to chronic tension headache, the greater occipital nerve derives its roots from the C2 nerve. Therefore, pulsed radiofrequency procedures performed at the C2 and C3 levels would be expected to treat all three causes of pain.

Patient Selection

In patients with headache pain of unknown origin, practitioners should suspect the diagnosis of cervicogenic headache. However, distinguishing pain emanating from the C1–C2 vs. C2–C3 joints is a difficult task [5]. Patients often complain of a dull aching or throbbing sensation at the base of the skull that sometimes radiates up the back of the head. The pain may be increased with turning of the head, axial loading, or bending toward the affected side. The pain is continuous but is often lessened by rest and increased by activity. They may report focal tenderness in the suboccipital area. The pain is often unilateral. This pain can be extremely debilitating, and some patients give up their work activities or schooling in order to cope with the pain. There are usually no associated neurological symptoms. The etiology is thought to be tearing of the joint capsule surrounding one of more of the upper cervical joints.

Additionally, tension-type headache is another cause for chronic posterior headache. These patients often complain of a dull aching or a squeezing sensation bilaterally at the posterior aspect of the head and radiates into the temporal, frontal areas. Patients with this type of pain can usually function in spite of the pain in contradistinction to migraine headache patients who usually must lie down in a dark room in order to cope with the pain. Usually the pain is not associated with nausea, vomiting, photophobia, or phonophobia. Anecdotally, patients with tension headaches originating in the occipital area have been found to respond to treatment with an interventional procedure described below at the C2 DRG level. Although there is no data showing clear advantage of this procedure, the theoretical basis for treatment is sound.

Indications

Only when more conservative treatment options have failed should pulsed radiofrequency lesioning of the C2 dorsal root ganglia be undertaken. The patient should have responded on two occasions with greater than 80 % relief to diagnostic blocks (third occipital nerve for C2–C3 joint pain, C2 DRG for A-A joint pain and occipital nerve blocks for headache pain).

Procedure (Fig. 3.30)

To facilitate proper imaging, the patient is positioned in the lateral position on the operating room table with the head built up sufficiently that it is parallel to the operating room

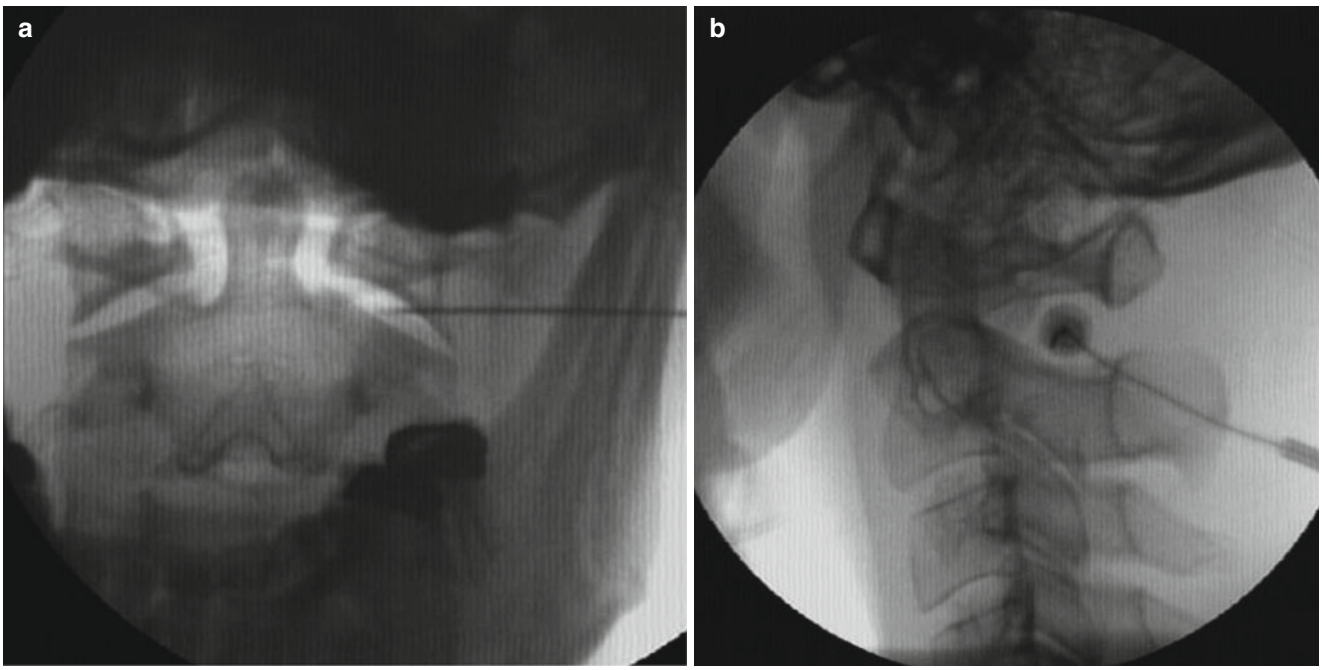


Fig. 3.30 Fluoroscopic images of C2 DRG RF procedure (Courtesy Richard Rosenthal). (**a**) AP view of C2 procedure. (**b**) Lateral view of C2 procedure

table and directly perpendicular to the shoulders. The neck is sterilely prepped and draped, and if IV sedation is planned, monitors are applied. Any IV sedation given should be very light in order to facilitate continuous communication between the patient and the operator, which serves as a monitor for any possibly type of complication. The target point is in the anterior aspect of the dome created by the C1–C2 lamina. Specifically the point lies in the mid aspect of the dome from cephalad to caudad and in the anterior aspect from dorsal to ventral. It should be stressed that a needle placed down to this point is not expected to contact the periosteum and can be placed directly through the spinal cord. Checking multiple AP views during needle insertion to assess the needle during needle placement is essential in order to prevent this complication.

A skin wheal overlaying this target point is raised, and a 22-g SMK needle with a 4-mm active tip is advanced through the skin wheal directly "down the beam" toward the target. Caution should be taken to make certain that the needle tip is not advanced into the muscle layers until it is pointed directly toward the intended target. In addition, if the skin wheal is placed more than 3 mm "off target," a new starting point should be made and the needle reinserted directly over the target. Once the needle is properly aligned, the needle is passed in a tunnel vision view down to the lamina of C2. Contact with lamina before passing the needle to the final target is done to give a sense of depth prior to advancing to the target. With the needle on the lamina, one retracts the needle slightly and redirects toward the target. At this point an AP view is obtained and the needle should be seen resting on the lateral aspect of the articular pillar. If there is difficulty visualizing the needle tip, an open-mouth view is helpful. The needle tip is carefully and slowly advanced toward the target. In the AP view, the target is usually directly over or slightly inferior to the mid aspect of the A-A joint. When the needle approaches this area, the operator should warn the patient and advance only 0.5 mm at a time while monitoring for a paresthesia. Once the patient feels a mild paresthesia, advancement is stopped and sensory testing is performed. With correct needle placement, the patient should report a tingling sensation in the back of the head at less than 0.2 V. There is no need for motor stimulation during a pulsed radiofrequency procedure. Before lesioning one should check the final needle position in two views. In the lateral view the needle will be seen in the anterior aspect of the dome created by the C1–C2 lamina and in a mid-position from cephalad to caudad. In an AP view the needle will be seen at or slightly below the A-A joint in the mid aspect of the articular pillar from lateral to medial. Lesioning in the pulsed mode is done by slowly turning up the voltage while monitoring the patient. It is not uncommon to note muscle contractions during the procedure. This is a normal occurrence and should not be a cause for alarm.

Efficacy

At this level of the cervical spine, pulsed RF lesioning of the nerves at this level of the cervical spine has not been well studied. One article specifically studying this issue was a

Table 3.5 Radiofrequency for cervicogenic headache

Author	Study design	*N*	Efficacy
Haspeslagh et al. (2006) [154]	Randomized controlled trial	30	No difference between group treated with occipital nerve block using steroids and group treated with cervical facet joint radiofrequency and upper cervical dorsal root ganglion radiofrequency
Chao et al. (2008) [42]	Retrospective analysis	49	55.10 % had at least 50 % pain relief at 3 month follow-up

randomized controlled trial comparing the results of occipital nerve block with RF treatment of the upper cervical area in patients with occipital headache. In each group there were 30 patients: 15 underwent occipital nerve blocks and 15 received pulsed radiofrequency. The first line of treatment for one group was an occipital nerve block. If the patient failed to obtain sufficient relief after 8 weeks, a second block was performed. Finally, if the patient remained symptomatic at 16 weeks, they were treated with TENS. The radiofrequency group first underwent RF of the C3–C6 z-joints from a posterolateral approach using 22-g SMK needles with a 4-mm active tip. If this procedure failed to relieve symptoms, diagnostic nerve blocks were performed at either the C2 or C3 levels followed by RF lesioning at the relevant level. The results revealed no statistical difference of either treatment between groups.

The study can be criticized on multiple points. First, they did not specify how they performed the DRG procedure. As mentioned earlier in this chapter, pulsed RF lesioning of the cervical dorsal root ganglion has been shown to have an effect in relieving pain, while DRG with heat (in the lumbar spine) definitely did not [154]. Additionally, the radiofrequency procedure performed would be unlikely to coagulate the third occipital nerve and therefore relieve the most common cause of spinal headache. In addition, radiofrequency lesions performed at other levels (C3–C6) are superfluous in the treatment of cervicogenic headache.

Two other small studies looked at outcomes from pulsed DRG treatment at the cervical levels, though they did not specifically study patients treated for headache with DRG treatment at the C2 or C3 levels. However, they did include some of these patients in their report. The first study, reported earlier, included 6 patients treated at either the C2 or C3 DRG for headache. All three patients rated their pain relief at 7 on the Likert scale corresponding to greater than 75 % improvement. Of 6 patients, 3 reported pain relief with an average of 20 months (2 reported 18 months and 1 had 24 months of relief). A second study reported results of pulsed radiofrequency lesioning at the C3–C7 levels. At 1 year 57 % of patients reported satisfactory pain relief (Table 3.5) [42, 43].

Conclusion

This chapter has sought to review the history of RF, summarize best practices in the use of RF, describe new methods of RF application, and present data on PRF to support its use in clinical practice. It has described commonly performed procedures utilizing RF including lumbar medial branch radiofrequency, the lumbar dorsal root ganglion procedure, and C2 radiofrequency treatment for cervicogenic headache.

While the early use of radiofrequency for chronic pain struggled with inaccuracy, today radiofrequency treatment has been used to relieve painful conditions such as trigeminal neuralgia, radicular pain syndromes, and facet-mediated pain. With the advent of better equipment including the Cosman RF generator in the 1970s and Suijeter and Metha's needle in the 1980s, widespread use of RF current spurred through anatomic and clinical studies.

Pioneering studies by Bogduk, Lord, Govind, Dreyfuss, and others identified proper anatomic targets for the cervical and lumbar medial branch procedures and devised the optimal means of destroying the nerves. When it came into question that RF current produces its effect via tissue destruction, researchers sought to develop a method for delivering radiofrequency energy in a manner that did not result in the production of heat. This led to the creation of pulsed RF, allowing for the treatment of targets for which heat is contraindicated.

The importance of this new modality has been recognized by researchers in multiple disciplines, and clinical studies suggest that PRF is effective though the exact mechanism of action remains elusive. Many possible theories have been proposed, though no single explanation has been able to elucidate the effects of PRF. Even still, clinical data support the notion that PRF is an effective tool for some types of chronic pain syndromes when applied to well-selected patients. Ongoing in vitro and animal studies will also be important in bolstering the evidence of its effectiveness.

PRF has had the most impact for patients who suffer from radicular pain and peripheral neuropathies. These patients are often refractory to medication and may require more expensive and invasive treatments such as

spinal cord stimulation in the absence of PRF. The majority of studies to date show only short-term efficacy (about 3 months). Further research is needed to determine the best methods of applying PRF for longer-term pain relief.

Beyond radiofrequency, other ablation techniques may soon have a direct impact on the treatment of spinal pain. Early studies suggest that at least one such technology, magnetic resonance-guided focused ultrasound treatment (MRgFUS), can safely ablate the facet joint in treating pain which can safely ablate the facet joint [8, 9]. Still, more research must be done to prove the effectiveness of any new treatments as well as to determine the long-term outlook of pulsed radiofrequency.

References

1. Sluijter ME, van Kleef M. Characteristics and mode of action of radiofrequency lesions. Curr Rev Pain. 1998;2:142–50.
2. Bogduk N. Practice guidelines for spinal diagnostic and treatment procedures. Bogduk N, editor. San Francisco: International Spine Intervention Society; 2004.
3. Sluijter ME. Radiofrequency, part 1. Meggen: FlivoPress; 2001.
4. van Kleef M, Sluijter M, Van Zundert J. Radiofrequency treatment. In: Benzon HT et al., editors. Raj's practical management of pain. 4th ed. Philadelphia: Mosby; 2008. p. 1039–62.
5. Van Zundert J, Sluijter M, van Kleef M. Thermal and pulsed radiofrequency. In: Raj PP et al., editors. Interventional pain management: image-guided procedures. Philadelphia: Saunders; 2008. p. 56–65.
6. Waldman S. Pain management. Philadelphia: Elsevier; 2007.
7. Newnham P. Chronic spinal pain. Meggen: FlivoPress; 2002.
8. Harnof S, Zibly Z, Shay L, Dogadkin O, Hanannel A, Inbar Y, Goor-Arneh I, Caspi I. Magnetic resonance-guided focused ultrasound treatment of facet joint pain: summary of preclinical phase. J Ther Ultrasound. 2014;2:9.
9. Weeks EM, Platt MW, Gedroye W. MRI-guided focused ultrasound (MRgFUS) to treat facet joint osteoarthritis low back pain—case series of an innovative new technique. Eur Radiol. 2012;22:2822–35.
10. McQuay HJ, Moore RA. An evidence-based resource for pain relief. Oxford/New York: Oxford University Press; 1998.
11. Kirschner M. Zür electrochirugie. Arch Klin Chir. 1931;167:761.
12. Rosomoff HL, et al. Percutaneous radiofrequency cervical cordotomy technique. J Neurosurg. 1965;23:639–44.
13. Uematsu S. Percutaneous electrothermocoagulation of spinal nerve trunk, ganglion and rootlets. New York: Grune & Stratton; 1977.
14. Cosman BJ, Cosman ER. Radionics procedure technique series monograph. Guide to radiofrequency lesion generation in neurosurgery. Burlington: Radionics, Inc; 1974.
15. Shealy CN. Percutaneous radiofrequency denervation of spinal facets. J Neurosurg. 1975;43:448–51.
16. Bogduk N, Long DM. The anatomy of the so-called "articular nerves" and their relationship to facet denervation in the treatment of low-back pain. J Neurosurg. 1979;51:172–7.
17. Savitz MD. Percutaneous radiofrequency rhizotomy of the lumbar facets ten years' experience. Mt Sinai J Med. 1991;58:177–8.
18. Stolker RJ, Vervest AC, Groen GJ. Percutaneous facet denervation in chronic thoracic spinal pain. Acta Neurochir (Wien). 1993;122:82–90.
19. Stolker RJ, Vervest AC, Groen GJ. The treatment of chronic thoracic segmental pain by radiofrequency percutaneous partial rhizotomy. J Neurosurg. 1994;80:986–92.
20. Goupille P, et al. Denervation of the posterior lumbar vertebral apophyses by thermocoagulation in chronic low back pain. Results of the treatment of 103 patients. Rev Rhum Ed Fr. 1993;60:791–6.
21. North RB, et al. Radiofrequency lumbar facet denervation: analysis of prognostic factors. Pain. 1994;57:77–83.
22. Cho J, Park YG, Chung SS. Percutaneous radiofrequency lumbar facet rhizotomy in mechanical low back pain syndrome. Stereotact Funct Neurosurg. 1997;68:212–7.
23. Gocer AI, et al. Percutaneous radiofrequency rhizotomy of lumbar spinal facets: the results of 46 cases. Neurosurg Rev. 1997;20:114–6.
24. Tzaan WC, Tasker RR. Percutaneous radiofrequency facet rhizotomy – experience with 118 procedures and reappraisal of its value. Can J Neurol Sci. 2000;27(2):125–30.
25. Van Wijk RM, Geurts JW, Wynne HJ. Long lasting analgesic effect of radiofrequency treatment of the lumbosacral dorsal root ganglion. J Neurosurg. 2001;94(2):227–31.
26. Podhajshy RJ, et al. The histological effects of pulsed and continuous radiofrequency lesions at 42 °C to rat dorsal root ganglion and sciatic nerve. Spine. 2005;30(9):1008–13.
27. Moringlane JR, et al. Experimental radiofrequency coagulation with computer-based on line monitoring of temperature and power. Acta Neurochir (Wien). 1989;96:126–31.
28. Brodkey JS, et al. Reversible heat lesions with radiofrequency current. A method of stereotactic localization. J Neurosurg. 1964;21:49–53.
29. Strohbehn JW. Temperature distributions from interstitial rf electrode hyperthermia systems: theoretical predictions. Int J Radiat Oncol Biol Phys. 1983;9(11):1655–67.
30. Bogduk N, Macintosh J, Marsland A. Technical limitations to the efficacy of radiofrequency neurotomy for spinal pain. Neurosurgery. 1987;20(4):529–35.
31. Lord SM, McDonald GJ, Bogduk N. Percutaneous radiofrequency neurotomy of the cervical medial branches: a validated treatment for cervical zygapophysial joint pain. Neurosurg Q. 1998;8:288–308.
32. Tekin I, et al. A comparison of conventional and pulsed radiofrequency denervation in the treatment of chronic facet joint pain. Clin J Pain. 2007;23(6):524–9.
33. Sluijter ME, Cosman E, Rittman W, van Kleef M. The effects of pulsed radiofrequency fields applied to the dorsal root ganglion – a preliminary report. Pain Clin. 1998;11:109–17.
34. Sluijter ME, Racz G. Technical aspects of radiofrequency lesioning. Pain Pract. 2002;2(3):195–200.
35. Bogduk N, editor. International Spine Intervention Society Practice guidelines for spinal diagnostic and treatment procedures. 2nd ed. San Francisco: International Spine Intervention Society; 2013.
36. Ahmed M, Brace CL, Lee Jr FT, Goldberg SN. Principles of and advances in percutaneous ablation. Radiology. 2011;258(2):1–9.
37. Smith HP, McWhorter JM, Challa VR. Radiofrequency neurolysis in a clinical model – neuropathic correlation. J Neurosurg. 1981;55:246–53.
38. Ford DJ, Pither C, Raj PP. Comparison of insulated and uninsulated needles for locating peripheral nerves with a peripheral nerve stimulator. Anesth Analg. 1984;63(10):925–8.
39. Cohen SP, Strassels SA, Kurihara C, Lesnick IK, Hanling SR, Griffith SR, Buckenmaier III CC, Nguyen C. Does sensory stimulation threshold affect lumbar facet radiofrequency denervation outcomes? A prospective clinical correlation study. Anesth Analg.

2011;113(5):1233–41. doi:10.1213/ANE.0b013e31822dd379. Epub 2011 Sep 14.
40. Simopoulos TT, et al. Response to pulsed and continuous radiofrequency lesioning of the dorsal root ganglion and segmental nerves in patients with chronic lumbar radicular pain. Pain Physician. 2008;11(2):137–44.
41. Teixeira A, Grandinson M, Sluijter M. Pulsed radiofrequency for radicular pain due to a herniated intervertebral disc – an initial report. Pain Pract. 2005;5(2):111–5.
42. Chao SC, et al. Percutaneous pulsed radiofrequency in the treatment of cervical and lumbar radicular pain. Surg Neurol. 2008;70(1):59–65.
43. Van Zundert J, et al. Percutaneous pulsed radiofrequency treatment of the cervical dorsal root ganglion in the treatment of chronic cervical pain syndromes: a clinical audit. Neuromodulation. 2003;6(1):6–14.
44. Cosman Jr ER, Dolensky JR, Hoffman RA. Factors that affect radiofrequency heat lesion size. Pain Med. 2014;15(12):2020–36.
45. Vinas FC, et al. In vivo and in vitro study of the lesions produced with a computerized radiofrequency system. Stereotact Funct Neurosurg. 1992;52(1–4):121–33.
46. Cosman Jr ER, Gonzales CD. Bipolar radiofrequency lesion geometry: implications for palisade treatment of sacroiliac joint pain. Pain Pract. 2011;11(I):3–22. Pain Practice 2010 World Institute of pain, 1530-708S/11, 15.00.
47. Cosman Sr ER, Cosman Jr ER. Methods of making nervous system lesions. In: Wilkens R, Rengachary SS, editors. Neurosurgery. New York: McGraw-Hill; 1984. p. 2490–9.
48. Provenzano DA, Lutton EM, Somers DL, The effects of fluid injection on lesion size during bipolar radiofrequency treatment. Reg Anesth Pain Med. 2012;37(3):267–76. http://www.cosman-medical.com/wp-content/uploads/2014/03/COSMAN-Straight-Trigeminal-RF-Electrode-TIC.pdf.
49. Tronnier VM, Rasche D, Hamer J, Kienle AL, Kunze S. Treatment of idiopathic trigeminal neuralgia: comparison of long-term outcome after radiofrequency rhizotomy and microvascular decompression. Neurosurgery. 2001;48:1261–7. discussion 1267–8. [PubMed].
50. van Loveren H, Tew JM Jr, Keller JT, Nurre MA. A 10-year experience in the treatment of trigeminal neuralgia. Comparison of percutaneous stereotaxic rhizotomy and posterior fossa exploration. J Neurosurg. 1982;57(6):757–64.
51. Verheul JB, Hanssens PE, Lie ST, Leenstra S, Piersma H, Beute GN. Gamma Knife surgery for trigeminal neuralgia: a review of 450 consecutive cases. J Neurosurg. 2010;113(Suppl):160–7.
52. Young B, Shivazad A, Kryscio RJ, St Clair W, Bush HM. Long-term outcome of high-dose Gamma Knife surgery in treatment of trigeminal neuralgia. J Neurosurg. 2013;119:1166–75.
53. Gofeld M, Faclier G. Radiofrequency denervation of the lumbar zygapophysial joints – targeting the best practice. Pain Med. 2008;9(2):204–11.
54. Sluijter ME, van Kleef M. Letters to the Editor – pulsed radiofrequency. Pain Med. 2007;8(4):388–9.
55. Cosman Jr ER, Cosman Sr ER. Electric and thermal field effects in tissue around radiofrequency electrodes. Pain Med. 2005;6(6):405–24.
56. Erdine S, et al. Effects of pulsed versus conventional radiofrequency current on rabbit dorsal root ganglion morphology. Eur J Pain. 2005;9(3):251–6.
57. Erdine S, et al. Ultrasound changes in axons following exposure to pulsed radiofrequency fields. Pain Pract. 2009;9(6):407–17.
58. Cohn S, Griffith S. Dorsal root ganglia radiofrequency procedures. In: Manchikanti L, Singh V, editors. Interventional techniques in chronic spinal pain. Paducah: ASIPP Publishing; 2007. p. 623–32.
59. Slappendel R, et al. The efficacy of radiofrequency lesioning of the cervical spinal dorsal root ganglion in a double blinded randomized study: no difference between 40 °C and 67 °C treatments. Pain. 1997;73(2):159–63.
60. Cahana A, et al. Pulsed radiofrequency: current clinical and biological literature available. Pain Med. 2006;7(5):411–23.
61. Gaucci CA. Manual of RF techniques. Meggen: FlivoPress; 2004.
62. Higuchi Y, et al. Exposure of the dorsal root ganglion in rats to pulsed radiofrequency currents activates dorsal horn lamina I and II neurons. Neurosurgery. 2002;50(4):850–5.
63. Cramer G, Darby S. Basic and clinical anatomy of the spine, spinal cord and ANS. St. Louis: Mosby; 1995.
64. Van Zundert J, et al. Pulsed radiofrequency adjacent to the cervical dorsal root ganglion in chronic cervical radicular pain: a double blind sham controlled randomized clinical trial. Pain. 2007;127(1–2):173–82.
65. Hamann W, et al. Pulsed radiofrequency applied to dorsal root ganglia causes a selective increase in ATF3 in small neurons. Eur J Pain. 2006;10(2):171–6.
66. Byrd D, Mackey S. Pulsed radiofrequency for chronic pain. Curr Pain Headache Rep. 2008;12:37–41.
67. Van Zundert J, Cahana A. Pulsed radiofrequency in chronic pain management: looking for the best use of electrical current. Pain Pract. 2005;5(2):74–6.
68. Sluijter M. Radiofrequency ablation in the management of spinal pain. Controversies Consens Imaging Interv. 2006;4(1):10–5.
69. Letcher FS, Goldring S. The effect of radiofrequency current and heat on peripheral nerve action potential in the cat. J Neurosurg. 1968;29(1):42–7.
70. Yamane T, et al. The effects of hyperthermia on the spinal cord. Spine (Phila Pa 1976). 1992;17(11):1386–91.
71. Froese G, Das RM, Dunscombe PB. The sensitivity of the thoracolumbar spinal cord of the mouse to hyperthermia. Radiat Res. 1991;125(2):173–80.
72. Protasoni M, et al. Pulsed radiofrequency effects on the lumbar ganglion of the rat dorsal root: a morphological light and transmission electron microscopy study at acute stage. Eur Spine J. 2009;18(4):473–8.
73. Van Zundert J, et al. Pulsed and continuous radiofrequency current adjacent to the cervical dorsal root ganglion of the rat induces late cellular activity in the dorsal horn. Anesthesiology. 2005;102(1):125–31.
74. Chua NHL, Vissers KC, Sluijter ME. Pulsed Radiofrequency treatment in interventional pain management: mechanisms and potential indications—a review. Acta Neurochir. 2011;153:763–71.
75. Eyigor C, Eyigor S, Korkman OK, Uyar M. Intra-articular corticosteroid injections versus pulsed radiofrequency in painful shoulder a prospective, randomized, single-blind study. Clin J Pain. 2010;24:386–92.
76. Goldthwait JE. The lumbosacral articulation: an explanation of many cases of lumbago, sciatica and paraplegia. Boston Med Surg J. 1911;164:365–72.
77. Curran MJ. Lumbosacral facet joint radiofrequency. In: Manchikanti L, Slipman CW, Fellows B, editors. Interventional pain management: low back pain – diagnosis and treatment. Paducah: ASIPP Publishing; 2002. p. 463–71.
78. Ghormley RK. Low back pain, with special reference to the articular facets, with presentation of an operative procedure. J Am Med Assoc. 1933;101:1773–7.
79. Rees WES. Multiple bilateral subcutaneous rhizolysis of segmental nerves in the treatment of the intervertebral disc syndrome. Ann Gen Pract (Melbourne). 1971;26:126.
80. Bogduk N, Long DM. Percutaneous lumbar medial branch neurotomy: a modification of facet denervation. Spine. 1980;5:193–200.

81. Shealy CN. Facet denervation in the management of back and sciatic pain. Clin Orthop. 1976;115:157–64.
82. Bogduk N, Dreyfuss P, Govind J. A narrative review of lumbar medial branch neurotomy for the treatment of back pain. Pain Med. 2009;10(6):1035–45.
83. Lau P, Mercer S, Govind J, et al. The surgical anatomy of lumbar medial branch neurotomy (facet denervation). Pain Med. 2004;5:289–98.
84. Bogduk N. The innervation of the lumbar spine. Spine. 1983;8(3): 286–93.
85. Bogduk N. The lumbar mamillo-accessory ligament. Spine. 1981;6(2):162–7.
86. Revel M, et al. Capacity of the clinical picture to characterize low back pain relieved by facet joint anesthesia. Proposed criteria to identify patients with painful facet joints. Spine. 1998;23(18): 1972–6.
87. Schwarzer AC, et al. Prevalence and clinical features of lumbar zygapophysial joint pain: a study in an Australian population with chronic low back pain. Ann Rheum Dis. 1995;54(2):100–6.
88. Bogduk N, Govind J. Medical management of acute lumbar radicular pain: an evidence-based approach. 1st ed. Newcastle: Cambridge Press; 1999.
89. Andersen KH, Mosdal C, Vaernet K. Percutaneous radiofrequency facet denervation in low-back and extremity pain. Acta Neurochir (Wien). 1987;87(1–2):48–51.
90. McCall IW, Park WM, O'Brien JP. Induced pain referral from posterior elements in normal subjects. Spine. 1979;4:441–6.
91. Cohen SP, Raja SN. Pathogenesis, diagnosis, and treatment of lumbar zygapophysial (facet) joint pain. Anesthesiology. 2007;106(3):591–614.
92. Bogduk N, MacVicar J, Borowczyk J. The pain of vertebral compression fractures can arise in the posterior elements. Pain Med. 2010;11:1666–73.
93. Park KD, Jee H, Nam HS, Cho SK, Kim HS, Park Y, Lim OK. Effect of medial branch block in chronic facet joint pain for osteoporotic compression fracture: one year retrospective study. Ann Rehabil Med. 2013;37(2):191–201.
94. Mooney V, Robertson J. The facet syndrome. Clin Orthop. 1976;115:149–56.
95. Schwarzer AC, et al. Clinical features of patients with pain stemming from the lumbar zygapophysial joints. Is the lumbar facet syndrome a clinical entity? Spine. 1994;19(10):1132–7.
96. Schwarzer AC, et al. Pain from the lumbar zygapophysial joints: a test of two models. J Spinal Disord. 1994;7(4):331–6.
97. Manchikanti L, Pampati S, Cash KA. Making sense of the accuracy of diagnostic lumbar facet joint nerve blocks: an assessment of the implications of 50% relief 80% relief, single block, or controlled diagnostic blocks. Pain Physician. 2010;13:133–43.
98. Derby R, Melnik I, Lee J-E, Lee S-H. Original research articles correlation of lumbar medial branch neurotomy results with diagnostic medial branch block cutoff values to optimize therapeutic outcome. Pain Med. 2012;13:1533–46.
99. Cohen SP, Strassels SA, Kurihara C, Griffith SR, Goff B, Guthmiller K, Hoang HT, Morlando B, Nguyen C. Establishing an optimal "cutoff" threshold for diagnostic lumbar facet blocks: a prospective correlational study. Clin J Pain. 2013;29(5): 382–91.
100. Dreyfuss P, et al. Specificity of lumbar medial branch and L5 dorsal ramus blocks: a computed tomography study. Spine. 1997;22(8):895–902.
101. Cohen SP, Williams KA, Kurihara C, Nguyen C, Shields C, Kim P, Griffin SR, Larkin TM, Crooks M, Williams N, Morlando B, Srarssels SA. Multicenter, randomized, comparative cost-effectiveness study comparing 0, 1, and 2 diagnostic medial branch (facet joint nerve) block treatment paradigms before lumbar facet radiofrequency denervation. Anesthesiology. 2010;113(2):395–405.
102. Derby R, Melnik I, Lee J-E, Lee S-H. Cost comparisons of various diagnostic medial branch block protocols and medial branch neurotomy in a private practice setting. Pain Med. 2013;14:378–91.
103. Van Zundert J, Mekhail N, Vanelderen P, van Kleef M. Diagnostic medial branch blocks before lumbar radiofrequency zygapophysial (facet) joint denervation: benefit or burden? Anesthesiology. 2010;113(2):276–8. doi:10.1097/ALN.0b013e3181e33b02.
104. Derby R, Melnik I, Choi J, Lee J-E. Indications for repeat diagnostic medial branch nerve blocks following a failed first medial branch nerve block. Pain Physician. 2013;16:479–88.
105. Dreyfuss P, et al. Efficacy and validity of radiofrequency neurotomy for chronic lumbar zygapophysial joint pain. Spine. 2000;25(10):1270–7.
106. Schofferman J, Kine G. Effectiveness of repeated radiofrequency neurotomy for lumbar facet pain. Spine. 2004;29(21):2471–3.
107. Kornick C, et al. Complications of lumbar facet radiofrequency denervation. Spine. 2004;29(12):1352–4.
108. Nath S, Nath CA, Pettersson K. Percutaneous lumbar zygapophysial (facet) joint neurotomy using radiofrequency current, in the management of chronic low back pain: a randomized double-blind trial. Spine. 2008;33:1291.
109. van Kleef M, Barendse GA, Kessels F, Voets HM, Weber WE, de Lange S. Randomized trial of radiofrequency lumbar facet denervation for chronic low back pain. Spine. 1999;24:1937–42.
110. Gofeld M, Jitendra J, Faclier G. Radiofrequency denervation of the lumbar zygapophysial joints: 10-year prospective clinical audit. Pain Physician. 2007;10:291.
111. Burnham RS, Holitski S, Dinu I. A prospective outcome study on the effects of facet joint radiofrequency denervation on pain, analgesic intake, disability, satisfaction, cost, and employment. Arch Phys Med Rehabil. 2009;90:201.
112. MacVicar J, et al. lumbar medical branch radiofrequency neurotomy in New Zealand. Pain Med. 2013;14:639–45.
113. Geurts J, et al. Radiofrequency lesioning of dorsal root ganglia for chronic lumbosacral radicular pain: a randomised, double-blind, controlled trial. Lancet. 2003;361(9351):21–6.
114. Raj P, et al. Lumbar sleeve and dorsal root ganglion block. In: Radiographic imaging for regional anesthesia and pain management. 1st ed. New York: Churchill Livingstone; 2003. p. 153–7.
115. Mathis JM, Golovac S. Image-guided spine interventions. New York: Springer; 2010.
116. Abejón D, et al. Pulsed radiofrequency in lumbar radicular pain: clinical effects in various etiological groups. Pain Pract. 2007;71:21–6.
117. Ahadian FM. Pulsed radiofrequency neurotomy: advances in pain medicine. Curr Pain Headache Rep. 2004;8(1):34–40.
118. Riew D, et al. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain a prospective, randomized, controlled, double-blind study. J Bone Joint Surg Am. 2000;82(11):1589–93.
119. Waldman S. Atlas of interventional pain management. 2nd ed. Philadelphia: WB Saunders; 2004.
120. Mahajan G. Pain clinic emergencies. Pain Med. 2008;9(S1): 113–20.
121. Trentman TL, et al. Vasovagal reactions and other complications of cervical vs. lumbar translaminar epidural steroid injections. Pain Pract. 2009;9(1):59–64.
122. Botwin KP, et al. Complications of fluoroscopically guided transforaminal lumbar epidural injections. Arch Phys Med Rehabil. 2000;81:1045–50.
123. Rosenthal RM, Starley D, Austin C. Avoiding complications from interventional spine techniques. Pract Pain Manag. 2010;10: 56–68.
124. Shabat S, et al. Pulsed radiofrequency in the treatment of patients with chronic neuropathic spinal pain. Minim Invasive Neurosurg. 2006;49:147–9.

125. Martin DC, et al. Pulsed radiofrequency application in the treatment of chronic pain. Pain Pract. 2007;7(1):31–5.
126. Pevzner E, et al. Pulsed radiofrequency treatment of severe radicular pain [in Hebrew]. Harefuah. 2005;144(3):178–80.
127. Cohen SP, et al. Pulsed radiofrequency of the dorsal root ganglia is superior to pharmacotherapy or pulsed radiofrequency of the intercostal nerves in the treatment of chronic postsurgical thoracic pain. Pain Physician. 2006;9(3):227–35.
128. Lord SM, Barnsley L, Wallis BJ, et al. Percutaneous radiofrequency neurotomy for chronic cervical zygapophyseal-joint pain. N Engl J Med. 1996;335(23):1721–6.
129. McDonald GJ, Lord SM, Bogduk N. Long-term follow-up of patients treated with cervical radiofrequency neurotomy for chronic neck pain. Neurosurgery. 1999;45(1):61–7.
130. Govind J, et al. Radiofrequency neurotomy for the treatment of third occipital headache. J Neurol Neurosurg Psychiatry. 2003;74(1):88–93.
131. Bogduk N. The clinical anatomy of the cervical dorsal rami. Spine. 1982;7(4):319–30.
132. Cusick JF, Pintar FA, Yoganandan N. Whiplash syndrome – kinematic factors influencing pain patterns. Spine. 2001;26(11):1252–8.
133. Barnsley L, et al. The prevalence of chronic cervical zygapophysial joint pain after whiplash. Spine. 1995;20(1):20–5.
134. Waldman SD. Atlas of common pain syndromes. 1st ed. Philadelphia: WB Saunders; 2002.
135. Manchikanti L, et al. The inability of the clinical picture to characterize pain from facet joints. Pain Physician. 2000;3(2):158–66.
136. Barnsley L, et al. False-positive rates of cervical zygapophysial joint blocks. Clin J Pain. 1993;9(2):124–30.
137. Lord SM, Barnsley L, Bogduk N. The utility of comparative local anesthetic blocks versus placebo-controlled blocks for the diagnosis of cervical zygapophysial joint pain. Clin J Pain. 1995;11(3):208–13.
138. Dwyer A, Aprill C, Bogduk N. Cervical zygapophyseal joint pain patterns. I: a study in normal volunteers. Spine. 1990;15(6):453–7.
139. Aprill C, Dwyer A, Bogduk N. Cervical zygapophyseal joint pain patterns. II: a clinical evaluation. Spine. 1990;15(6):458–61.
140. Cohen SP, et al. Factors predicting success and failure for cervical facet radiofrequency denervation: a multi-center analysis. Reg Anesth Pain Med. 2007;6:495–503.
141. Dreyfuss P. ISIS bioskills lab on cervical and lumbar radiofrequency neurotomy. 2008.
142. Derby R, Lee CH. The efficacy of a two needle electrode technique in percutaneous radiofrequency rhizotomy: an investigational laboratory study in an animal model. Pain Physician. 2006;9(3):207–13.
143. Sluijter ME. Radiofrequency, part 2. Meggen: FlivoPress; 2001.
144. Slipman CW, et al. Interventional spine: an algorithmic approach. Philadelphia: Saunders; 2007.
145. van Eerd M, et al. Cervical facet pain. Pain Pract. 2010;10(2):113–23.
146. Ahmed MM, Lake WB, Resnick DK. Progressive severe kyphosis as a complication of multilevel cervical percutaneous facet neurotomy: a case report. Spine J. 2012;12(10):e5–8. doi:10.1016/j.spinee.2012.09.037. Epub 2012 Oct 12.
147. Stoker GE, Buchowski JM, Kelly MP. Dropped head syndrome after multilevel cervical radiofrequency ablation: a case report. J Spinal Disord Tech. 2013;26(8):444–8. doi:10.1097/BSD.0b013e31825c36c0.
148. Holmes G. Headaches of organic origin. Practitioner. 1913;1:968–84.
149. Lord SM, et al. Third occipital nerve headache: a prevalence study. J Neurol Neurosurg Psychiatry. 1994;57(10):1187–90.
150. Bogduk N, Marsland A. On the concept of third occipital headache. J Neurol Neurosurg Psychiatry. 1986;49(7):775–80.
151. Bogduk N, Marsland A. Third occipital headache. Cephalalgia. 1985;5 Suppl 3:310–1.
152. Dreyfuss P, Michaelsen M, Fletcher D. Atlanto-occipital and lateral atlanto-axial joint pain patterns. Spine. 1994;19(10):1125–31.
153. Bogduk N. Local anesthetic blocks of the second cervical ganglion: a technique with application in occipital headache. Cephalalgia. 1981;1:41–50.
154. Haspeslagh SRS, et al. Randomised controlled trial of cervical radiofrequency lesions as a treatment for cervicogenic headache. BMC Anesthesiol. 2006;6:1.
155. Gallagher J, Vadi PLP, Wesley JR. Radiofrequency facet joint denervation in the treatment of low back pain—a prospective controlled double-blind study to assess its efficacy. Pain Clinic. 1994;7:193–8.
156. Leclaire R, Fortin L, Lambert R, Bergeron YM, Rossignol M. Radiofrequency facet joint denervation in the treatment of low back pain: a placebo-controlled clinical trial to assess efficacy. Spine. 2001;26:1411–6.

Radiofrequency Gangliolysis of the Trigeminal Nerve for Trigeminal Neuralgia

4

Andrew L. Ko and John D. Loeser

Introduction and History

Trigeminal neuralgia (TN) is characterized by lancinating, paroxysmal, excruciating pain in one or more divisions of the trigeminal nerve. It is usually unilateral. The onset is generally recalled by the patient and should not be associated with trauma or a surgical procedure of the face or dentition. Pain within the affected divisions can be generated spontaneously or triggered by light touch, wind, changes in temperature, or movements such as speaking or chewing. It is episodic with clear-cut pain-free intervals and may often enter remission for days, weeks, or even years. During pain attacks, patients may be left unable to eat or drink, speak, shave, or wash.

While historical descriptions of facial pain have been in existence since at least the time of Hippocrates [16], it was not until the late eighteenth century that Andre and Fothergill, a French surgeon and English physician, independently described the distinct clinical entity known as "tic douloureux" or "Fothergill disease"; neither localized the disease to the trigeminal nerve [9, 16]. It was not until Charles Bell described the distinct functions of the trigeminal and facial nerves that trigeminal neuralgia would be defined as we know it today [9, 16].

The pathophysiology underlying development of TN remains unclear. In 1934, Walter Dandy surmised that compression of the nerve by tumor or artery might serve as a cause [11]. Jannetta's 1967 paper postulating neurovascular compression (NVC) as the root cause of TN [20] and the remarkable success of microvascular decompression (MVD) as a treatment for TN [2] have led to the unfortunate conflation of NVC with TN. This belief persists in spite of the fact that TN clearly occurs and recurs in the absence of NVC [28] and that NVC of the trigeminal nerve is seen in up to 17 % of asymptomatic patients [33]. While NVC cannot be the sole cause of TN, it is likely that some injury to the nerve (with or without NVC) causes demyelination and reinforces excitability [13, 14, 23, 26]. Subsequently, more widespread gray and white matter changes may occur [12, 27, 29, 36].

The primary treatment for TN is medical. The use of anticonvulsants to treat trigeminal neuralgia was introduced by Bergouignan [3] in 1942, and since the introduction of carbamazepine by Blom [4] in 1962, medical science has not found a more effective medical treatment for TN than the sodium channel-blocking antiepileptics [54, 57]. Oxcarbazepine may have a more favorable side effect profile than carbamazepine, which is significant because treatment failure with medications is most often related to intolerance of the treatment rather than treatment failure [15]. There are few studies focusing on effectiveness of medical treatment over time. However, 20–30 % of patients fail medical treatment acutely due to side effects [15, 54], with another 10 % failing over the long term [15].

Surgical treatment for TN can be classified as ablative or non-ablative. A pain-free patient off of medications is considered a success. It is paramount to remember that all of these treatments have a half-life; that is, pain recurrence is not a complication but an expected consequence of TN. The duration of pain-free outcomes must be considered when presenting treatment options to patients and making the clinical decision of what treatment option to pursue. These factors will be discussed in more depth later in this chapter.

MVD is nondestructive and is the most effective and durable treatment for TN [2, 43]. Initial response to treatment is excellent. At 10 years, the rate of continued freedom from pain ranges from 50 to 85 % [2, 7, 43]. However, it is the most invasive procedure, requiring a craniotomy, posterior fossa exploration, and its attendant hospitalization and recovery time. Moreover, this surgery is not possible when there is no NVC.

All other procedures to treat TN are ablative in nature. Alternatives to MVD during a posterior fossa exploration are directed at the trigeminal root entry zone (REZ) and include partial sensory rhizotomy (PSR), nerve compression, and

A.L. Ko, MD • J.D. Loeser, MD, FIPP (✉)
Department of Neurological Surgery, University of Washington, Seattle, WA 98195, USA
e-mail: jdloeser@uw.edu

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_4

internal neurolysis. These interventions are less successful and less durable [21, 31, 38, 39, 53].

Stereotactic radiosurgery (SRS) is also used to ablate the REZ and is far less invasive than posterior fossa exploration. It is often pursued in patients where no NVC is noted or when medical comorbidities significantly increase surgical risk. It is also the least effective surgical treatment for TN [32, 51, 52]. This is particularly notable insofar as most studies of SRS consider improvement in pain (while on medications) a treatment success, in contrast to the complete abolition of pain that is the goal of craniotomy or percutaneous procedures.

Other commonly employed ablative treatments employ a percutaneous approach to the trigeminal ganglion. Methods for ablating the ganglion include radiofrequency gangliolysis, balloon compression, and glycerol gangliolysis. The efficacy and durability of these percutaneous treatments are in large part equivalent, with excellent initial results comparable to MVD, but a significantly shorter duration of pain relief [6, 8, 30].

Radiofrequency gangliolysis was first described by Sweet in 1974 [44]. Other percutaneous techniques for trigeminal gangliolysis include chemoneurolysis by glycerol injection, first described in 1981 by Hakanson [17], and balloon compression of the ganglion within Meckel's cave, reported by Mullan in 1983 [35]. These other techniques employ the same approach to the ganglion through the foramen ovale. The remainder of this chapter will focus on the first of these approaches.

The extraoral, percutaneous approach to the trigeminal ganglion was first described in 1914 [18] and is still in use today [37]. The use of electrocautery to ablate the ganglion was described by Kirshner in 1931 [24], but this technique was fraught with complications, as it employed monopolar current [9]. It was not until the introduction of radiofrequency thermoablation by Sweet, with the ability to provide precise temperature control during lesion creation, that the technique became safer and gained in popularity [44]. Further development of this procedure included the addition of short-acting anesthesia, stimulation mapping, and curved, guidable electrodes that allowed even more precise lesions [9].

Today, the goal of radiofrequency gangliolysis is to provide a selective destruction of pain-sensing fibers within the preganglionic fibers of the trigeminal nerve, providing instant pain relief in an outpatient setting. It has the benefit of allowing intraoperative confirmation of the site and density of lesion creation, making possible the specific targeting of one or more divisions of the nerve and selectively destroying the Aδ and C-fibers thought responsible for conveying the painful sensations in TN while minimizing loss of other modes of sensation [19]. It does not require general anesthesia and is minimally invasive, thus being safe in patients with medical comorbidities, and patients are generally discharged the same day.

Technical Aspects and Equipment

Radiofrequency gangliolysis can be performed with an RF generator with the ability to measure impedance, perform stimulation, and measure temperature. The authors use a Cosman® RFG-1A mode RF generator [10]. Impedance measurements can be useful in determining whether the electrode is within the ganglion or in CSF. Impedance within the ganglion is 150–300 Ω. Stimulation is performed at high frequency (50 Hz), with pulse width of 1 msec, to induce paresthesias. Positive stimulation should occur at 0.1–0.3 V. A normal body temperature reading should be confirmed after insertion of electrode to confirm that the generator is working properly.

Straight (TIC) [48] and curved (TEW) [47] electrode kits are also available from Cosman®. The former were developed by Sweet and include different length exposed tips to adjust lesion size (2, 5, 7, and 10 mm). The TEW kit includes a straight and curved electrode. The latter allows for off-axis stimulation and lesion creation using the curved electrode. This may facilitate lesion creation in the maxillary division.

A cable is necessary to connect the electrode with the RF generator. The Cosman® CB112-TC cable is compatible with both types of electrodes [47, 48].

Fluoroscopy is essential for safe lesion generation. Radiation safety protocols must be followed. Radio-opaque gloves may offer some additional protection for the surgeon. The senior author notes that with experience, the amount of fluoroscopy needed for localization is drastically reduced.

Indications and Contraindications

The indication for this procedure is trigeminal neuralgia. The diagnosis of this disease is a clinical one. The decision to pursue percutaneous gangliolysis may depend on patient-specific factors, such as age and medical comorbidities, or disease-dependent factors, such as the presence or absence of NVC.

Medical comorbidities that significantly increase the risk of general anesthesia and surgery should be considered. Patient tolerance of risk should play a role in decision-making. Major complications such as stroke, infection, and CSF leak are rare for craniotomy but are nearly unheard of during percutaneous procedures. Hospitalization and recovery time must also be taken into account, as RF gangliolysis is an outpatient procedure that generally causes minimal discomfort and requires minimal recovery time, in contrast to craniotomy, which requires ICU care, hospitalization, and

recovery over weeks. Finally, while age does not affect pain outcomes for MVD for TN [42], it is important to consider whether the additional risks and the burden of recovery from open surgery is worthwhile in patients whose life expectancy may not exceed a one or two half-lives of a less-invasive procedure such as RFL that may in most cases be repeated if necessary.

Disease-dependent factors that may indicate for a percutaneous approach rather than open surgery include the presence or absence of NVC and the diagnosis of multiple sclerosis (MS). When posterior fossa exploration for TN reveals no NVC, MVD is not possible; while ablative procedures such as PSR are often successful, they have proven less effective and durable than MVD [39, 53]. With the advent of high-resolution MRI combined with MR angiography, it is possible to ascertain whether a patient has NVC with a very high level of sensitivity and specificity [28, 33]. It is thus possible to counsel patients as to whether a posterior fossa exploration is likely to result in a MVD or a less effective procedure such as PSR.

Admittedly, a rigorous comparison of percutaneous procedures versus posterior fossa exploration has not been performed. The reported half-life of partial sensory rhizotomy via posterior fossa approach ranges widely, with 50 % recurrence rate reached from 2 to 5 years after surgery [6, 53]. A similar range in recurrence rates is reported for RFL but often includes retreatment [6, 22]. Thus, proceeding with RFL in the tic patient without NVC is a reasonable option.

The utility of MVD in the patient with MS has generated some controversy. Some advocate that patients with MS and NVC should be offered MVD, as nearly 50 % maintain pain-free results for more than 4 years [41]. Others report that 50 % of patients with MS undergoing MVD relapse in 3 months [1]. The largest series evaluating posterior fossa exploration for TN in patients with MS contained only 35 patients [5]. This series found no relationship between pain recurrence and the presence of NVC [5]. Importantly, comparison of varying treatments for TN in MS patients finds no significant difference in pain-free outcomes between MVD and RFL [34]. This same review advocates for MVD based on a lower complication rate for open surgery; however, hypoesthesia was considered a complication of RFL [34]. This is confusing, as some degree of hypoesthesia is generally a goal of the procedure. Given equal efficacy between MVD and RFL in the short and long term [34], the present authors advocate percutaneous approaches in MS patients as first-line treatment for TN.

Major contraindications to RFL of the trigeminal nerve relate by and large to the proper diagnosis of idiopathic trigeminal neuralgia.

It is important to confirm that the distribution of pain lies within the distribution of the trigeminal nerve. Nervus intermedius neuralgia presents with lancinating pain deep within the ear and would not be affected by ablation of the trigeminal nerve. Likewise, glossopharyngeal neuralgia, characterized by lancinating pain deep in the oropharynx, particularly with swallowing, should not be treated with a trigeminal nerve lesion. Both of these non-trigeminal tic pain syndromes are quite rare when compared to trigeminal distribution. The possibility of other specific syndromes associated with facial pain (e.g., Gradenigo, Raeder, Tolosa-Hunt) should be considered and addressed appropriately.

Facial pain syndromes that are not idiopathic trigeminal neuralgia should not be treated with ablative procedures. Examples of this include postherpetic pain, traumatic neuropathic pain, and trigeminal deafferentation pain. The first is usually characterized by a deep, constant, burning pain, often affects the first division in elderly patients, and is preceded by appearance of characteristic vesicles. The latter two are often the result of iatrogenic injury, whether it is directed at the trigeminal nerve intentionally, after ablative procedures for trigeminal neuralgia, or unintentionally, as seen after sinus surgery or dental procedures.

The rationale for ablative procedures in such cases is questionable, as onset of pain in these syndromes is related to damage to the nerve. It is unlikely that further damage with radiofrequency thermoablation, or any other technique, would be of benefit in such cases.

There are other contraindications to performing an RFL that are patient related. The patient must be able to communicate in order to participate in stimulation mapping. In some MS patients, verbal communication is not possible. In cases where the surgeon and patient do not share a common language, communication is also difficult. The use of an interpreter in the OR can be problematic; needle insertion has, in the experience of the senior author, caused dramatic vasovagal response in personnel unaccustomed to the OR, with predictable and unwelcome results.

Finally, the authors do not use RFL when trigeminal first division pain is being treated. Because the procedure results in hypoesthesia, the risk of corneal numbness, and subsequent keratitis, rises when treating V1. Balloon gangliolysis is our recommendation for these cases.

Technique

The operating room should be configured with the following in mind:

1. The position of the surgeon should account for the side of the pain to be treated, the handedness of the surgeon, and the comfort of the surgeon in handling the needle with either hand. The senior author stands to the patient's right for all procedures, using the right hand to direct needle for left- or right-sided pain; alternately, the surgeon may

find it easier to stand on the affected side, using either hand to guide the needle. In either case, the room should be arranged accordingly (Fig. 4.1).
2. Anesthesia should have access to the airway to provide assistance with ventilation if needed. The IV should be placed in the arm nearest anesthesia to allow access during the procedure if necessary.
3. Fluoroscopy is essential for performing the procedure safely. The C-arm should be positioned prior to induction of anesthesia. The monitor should be easily visible to the surgeon. Radiation safety for operating room personnel must be considered.
4. Simultaneous access by the surgeon to the radiofrequency generator and the patient must be possible during stimulation mapping and lesion creation.

A useful schematic for the procedural setup is shown in Fig. 4.1.

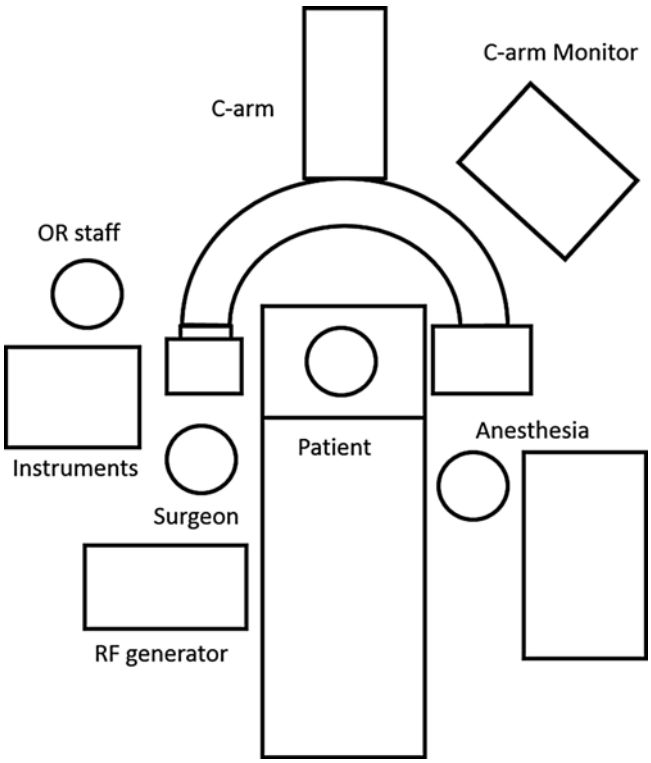


Fig. 4.1 Schematic for operating room during RFL procedure. This diagram represents a right-sided procedure for TN. The surgeon stands to the patient's right. Anesthesia is positioned contralaterally, with the anesthesia machine available for ventilation if needed, and IV access obtained on the left. The C-arm should be positioned so that an SMV and a lateral view are possible. The monitor should be easily visible to the surgeon. OR staff is shown on the patient's right, with enough proximity to hand instruments to the surgeon. The surgeon is able to reach and manipulate the RF generator while monitoring the patient during stimulation mapping and lesion creation

The patient is positioned supine with the head in a neutral position. It is helpful to place the operating table in a "beach-chair" position, slightly elevated at the knees, flexed at the hip, with the neck extended. The arms should be secured to minimize movement during sedation and during the procedure. Glycopyrrolate, 0.2 mg, should be administered IV prior to the initiation of the procedure to ameliorate the effects of the trigemino-cardiac reflex, which can be severe enough to induce asystole. With this precaution, we have not found it necessary to place transcutaneous pacer electrodes as others advocate. Transient tachycardia is the most troubling side effect. Additionally, no premedication with benzodiazepines should be given, to allow for faster awakening and more accurate testing.

Fluoroscopy is used to obtain a submentovertex view (SMV) of the base of the skull. The foramen ovale can thus be visualized, which is helpful for needle placement within the ganglion (Fig. 4.2). The senior author notes that, with experience, this view is unnecessary. In this case, a straight lateral view should be obtained, with care taken to align both auditory canals and the planum sphenoidale oriented perpendicular to the floor.

Preoxegenation for 3–5 min on 100 % oxygen with anesthesia mask is initiated, followed by conscious sedation with Propofol®. Ideally, the patient should be in Plane I of Stage III anesthesia for the placement of the radiofrequency needle. A variety of agents have been used in the past, with varying degrees of success. At a minimum, the choice of anesthesia must control the pain induced by introduction of the radiofrequency needle, and it must be short-acting, to allow for stimulation mapping and evaluation of the lesion created. In our experience, a bolus dose of 40 mg of Propofol®, repeated once per minute, is most effective for achieving the necessary sedation, while allowing the patient to awaken in a timely fashion.

A nasopharyngeal airway may be placed for ventilation if needed. During the procedure, jaw thrust may be needed to maintain the airway. Ventilation via the nasopharyngeal airway, or even mask ventilation, may be needed if the patient becomes apneic or hypoxic. Esmolol or nicardipine boluses may be used to control hypertension. We usually suggest that the systolic blood pressure be maintained below 160 mmHg.

The patient's cheek should be prepared with an antiseptic solution. With TN, it is more humane to wait until the patient is anesthetized before this step. Betadine has the advantages of being visible on the skin and can be used near mucus membranes. The patient's chest and neck should be draped with sterile towels, but the patient's face should remain exposed. This allows identification of anatomic landmarks and assessment of sensation once the lesion is created.

There are three anatomic landmarks important for needle placement:

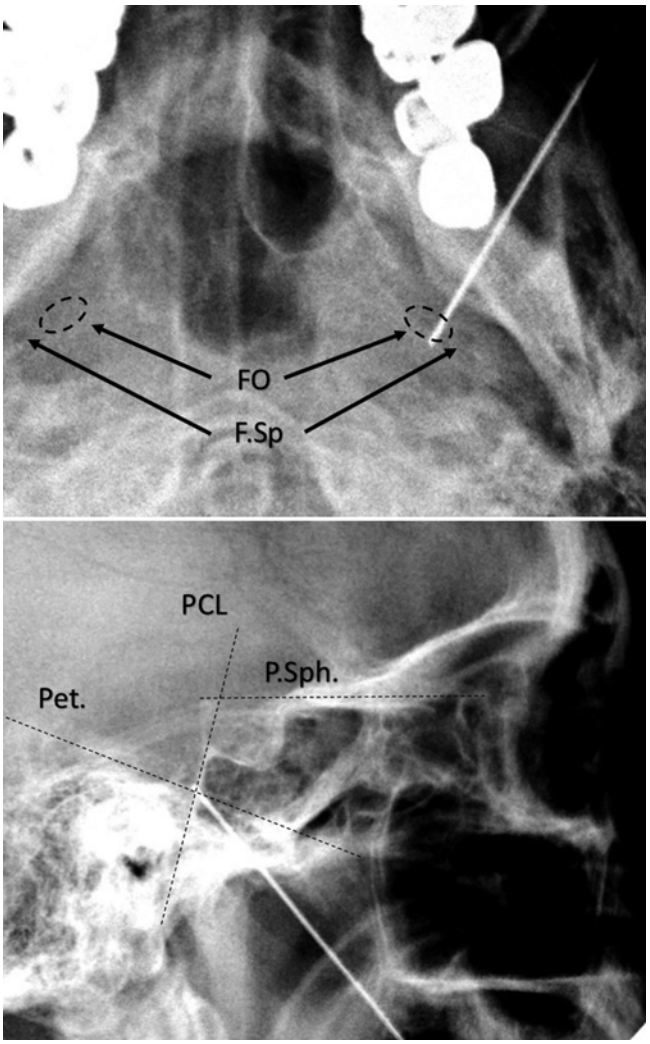


Fig. 4.2 Submentovertex (SMV) and lateral view of RF needle within foramen ovale (*FO*). *Top*, SMV view of the skull base with RF needle in FO. Note that the foramen spinosum (*F.Sp.*) is often easier to see than the FO itself. The FO will be anterior and medial to F.Sp. As seen here, the contralateral side can also be useful in localizing the needle. *Bottom*, lateral view of the skull base. This view should be as true as possible, which can be confirmed by aligning the auditory canal. The needle is directed at a 45° angle to the planum sphenoidale (*P.Sph.*), directed at the intersection between the petrous ridge (*Pet.*) and the posterior clival line (*PCL*). The electrode pictured is positioned with the tip at the PCL. In this patient, stimulation at 50 Hz with the electrode in this position produced parasthesias in V2

1. A coronal plane 3 cm anterior to the external auditory meatus
2. A sagittal plane at the mid-pupillary line
3. A point 2.5 cm lateral to the labial commissure in the mid-occlusal plane

The first two landmarks define the location of the foramen ovale; the third represents the site of needle insertion.

A nick is made in the skin, 2.5 cm lateral to the labial commissure, in the mid-occlusal plane. A finger may be introduced into the mouth to help prevent introducing the radiofrequency needle through the buccal mucosa and into the oral cavity. If doing so, the finger should be removed once the needle is past the coronoid process of the mandible, and gloves should be exchanged. The cannula with stylet inserted should be directed toward the ipsilateral pupil and toward a point 3 cm anterior to the external auditory meatus. The intraoral finger technique is not necessary once one has experience with this operation.

If using an SMV view, this trajectory will often direct the needle onto the greater wing of the sphenoid, anterior to the foramen ovale. Once the skull base is reached, the cannula can be redirected using fluoroscopic guidance, which will provide orientation in the lateral and anterior-posterior directions. With the needle in view, the foramen ovale may be obscured or difficult to visualize. The ipsilateral foramen spinosum may be a useful landmark in this case, with the foramen ovale located anteromedially; the configuration of the contralateral side may also be useful for localizing the target (Fig. 4.2).

The needle will "pop" into the foramen ovale; entering the ganglion is often accompanied by a jaw-jerk produced by a brief contraction of the masseter muscle. The C-arm should then be directed into a straight lateral view as described above. With experience, it is feasible to use this view during the entire procedure and avoid moving the C-arm. The needle trajectory should be at 45° to the planum sphenoidale. The needle should be advanced toward the intersection of the posterior margin of the clivus (clival line) and the petrous ridge (Fig. 4.2).

The stylet is withdrawn and replaced with the RF electrode. CSF is often seen when the stylet is withdrawn. However, this may not be noted when performing a repeat procedure. The electrode should read body temperature. This is important to confirm that the RF generator is functioning properly. Impedance within the ganglion is 150–350 Ω. This is helpful to confirm that the needle is within neural tissue rather than CSF.

Advancing the needle past the clival line, within 5 mm, results in more contact with V1; contact with V3 is facilitated by keeping the needle slightly anterior to the clival line. A curved Tew electrode can facilitate contact with the second division, by directing the tip of the electrode medially or cephalad, at the level of the clival line.

Once the electrode is in the desired position, the patient is allowed to awaken. Stimulation at 50 Hz produces paresthesias. This is usually noted with stimulation amplitude between 0.1 and 0.3 V. Stimulation at low frequency (2 Hz) should not elicit motor activity at less than 0.5 V. If motor activity is noted at lower voltage, the needle is likely within V1 fibers and too close to the motor fibers. If paresthesias are not noted in the affected division, the electrode should be repositioned.

To do so, it is useful to remember that the preganglionic fibers of CN V are arranged with V1 fibers superomedially, while V3 lies more laterally and inferiorly. As a general rule, advancing the electrode along the axis of the foramen ovale will move stimulation from V3 toward V2 and then V1. The use of a curved electrode directed medially and cranially has a similar effect. For example, if a straight electrode located at the clival line stimulates V2, and a lesion is desired in V3, the curved electrode can be introduced pointing laterally and caudally to reach these fibers. Alternately, if the electrode is withdrawn a few millimeters, the straight electrode is likely to be within V3 as well.

When electrode localization is confirmed, the patient is re-anesthetized for lesion creation, as this can be quite uncomfortable. Raising the temperature very slowly can ameliorate the patient response to this process. An initial lesion is made at 70° for 90 s. The patient is then reawakened, and sensation is tested. The goal is to create a lesion where the patient cannot distinguish pinprick from dull sensation in the affected division. This demonstrates selective lesioning of A-delta and C-fibers that carry sensation of pain and temperature. Additional lesions can be created as needed, using higher temperatures if necessary. This is often the case for repeat procedures. Creating the minimum lesion necessary to abolish pain lessens the incidence of dysesthesias after this procedure.

Once lesion creation is completed, the cannula and electrode are withdrawn without administration of further anesthesia. A small dressing may be placed. The patient is recovered in a postanesthesia care unit and discharged home. Patients may require some analgesic medications for tenderness in the face after this procedure. A typical procedure takes about 45 min of operating room time, and the patient goes home after an hour or two in recovery. If the desired sensory loss and pain relief have occurred, the patient should taper his/her oral tic medications by one less pill of each medicine per day.

Complications

Complications of this procedure can occur intraoperatively or may represent sequelae from the lesioning itself.

There are several structures to avoid during cannulation of the foramen ovale. The superior orbital fissure is anterior and superior to the foramen ovale. The jugular foramen lies posteriorly and inferiorly. The foramen of Vesalius lies anteromedially. The canal of Arnold, containing the lesser petrosal nerve, is located posterior to the foramen ovale. Advancing the needle into these structures results in piercing the temporal lobe. Attention to anatomic landmarks and use of fluoroscopy during needle manipulation are important in avoiding these structures. On a lateral x-ray, the proper trajectory should be at a 45° angle to the planum sphenoidale. The needle tip should be directed at the intersection of the petrous ridge and the posterior clivus. If the needle is directed at the sella turcica or anterior to the sella, it is too anterior; this is particularly important, as stimulation at these sites has been known to cause paresthesias in V2, in which case stimulation mapping provides an inaccurate assessment of localization [45].

The internal carotid artery is at risk at three sites: at the foramen lacerum (posterior and medial to the foramen ovale); within Meckel's cave, at the petrous bone (posterior and lateral); or within the cavernous sinus (anterior and medial to the ganglion). If the carotid is penetrated (a very rare event), the needle should be withdrawn immediately and repositioned. Once within the foramen, the needle should not be advanced more than 5 mm past the clival line, as this may result in damage to CN VI. The incidence of diplopia from injury to this nerve, or to CN III and IV, is about 1 % [45].

Some degree of hypoesthesia within the treated distribution is expected with RFL in nearly all patients and should not be considered a complication [6, 22, 45, 46]. The presence of unpleasant or painful dysesthesias, however, is much less common. The incidence of dysesthesias has been seen in as much as 15–20 % of patients [6, 45] but are considered bothersome or major (anesthesia dolorosa) in 0.5–4 % of patients [6, 8, 22, 45, 46]. The overall incidence of keratitis is rare and reported in less than 2 % of patients [6, 45, 46], though the rates of corneal numbness can be as high as 20 % [8]. It is important to note that innervation of the inferior cornea is often by V2, so patients with pain treated in this distribution should be warned regarding the possibility of corneal abrasion. Of note, most large studies report that the incidence of these complications has dropped as larger, more complete sensory lesions have been abandoned for more precise lesions [6, 22, 46].

Temporary masseter weakness can be seen in a sizeable proportion of patients (15 %) but is nearly always temporary, resolving within 6 months [8, 45, 46]. Infection, intraparenchymal hemorrhage, stroke, and death have been reported, but are extremely rare, with a handful of cases reported in several thousand cases [45, 46].

Outcomes Data

All treatments for TN have a half-life. It is important to bear this in mind when discussing treatment modalities with TN patients. No large, comprehensive, randomized-controlled trials comparing treatments for TN have been performed, and as of 2011, there is no Class I evidence for the efficacy of even the most widely accepted surgical treatments for TN [56]. Nevertheless, several salient points can be made regarding treatment effectiveness and durability when considering the options for treating TN.

It is extremely important to bear in mind what is considered successful treatment. We define success as a patient who is pain-free on no medications for tic. For most surgical procedures, including MVD, PSR, and RFL, success is defined similarly. However, most reports on the efficacy of SRS do not use these criteria for success, which can result in some confusion when considering results for gamma knife procedures. The Barrow Neurological Institute Pain Scale (BNI-PS) is a widely used outcome scale for facial pain. In its simplest form, this score is determined as follows:

BNI-PS Grade:

I: No trigeminal pain; no medication
II: Occasional pain, not requiring medication
III: Some pain, adequately controlled with medication
IV: Some pain, no adequately controlled with medication
V: Severe pain, no relief

This scale was initially introduced to grade outcomes from SRS. It is imperative to bear in mind that for outcomes for RFL, only BNI-PS Grade I patients are considered treatment successes. For many SRS studies, Grades I–III are treatment "successes" [25, 32]. Thus, SRS outcomes must be considered in light of these differing criteria for success.

Initial rates for pain-free outcomes using RFL are quite good. Complete pain relief has been reported as high as 97.6 % [22]. Median time to recurrence may be as short as 24 months [49, 55]. Our experience, as reported by Burchiel et al. in 1981, shows a median time to recurrence of about 3 years; allowing for repeat procedures, the rate of pain-free outcomes at 6 years is 78 % [6]. The upper range of treatment durability is seen in two large studies, by Kanpolat and van Loveren of about 1500 and 700 patients, respectively, reporting about 60 % of patients remaining pain-free at 5 years [22, 50]. At 5 years, recurrence has been reported as high as 65 % [6] and as low as 39 % [50]. The durability of this treatment is affected by the density of hypoesthesia achieved during treatment, with large, dense lesions leading to a lower rate of recurrence, at the expense of a higher rate of sensory dysfunction and dysesthesias [46]. This may explain the large variation in reported outcomes [8, 49]. Pain recurrence can be retreated with RFL with similar effectiveness [22], with the same caveats. Importantly, the presence of dense hypoesthesias in the same distribution of pain may indicate that a repeat lesioning will not be effective.

Microvascular decompression has long been considered the gold standard for treatment of TN when NVC is present, with several large observational studies supporting its safety and efficacy [2, 6, 43]. However, when MVD is not possible because of the lack of NVC, or when medical comorbidities increase surgical risk unacceptably, other modalities of treatment must be considered. In comparison to percutaneous procedures or SRS, the invasive nature of MVD must also be taken into account when counseling patients of more advanced age, in whom less durable but effective percutaneous procedures may provide quality results at less risk, with less recovery time.

The three widely practiced percutaneous treatments for TN are comparable in outcomes. Glycerol rhizolysis and RFL share similar pain-free outcomes that are often related to the degree of hypoesthesias obtained during treatment [8]. Balloon compression may have lower rates of post-procedural dysesthesias and is preferred by the authors when V1 distribution pain is present but tends to have slightly higher rates of recurrence [8]. Each of these procedures has significantly less recovery time than MVD.

Long-term pain control (not abolition of pain, BNI-PS Grade I–III) is achieved with SRS in 50–75 % of patients at 5 years [25, 32]. While this seems comparable to results of other ablative procedures, one must bear in mind several caveats regarding radiosurgery. Pain relief may be delayed by weeks, and criteria for successful treatment are much less stringent, as improvement in symptoms while on medications is a successful SRS result, in contrast to percutaneous procedures which aim for immediate abolition of symptoms without the need for medications.

In discussions with patients, the authors summarize these results as follows: 90 % of patients get immediate pain relief with MVD, and 50 % of patients undergoing MVD in the context of NVC are pain-free at 10 years; without NVC, the rate of being pain-free is about 50 % at 5 years; treatment with RFL has similar results in the short term, with 90 % of patients experiencing immediate pain relief, but the average half-life of treatment is 3 years; importantly, the rate of pain-free outcomes with repeated treatment is about 80 % at 6 years. SRS provides 70–80 % of patients with some relief of their symptoms, and 50 % of patients maintain improved symptoms at 5 years, but the chance of being off all medications is significantly lower, with only 30 % of patients having a Grade I outcome [25].

Conclusion

RFL is an effective treatment for TN. Major complication rates are low. The most likely complications are related to the extent and density of lesion created and has been mitigated by the treatment strategy of minimizing the amount of hypoesthesia created during thermoablation.

While acutely effective, RFL has a treatment half-life of about 3 years. However, the lesion can be repeated several times. Allowing for multiple procedures, pain-free results for TN treated with RFL can be as high as 80 % over 6 years. Given that this is a minimally invasive, well-tolerated outpatient procedure with low risk of complication, this is a very reasonable option for the management of TN.

Examination of practice patterns in the USA show that the rate of MVD for TN has remained relatively steady from 1988 to 2010 at over 2000 cases per year, while the number of percutaneous procedures has dropped from about 1500 cases a year to 250 cases a year [40]. It is difficult to say what has driven this change. There has not been a significant change in reported outcomes for percutaneous procedures during that time. This decrease in percutaneous procedures is not due to an increased use of SRS [40]. One possible interpretation is that there has been a decrease in the number of practitioners the expertise necessary to perform these procedures.

Given that RFL is a safe and effective treatment for TN, it is important that the surgeon or physician treating facial pain maintains the ability to offer this treatment.

References

1. Ariai MS, Mallory GW, Pollock BE. Outcomes after microvascular decompression for patients with trigeminal neuralgia and suspected multiple sclerosis. World Neurosurg. 2014;81:599–603.
2. Barker FG, Jannetta PJ, Bissonette DJ, Larkins MV, Jho HD. The long-term outcome of microvascular decompression for trigeminal neuralgia. N Engl J Med. 1996;334:1077–84.
3. Bergouignan M. Fifteen years of trial therapy of essential trigeminal neuralgia: the place of diphenylhydantoin and its derivatives. Rev Neurol (Paris). 1958;98:414–6.
4. Blom S. Trigeminal neuralgia: its treatment with a new anticonvulsant drug (G-32883). Lancet. 1962;1:839–40.
5. Broggi G, Ferroli P, Franzini A, Nazzi V, Farina L, La Mantia L, et al. Operative findings and outcomes of microvascular decompression for trigeminal neuralgia in 35 patients affected by multiple sclerosis. Neurosurgery. 2004;55:830–9.
6. Burchiel KJ, Steege TD, Howe JF, Loeser JD. Comparison of percutaneous radiofrequency gangliolysis and microvascular decompression for the surgical management of tic douloureux. Neurosurgery. 1981;9:111–9.
7. Burchiel KJ, Clarke H, Haglund M, Loeser JD. Long-term efficacy of microvascular decompression in trigeminal neuralgia. J Neurosurg. 1988;69:35–8.
8. Cheng JS, Lim DA, Chang EF, Barbaro NM. A review of percutaneous treatments for trigeminal neuralgia. Neurosurgery. 2013. Available: http://www.ncbi.nlm.nih.gov/pubmed/24064481.
9. Cole CD, Liu JK, Apfelbaum RI. Historical perspectives on the diagnosis and treatment of trigeminal neuralgia. Neurosurg Focus. 2005;18:1–10.
10. Cosman Radiofrequency Generators, Product Brochure 11560 Rev. A:2010.
11. Dandy WE. Concerning the cause of trigeminal neuralgia. Am J Surg. 1934;24:447–55.
12. DeSouza DD, Hodaie M, Davis KD. Abnormal trigeminal nerve microstructure and brain white matter in idiopathic trigeminal neuralgia. Pain. 2014;155:37–44.
13. Devor M, Amir R, Rappaport ZH. Pathophysiology of trigeminal neuralgia: the ignition hypothesis. Clin J Pain. 2002;18:4–13.
14. Devor M, Govrin-Lippmann R, Rappaport ZH. Mechanism of trigeminal neuralgia: an ultrastructural analysis of trigeminal root specimens obtained during microvascular decompression surgery. J Neurosurg. 2002;96:532–43.
15. Di Stefano G, La Cesa S, Truini A, Cruccu G. Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain. J Headache Pain. 2014;15:34.
16. Eboli P, Stone JL, Aydin S, Slavin KV. Historical characterization of trigeminal neuralgia. Neurosurgery. 2009;64:1183–6; discussion 1186–7.
17. Hakanson S. Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. Neurosurgery. 1981;9:638–46.
18. Härtel F. Über die intrakranielle Injektion Behandlung der Trigeminusneuralgie. Med Klin. 1914;10:582–4.
19. Howe JF, Loeser JD, Black RG. Percutaneous radiofrequency trigeminal gangliolysis in the treatment of tic douloureux. West J Med. 1976;124:351.
20. Jannetta PJ. Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. J Neurosurg. 1967;26(Suppl):159–62.
21. Jie H, Xuanchen Z, Deheng L, Kun G, Fengyang X, Xiang C, et al. The long-term outcome of nerve combing for trigeminal neuralgia. Acta Neurochir (Wien). 2013;155:1703–8.
22. Kanpolat Y, Savas A, Bekar A, Berk C. Percutaneous controlled radiofrequency trigeminal rhizotomy for the treatment of idiopathic trigeminal neuralgia: 25-year experience with 1600 patients. Neurosurgery. 2001;48:524–34.
23. Kerr FWL. Pathology of trigeminal neuralgia: light and electron microscopic observations. J Neurosurg. 1967;26:151–6.
24. Kirschner M. Zur Elektrochirurgie. Arch Klin Chir. 1931;167:761–8.
25. Kondziolka D, Zorro O, Lobato-Polo J, Kano H, Flannery TJ, Flickinger JC, et al. Gamma Knife stereotactic radiosurgery for idiopathic trigeminal neuralgia. J Neurosurg. 2009;112:758–65.
26. Koplovitch P, Minert A, Devor M. Spontaneous pain in partial nerve injury models of neuropathy and the role of nociceptive sensory cover. Exp Neurol. 2012;236:103–11.
27. Leal PRL, Amédée Roch J, Hermier M, Souza MAN, Cristino-Filho G, Sindou M. Structural abnormalities of the trigeminal root revealed by diffusion tensor imaging in patients with trigeminal neuralgia caused by neurovascular compression: a prospective, double-blind, controlled study. Pain. 2011;152:2357–64.
28. Lee A, McCartney S, Burbidge C, Raslan AM, Burchiel KJ. Trigeminal neuralgia occurs and recurs in the absence of neurovascular compression: clinical article. J Neurosurg. 2014;120:1048–54.
29. Liu Y, Li J, Butzkueven H, Duan Y, Zhang M, Shu N, et al. Microstructural abnormalities in the trigeminal nerves of patients with trigeminal neuralgia revealed by multiple diffusion metrics. Eur J Radiol. 2013;82:783–6.
30. Lunsford LD, Apfelbaum RI. Choice of surgical therapeutic modalities for treatment of trigeminal neuralgia: microvascular decompression, percutaneous retrogasserian thermal, or glycerol rhizotomy. Clin Neurosurg. 1985;32:319–33.
31. Ma Z, Li M. "Nerve combing" for trigeminal neuralgia without vascular compression: report of 10 cases. Clin J Pain. 2009;25:44–7.
32. Maesawa S, Salame C, Flickinger JC, Pirris S, Kondziolka D, Lunsford LD. Clinical outcomes after stereotactic radiosurgery for idiopathic trigeminal neuralgia. J Neurosurg. 2001;94:14–20.
33. Miller JP, Acar F, Hamilton BE, Burchiel KJ. Radiographic evaluation of trigeminal neurovascular compression in patients with and without trigeminal neuralgia: clinical article. J Neurosurg. 2009;110:627–32.
34. Montano N, Papacci F, Cioni B, Di Bonaventura R, Meglio M. What is the best treatment of drug-resistant trigeminal neuralgia in patients affected by multiple sclerosis? A literature analysis of surgical procedures. Clin Neurol Neurosurg. 2013;115:567–72.

35. Mullan S, Lichtor T. Percutaneous microcompression of the trigeminal ganglion for trigeminal neuralgia. J Neurosurg. 1983;59:1007–12.
36. Parise M, Kubo TTA, Doring TM, Tukamoto G, Vincent M, Gasparetto EL. Cuneus and fusiform cortices thickness is reduced in trigeminal neuralgia. J Headache Pain. 2014;15:17.
37. Peris-Celda M, Graziano F, Russo V, Mericle RA, Ulm AJ. Foramen ovale puncture, lesioning accuracy, and avoiding complications: microsurgical anatomy study with clinical implications. J Neurosurg. 2013;119:1176–93.
38. Revuelta-Gutiérrez R, López-González MA, Soto-Hernández JL. Surgical treatment of trigeminal neuralgia without vascular compression: 20 years of experience. Surg Neurol. 2006;66:32–6.
39. Revuelta-Gutierrez R, Martinez-Anda JJ, Coll JB, Campos-Romo A, Perez-Peña N. Efficacy and safety of root compression of trigeminal nerve for trigeminal neuralgia without evidence of vascular compression. World Neurosurg. 2013;80:385–9.
40. Rosenbaum BP, Kelly ML, Kshettry VR, Vadera S, Weil RJ. Practice patterns of in-hospital surgical treatment of trigeminal neuralgia from 1988 to 2010. Clin Neurol Neurosurg. 2014;120:55–63.
41. Sandell T, Eide PK. The effect of microvascular decompression in patients with multiple sclerosis and trigeminal neuralgia. Neurosurgerg. 2010;67:749–54.
42. Sekula Jr RF, Frederickson AM, Jannetta PJ, Quigley MR, Aziz KM, Arnone GD. Microvascular decompression for elderly patients with trigeminal neuralgia: a prospective study and systematic review with meta-analysis. J Neurosurg. 2011;114:172–9.
43. Sindou M, Leston J, Decullier E, Chapuis F. Microvascular decompression for primary trigeminal neuralgia: long-term effectiveness and prognostic factors in a series of 362 consecutive patients with clear-cut neurovascular conflicts who underwent pure decompression. J Neurosurg. 2007;107:1144–53.
44. Sweet WH, Wepsic JG. Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers. J Neurosurg. 1974;40:143–56.
45. Taha JM, Tew JM. Percutaneous rhizotomy in the treatment of intractable facial pain. In: Schmidek H, editor. Operative neurosurgical techniques, vol. 2. 4th ed. W.B. Saunders Company; Philadelphia. 2000. p. 1537–51.
46. Taha JM, Tew JMJ. Comparison of surgical treatments for trigeminal neuralgia: reevaluation of radiofrequency rhizotomy. Neurosurgery. 1996;38:865–71.
47. TEW Trigeminal neuralgia kit, Product Brochure 10731 Rev. A:2006.
48. TIC trigeminal neuralgia kit, Product Brochure 10750, Rev. A:2006.
49. Tronnier VM, Rasche D, Hamer J, Kienle A-L, Kunze S. Treatment of idiopathic trigeminal neuralgia: comparison of long-term outcome after radiofrequency rhizotomy and microvascular decompression. Neurosurgery. 2001;48:1261–8.
50. Van Loveren H, Tew JM, Keller JT, Nurre MA. A 10-year experience in the treatment of trigeminal neuralgia. J Neurosurg. 1982;57:757–64.
51. Verheul JB, Hanssens PE, Lie ST, Leenstra S, Piersma H, Beute GN. Gamma Knife surgery for trigeminal neuralgia: a review of 450 consecutive cases: clinical article. J Neurosurg. 2010;113:160–7.
52. Young B, Shivazad A, Kryscio RJ, St. Clair W, Bush HM. Long-term outcome of high-dose Gamma Knife surgery in treatment of trigeminal neuralgia: clinical article. J Neurosurg. 2013;119:1166–75.
53. Young J, Wilkins R. Partial sensory trigeminal rhizotomy at the pons for trigeminal neuralgia. J Neurosurg. 2009;79:680–7.
54. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. BMJ. 2014;348:g474.
55. Zakrzewska JM, Thomas DG. Patient's assessment of outcome after three surgical procedures for the management of trigeminal neuralgia. Acta Neurochir (Wien). 1993;122:225–30.
56. Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. Cochrane Database Syst Rev. 2011;(9):CD007312.
57. Zhang J, Yang M, Zhou M, He L, Chen N, Zakrzewska JM. Non-antiepileptic drugs for trigeminal neuralgia. Cochrane Database Syst Rev. 2013;12:CD004029.

Block and Lesioning of the Splanchnic Nerves

5

P. Prithvi Raj

History

The first anterior percutaneous approach was when Kappis introduced splanchnic anesthesia in 1914 [1] and followed it up in 1918 [2] with the publication of a series of 200 cases. The recognition that splanchnic nerve block may provide relief of pain in a subset of patients who fail to obtain relief from celiac plexus block has led to a renewed interest in this technique. Interest in this technique has been regenerated by the introduction of the computed tomography (CT)-guided approach and, recently, by the use of RF -produced lesions. Raj and associates reported good outcome with RF lesioning using the Racz Finch curved needles."

The technique for splanchnic nerve block differs little from the classic retrocrural approach to the celiac plexus, except that the needles are aimed more cephalad in order to ultimately rest at the anterolateral margin of the T12 vertebral body [2]. It is imperative that both needles be placed medially against the vertebral body to reduce the incidence of pneumothorax. Abram and Boas [3] described a technique for splanchnic nerve block that used a paravertebral transthoracic approach. The needle was advanced to rest against the anterolateral aspect of the T11 vertebral body. In the Boas technique, the needles are bilaterally advanced 6 mm lateral to the midline of T11 intercostal space contacting vertebral body. Despite neurolytic agents having been used widely for splanchnic blockade, Raj defined RF lesioning for more selective cases with fewer side effects [4]. The predictable relationship of the splanchnic nerves to other structures allows for accurate needle placement and hence a low risk of iatrogenic damage. Other authors had different results in the application of splanchnic nerve blockades via various methods.

Anatomy

The splanchnic nerves innervate the following viscera:

- Stomach-duodenum
- Liver-pancreas
- Kidney
- Intestines (Table 5.1)

Autonomic Innervation of the Abdominal Viscera

Sympathetic nerves leave the spinal cord from T4 to T9 and pass the thoracic sympathetic chain at these segmental levels and enter the celiac ganglion before entering the specific viscera. In addition, from T(-&12 sympathetic chain travel and form the sympathetic fibers, superior and inferior messenteric ganglions, they innervate in addition the kidneys and intestines (Fig. 5.1).

Nociceptive Pathways

Pain-carrying nerve fibers, which originate from the stomach, duodenum, liver, kidneys, and intestines, enter celiac ganglion and ascend into the spinal cord via the greater, lesser, and least splendoric nerves. The nociceptive pathway from the large intestine passes through lesser mesenteric ganglion and enters the relevant sympathetic chain and enters the relevant portions of the spinal cord (Fig. 5.2).

In addition, the pain fibers from male and female reproductive structures enter the segment of the sympathetic chain

Table 5.1 Abdominal pain

Common examples
Stomach and duodenum (gastritis – peptic ulcer – neoplasm)
Liver or spleen
Biliary ducts and gall bladder –inflammation

P.P. Raj, MD, FIPP, FRCA
Department of Anesthesiology, Texas Tech University Health Science Center 5-10, Lubbock, TX, USA
e-mail: prithviraj@fuse.net

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_5

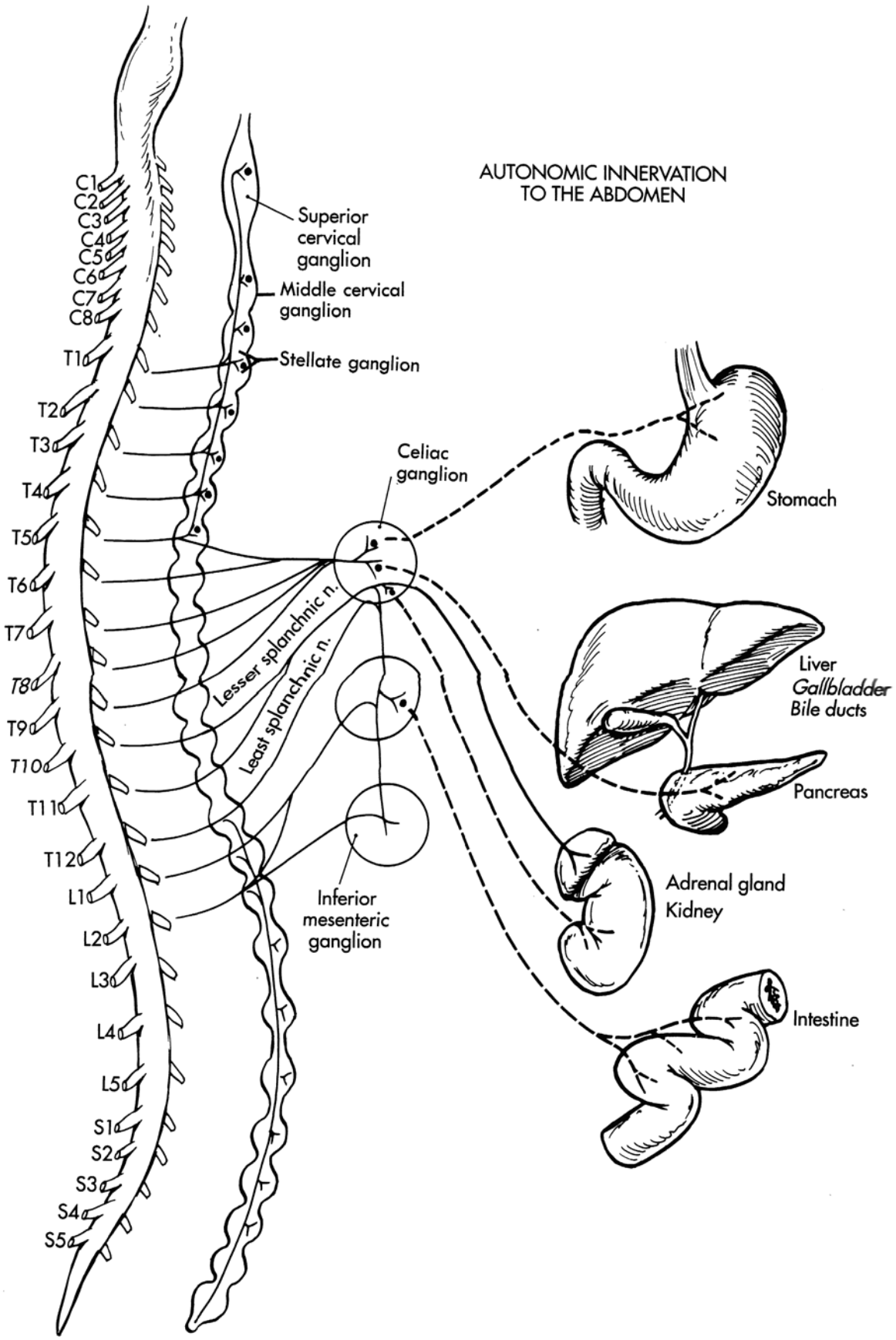


Fig. 5.1 Efferent sympathetic outflow of the autonomic nerves to the abdominal viscera

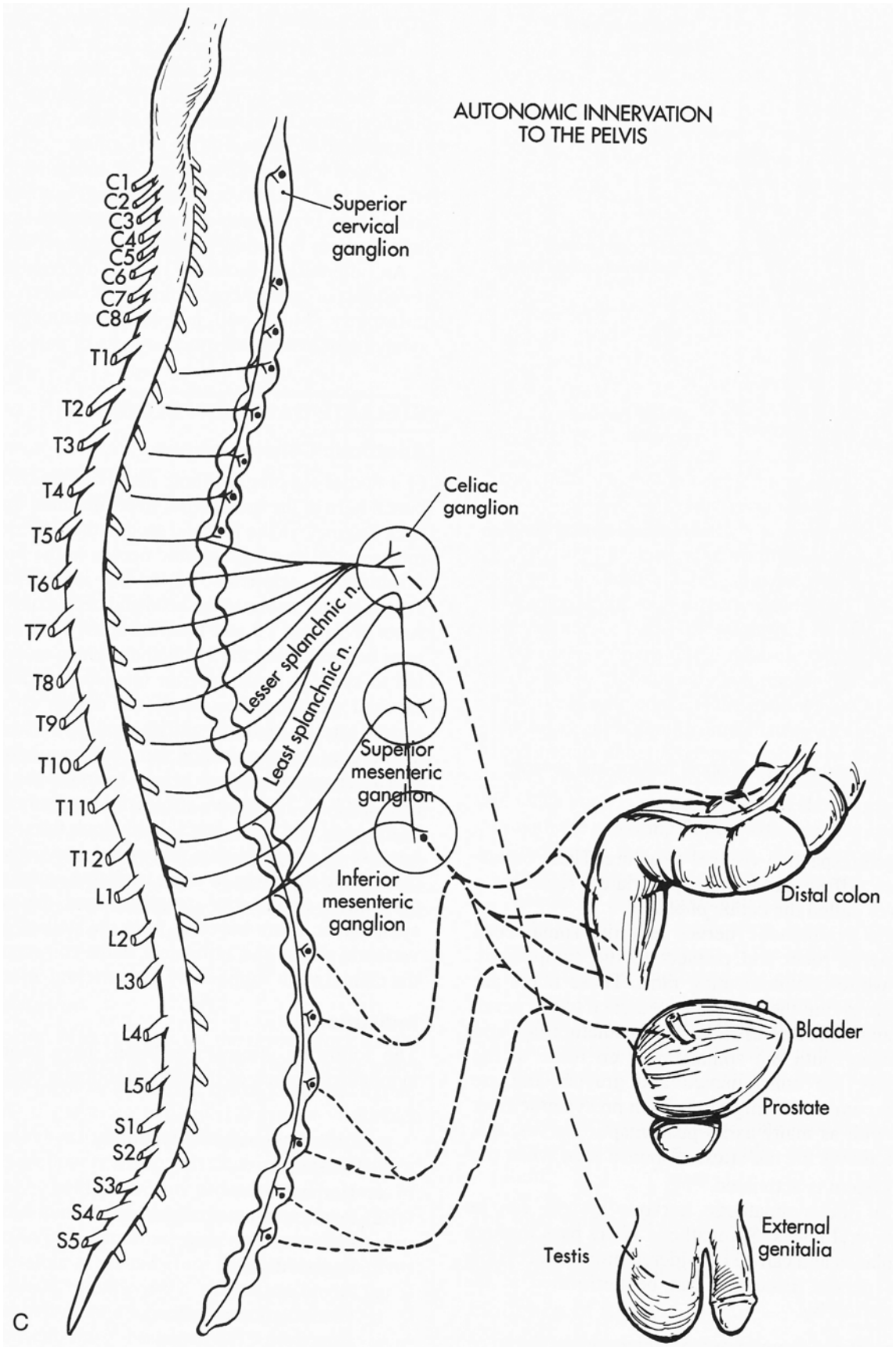


Fig. 5.2 Autonomic pain pathway arising from autonomic afferent pathway arising from upper abdominal viscera and pelvic organs

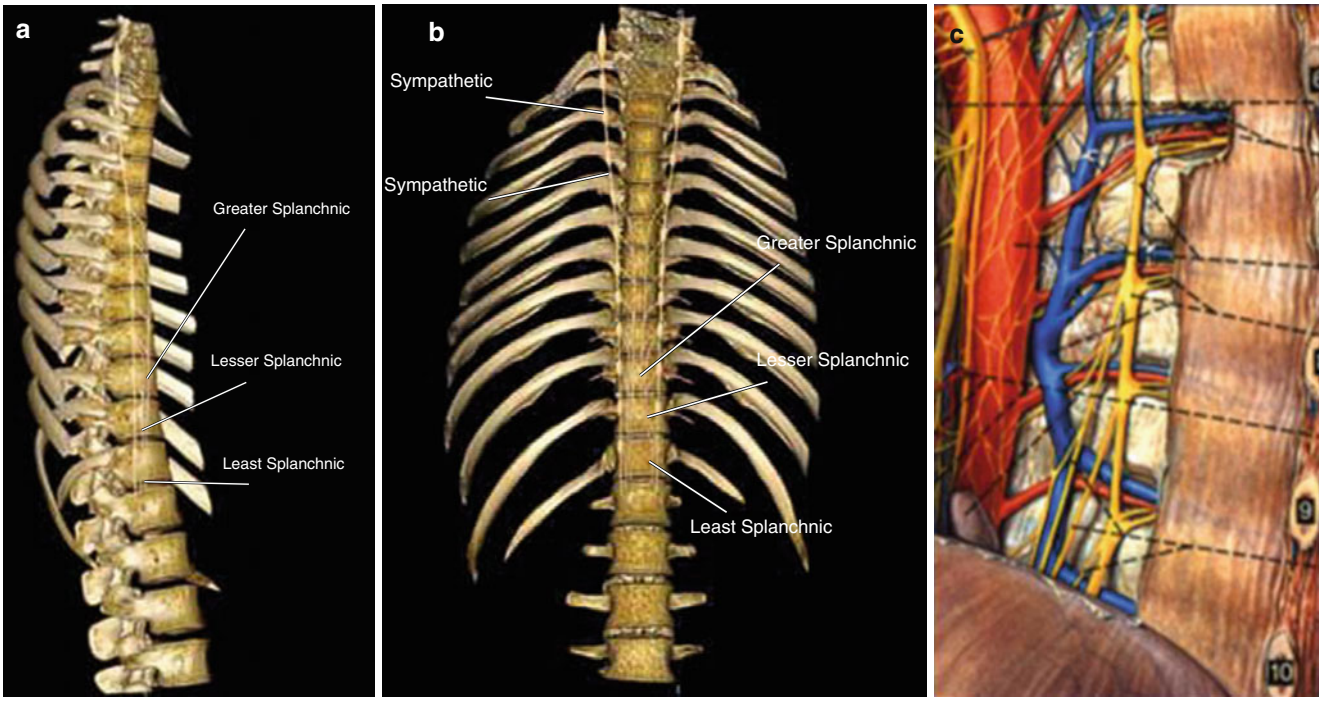


Fig. 5.3 (**a**) The formation of greater, lesser, and least splanchnic nerves from the nerve roots T5–12 in a lateral view (with permission from P. Prithvi Raj and Serdar Erdine). (**b**) The formation of the splanchnic nerves in the anteroposterior view of the thoracic spine (with permission from P. Prithvi Raj and Serdar Erdine). (**c**) Splanchnic nerves in a narrow compartment. Medial relations – vertebral bodies and discs. Lateral relations – crus of the diaphragm and parietal pleura. Anterior relations – posterior mediastinal structures. Posterior relations-pleural attachment to the vertebral body

via the inferior and superior mesenteric ganglion as well as from the celiac ganglion.

Origin and Relationship of the Splanchnic Nerves

The splanchnic nerves are formed by the greater, lesser, and least splanchnic nerves. The greater splanchnic nerve is derived from the T5 to T10 spinal roots. The lesser splanchnic nerve arises from the T10 to T11 roots, whereas the least splanchnic nerve arises from the T11 to T12 spinal roots. All these three nerves coalesce in the celiac plexus. They are preganglionic fibers entering the celiac plexus.

These nerves lie in a narrow tubular space bounded by the vertebral body medially, pleura laterally, the posterior mediastinum ventrally, and crura of the diaphragm caudally (Fig. 5.3a–c).

Indications for Splanchnic Nerve Block and Lesion

- Pain syndromes involving upper abdominal viscera
- Acute and chronic pancreatitis
- Cancer pain from the upper abdominal viscera (Table 5.2)

Table 5.2 Splanchnic nerve block indications

Diagnostic for sympathetically maintained pain in
Retroperitoneal structures
Upper abdomen
Flank pain
Therapeutic
Cancer (upper abdominal viscera)
Pancreatitis
Acute pain of arterial embolism of liver (cancer therapy)
Abdominal angina

Labat [9]

Techniques of Splanchnic Block and Lesioning

Preoperative Procedure

There are two common approaches for the splanchnic block. Posterior approaches are as follows: (1) retrocrural approach (of Hartel) and (2) paravertebral lateral approach (Fig. 5.4).

Retrocrural approach of Hartel:

Prepare the patient before the major invasive procedure. A recent CT scan is necessary to see the anatomical structures at the entry site or near the splanchnic nerve.

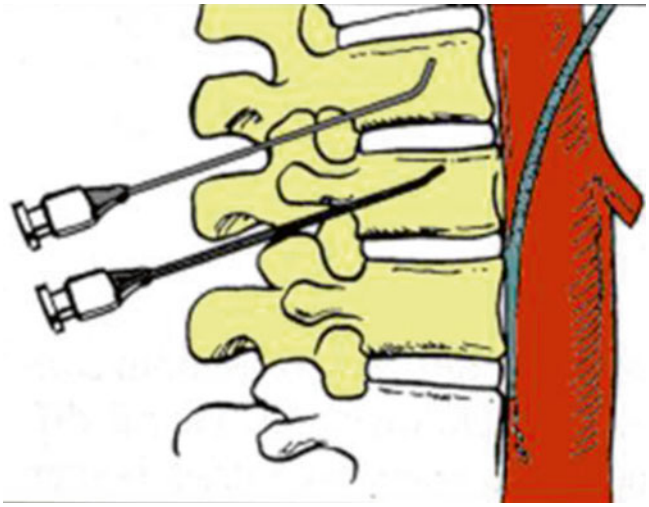


Fig. 5.4 Transthoracic approach of splanchnic nerve block, lateral view

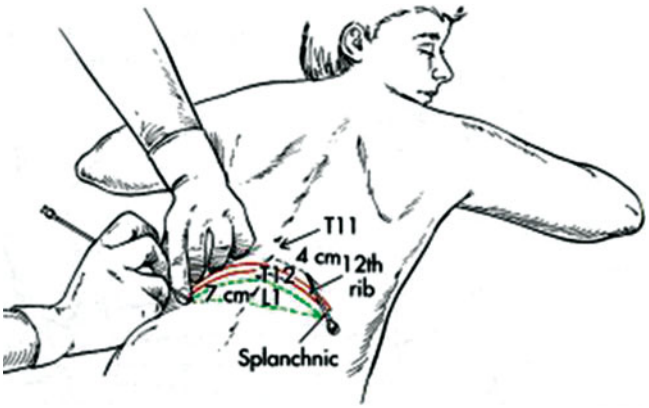


Fig. 5.5 Landmarks of the classical approach to Celiac plexus and splanchnic nerve block and also the more medially transthoracic approach from 4 cm lateral to the T12 vertebral body and 12th rib

Monitoring

All patients should have an intravenous catheter inserted in a large vein and securely anchored. A 500 ml solution of dextrose-Ringer's lactate should be started, with at least 200 ml of solution infused before the procedure.

The type of analgesia or sedation needs to be ascertained before performance of the procedure. The type of sedation varies based on the technique being used. If a diagnostic epidural block with a local anesthetic is considered, some form of sedation and analgesia may be appropriate for some patients. Intravenous fentanyl, midazolam, and/or propofol may be used judiciously for the patient's comfort.

Position and monitor the patient.

Place the patient prone on the table. Place a pillow under the abdomen to flex the thoracolumbar spine. The patient's head is turned to the side, and the arms are permitted to hang freely off each side of the table.

- An intravenous cannula is inserted for medication injections.
- Oxygen is provided by nasal cannula.
- Monitoring of vital signs is mandatory.
- The area for needle entry is prepared in a sterile fashion.

Equipment and Drugs for the Technique

- Small, thin syringe for local anesthetic
- Needle for local infiltration
- 10 ml syringe for the splanchnic block
- Two 10 cm. 22 gauge needles for the splanchnic block
- 5 ml syringe for the contrast material
- 1 % lidocaine for skin infiltration or for diagnostic
- Nonionic contrast solution
- 5 ml of 0.5 % bupivacaine and 40 mg methylprednisolone for neurolysis, 6 % phenol in glycerin or saline or with iohexol.

Visualization

1. Place the C-arm for posteroanterior view of the T10–L2 region first. The anatomical landmarks to be determined are the 12th rib and vertebral body of T12 and T11. To identify the T12 vertebral body easily, one may first identify the L4–L5 interspace and the posterior superior iliac crests under fluoroscopy and course upward (Fig. 5.5).
2. Then rotate the C-arm approximately 45° to view the edge of the vertebral body and the diaphragm. The lateral side of the T12 vertebral body should be in view. Note the movement of the diaphragm during inspiration and expiration and note the image of the lateral side of the vertebral body during the expiration phase.

Direction of the Needle

The point of entry is at the junction of the rib and vertebral body (T10–T11).

Infiltrate the skin with 1 % lidocaine. Insert a 10 cm, 22 gauge needle through the skin and advance under fluoroscopy using tunneled vision. After advancing 1–1.5 cm anteriorly, turn the C-arm laterally.

Advance the needle until it reaches the junction of the anterior one-third and posterior two-thirds of the vertebral body. One should always have a bony contact with the vertebral body while advancing the needle.

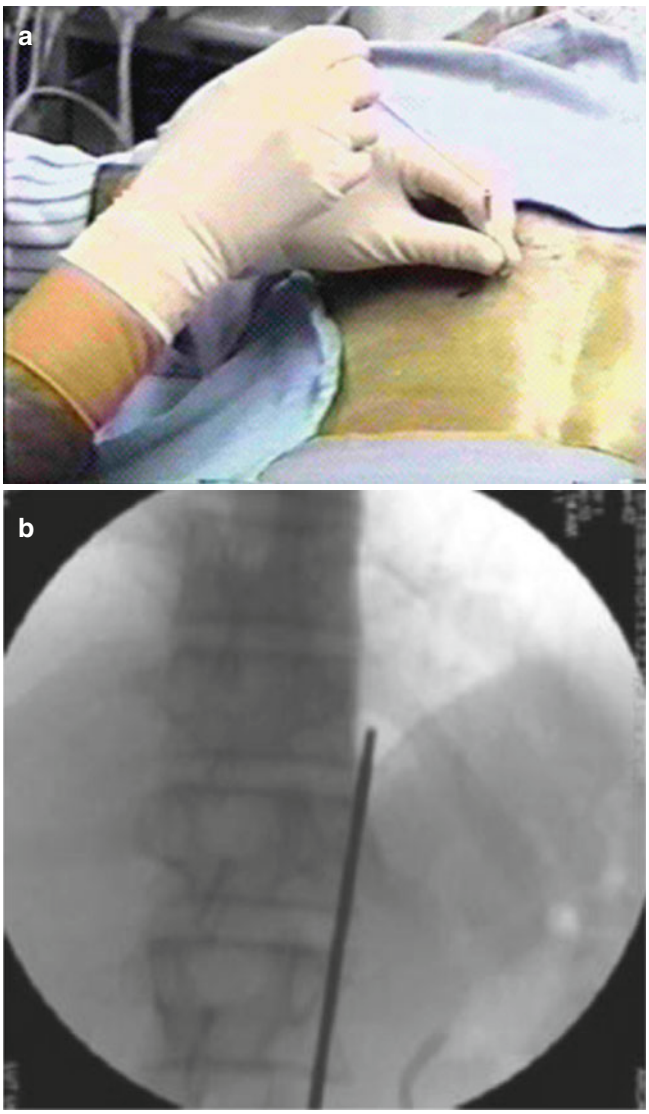


Fig. 5.6 (**a**) Point of entry for the needle for the splanchnic nerve block in prone position. (**b**) Radiographic image for the splanchnic nerve block entry point

Now position the C-arm for the posteroanterior view again to verify the bony contact of the needle with the vertebral body.

Aspirate for blood or cerebrospinal fluid. If the aspiration test is positive, withdraw and redirect the needle. Repeat the procedure on the contralateral side (Fig. 5.6a, b).

Confirmation of the Position of the Needle

Inject 5 ml of contrast material. On the posteroanterior view, the contrast material will spread adhering to the no, T11, or T12 vertebral body. A smooth contoured image will appear in the lateral view. The tip on the lateral view should stay retrocrural to the aorta.

For diagnostic and prognostic purposes, inject 5 ml of lidocaine bilaterally.

For neurolysis, inject 5 ml of 6 % phenol in glycerin or saline or with iohexol bilaterally. The risk of neuritis is higher with alcohol if that is preferred for neurolysis.

Repeat the same procedure on the contralateral side if bilateral block is required.

Technique of Paravertebral Transthoracic Approach

Visualization

Identify the 12th ribs under the posteroanterior view with the C-arm (Fig. 5.7a, b).

Mark the entry point approximately 6 cm from the midline. Infiltrate the skin with 1 % lidocaine.

Direction of the Needle

Advance the needle 45° toward the midline and about 35° cephalad toward the anterolateral aspect of the T11 vertebral body, passing beneath the eleventh rib.

Then position the C-arm laterally.

Advance the needle until it reaches the junction of the anterior one-third and posterior two-thirds of the vertebral body. One should always have a bony contact with the vertebral body while advancing the needle (Fig. 5.8a, b).

Confirm the Position of the Needle

When confirmed to be in the right position, inject 2–3 ml of contrast solution. The contrast material should be confined just lateral to the vertebral body on the posteroanterior view

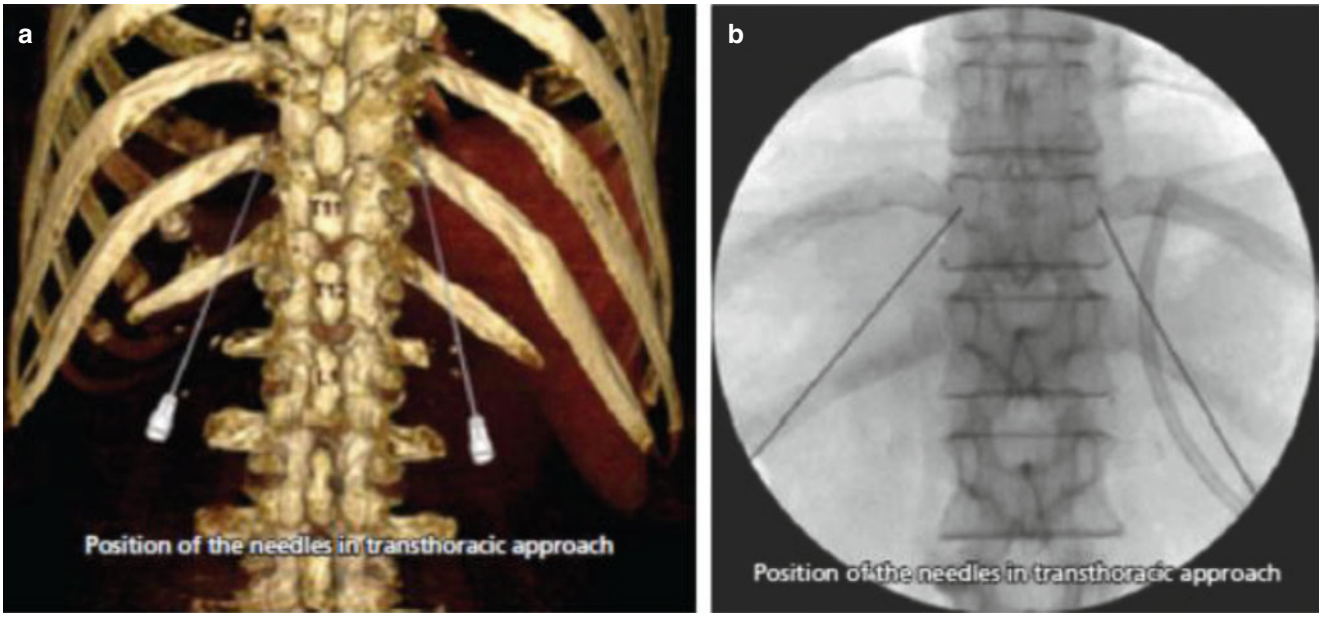
Confirm the spread also in the lateral view.

Repeat the procedure for the contralateral side or bilateral block.

If the needle is too superficial, the contrast solution may spread to the epidural space, and if too deep, it will contact the diaphragm (Fig. 5.9).

Neurolytic Block

After verifying the correct position of the needle, inject 3–6 ml of 6 phenol in glycerin or saline or iohexol for neurolysis.



Figs. 5.7 (**a**) Direction of the needles for transthoracic block, skeletal view. (**b**) The needles shown in radiographic image for the transthoracic splanchnic nerve block. (Permission from P. Prithvi Raj and Serdar Erdine "Pain Relieving Procedures The Illustrated Guide")

Technique of RF Lesioning of the Splanchnic Nerve

Because splanchnic nerves are contained in a narrow compartment, they are accessible for RF lesioning. This approach has been described by P. Raj in 1999 [4].

Equipment for RF Lesioning of the Splanchnic Nerves

- RF machine
- 15 cm curved RF needle with 15 mm electrode tip
- 14 gauge, 5 cm extracath (for skin entry before RF needle insertion)
- 2-IOml plastic syringe with local anesthetic and steroids (for injections before lesion)
- 1-IOml syringe with Omnipaque (contrast solution) (to confirm the correct placement the needle tip)
- 1–2 ml syringe with local anesthetic for skin infiltration
- One extension set to help manipulate the needle and for easy injection of solutions
- Radiofrequency (RF) machine with cables and electrodes
- Two 10 cm needles with 5 mm active tip electrode for the RF

Visualization

In the prone position, the T12 vertebral body is identified in the posteroanterior view of the fluoroscope. Keeping a mark on the T12 or T11 vertebra, the C-arm is moved to an oblique position (about 45 °C).

The edge of the diaphragm lateral to the vertebral body is viewed. Its movement during inspiration and expiration is noted. If the diaphragm shadows the T12 vertebra and its rib, then the T11 rib is identified.

Mark the surface landmarks for the needle entry. The point of entry for both levels is at the junction of the rib and vertebra. Skin infiltration is made at this point. With the oblique fluoroscopic view still in place, a 14 gauge, 5 cm extracath is inserted so that the catheter transverses toward the target as a pinhead.

Direction of the Needle

After the extracath is inserted two-thirds of the way, the stylet is removed and the RF needle is inserted. The oblique view of the fluoroscope is maintained. Extension tubing is attached to the needle.

With short thrusts of 0.5 cm at a time, the tip of the needle is advanced anteriorly, keeping in mind that the needle stays hugging the lateral aspect of the T11 or T12 vertebral body, close to the costovertebral angle.

Confirmation of the Position of the Needle (Fig. 5.10a, b)

After advancing 1–1.5 cm anteriorly, the lateral fluoroscopic view is taken. In the lateral view, the needle is advanced

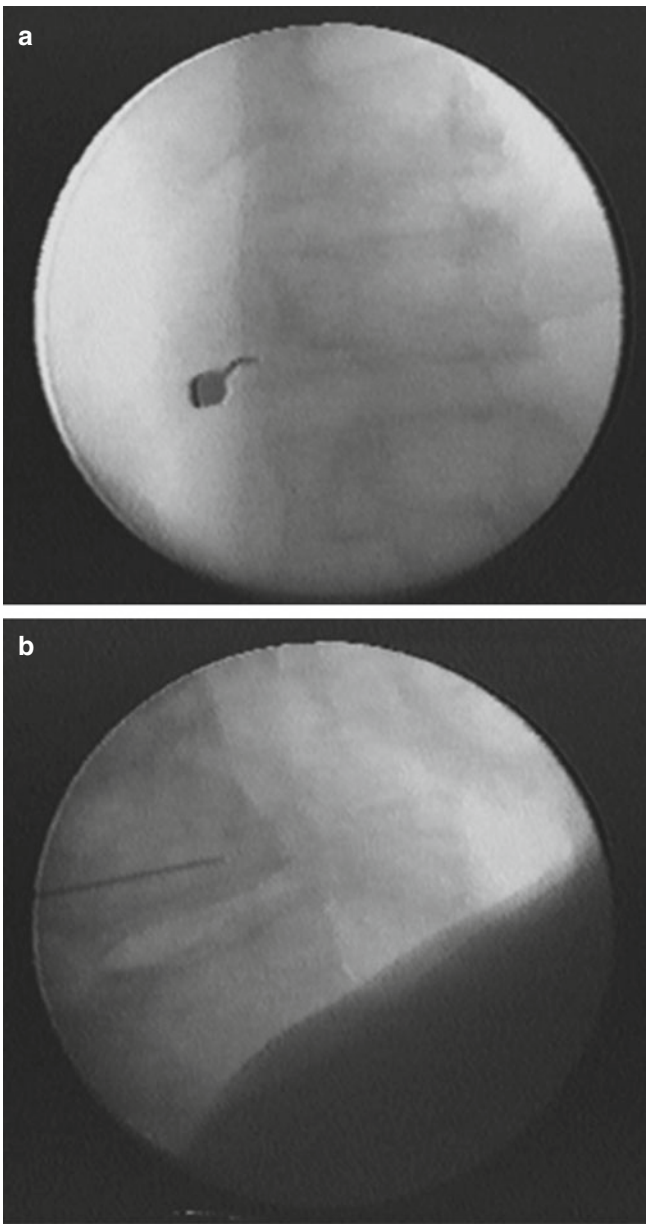


Fig. 5.8 (**a**) Oblique view of the radiographic image showing the curved needle in correct position for the splanchnic nerve block. (**b**) Lateral view of the radiographic image showing the curved needle in correct position for the splanchnic nerve block

until it reaches the junction of the anterior one-third and posterior two-thirds of the lateral surface of the vertebral body.

The needle is then aspirated for fluid, which could be blood, cerebrospinal fluid, or chyle. If negative for any fluid aspiration, then oblique views are taken to confirm the final position of the curved needle on the vertebral body. Omnipaque (5 ml) is injected to note that the solution in anteroposterior and lateral views hugs the spine. It should

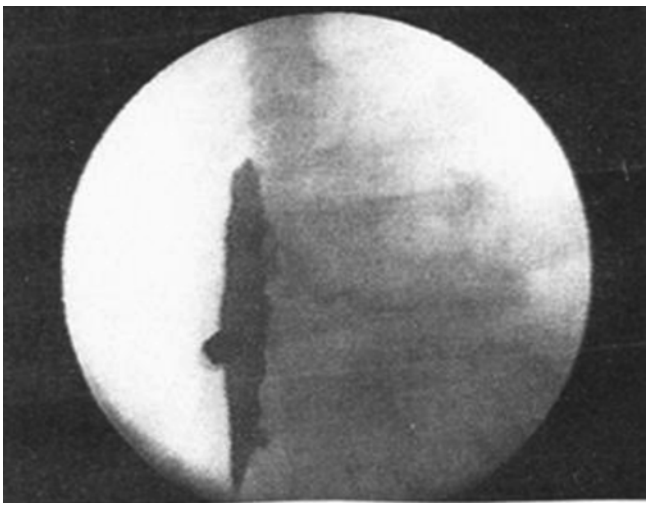


Fig. 5.9 Oblique view of the spread of the dye (5 ml of iohexol) for the splanchnic nerve block with the correct positioning of the needle. Note the vertical spread of the dye hugging the vertebra

flow medial to the interpleural space, above the crus of the diaphragm, and anterior to the foramen.

Stimulation Test

1. Once the needle is in place, a 15 mm electrode is introduced through the RF needle. The electrical circuit is tested.
   The impedance should be below 2500 hms.
2. At 50 Hz, the sensory stimulation is conducted up to I V.
   The patient may report that he or she feels stimulation in the epigastric region. This is typical and satisfactory. If the stimulation is in a girdle-like fashion around the intercostal spaces, then the needle needs to be pushed anteriorly.
3. At 2 Hz motor stimulation is done lip to 3 V. One tries to palpate or see the intercostal muscle contraction. If this is negative, then test stimulation is satisfactory.

RF Lesioning

Lesion: after satisfactory test stimulation, 2–5 ml of local anesthetic (ropivacaine 0.5 with steroid, 40 mg of triamcinolone) is injected through the RF needle. After waiting for 1–2 min, the RF lesion is created with a setting 90 s at 80 °C. The second lesion at the same setting is done turning the RF needle 180°. If the procedure is for bilateral neurolysis, then the same procedure of testing and lesioning is done on the opposite site

After RF lesioning, 40 mg of triamcinolone is injected to prevent inflammation due to lesioning. The electrodes are then withdrawn.

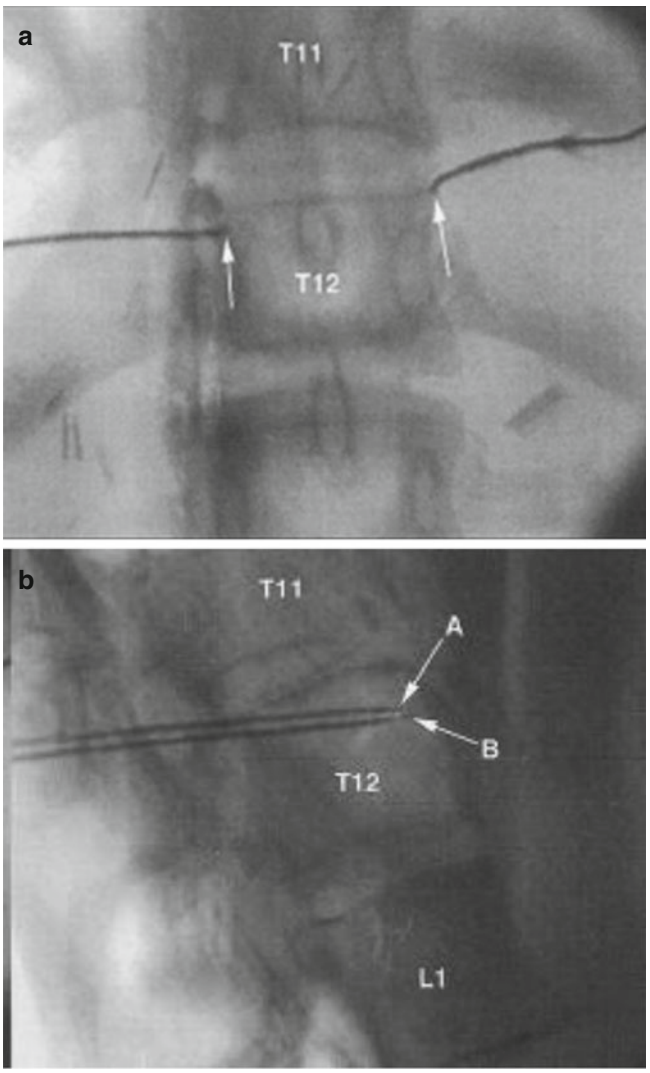


Fig. 5.10 (**a**) Bilateral AP view of radiofrequency needles in correct position at upper edge of T12 for radiofrequency lesioning of the splanchnic nerves. The *arrows* show the tips of the needle at the upper third of T-12 of right and left of vertebral body. (**b**) Lateral view of radiofrequency needles in correct position at upper edge of T12 for radiofrequency lesioning of the splanchnic nerves. The *arrows* show the tips of the needle from left to right bilaterally in this lateral image

Postprocedure Care

After the procedure is completed, the patient needs to be observed for at least 2 h. Monitoring of vital signs is mandatory. In addition to monitoring vital functions, pain relief should be documented. After a satisfactory observation in the recovery room, the patient should be discharged to the inpatient floor to continue with the protocol for the procedure or to home with appropriate and adequate instructions given to their escort. Written instructions are preferable for emergencies and are helpful to the patient and their family.

Complications

- Pneumothorax

Pneumothorax may occur by mistakenly identifying the eleventh rib for the twelfth when outlining surface anatomy relationships. The pleural reflection can extend as low as the neck of the twelfth rib posteriorly. The use of smaller gauge needles is recommended to prevent pneumothorax (see Table).

- Sensory and motor loss

Injection or contact of neurolytic solutions to neural structures other than the celiac plexus may cause sensory motor loss in the lower extremities.

- Spinal cord ischemia, paraparesis, and paraplegia

Paraplegia generally is regarded as an idiosyncratic event that is unrelated to technique, expertise, or negligence. Although still a remote complication, paraplegia now has been reported with essentially every major posterior approach to celiac and splanchnic nerve block except blockade by the anterior percutaneous route.

The pyramidal and spinothalamic tracts typically are affected, with relative sparing of proprioception. Given the wide acceptance of the use of radiologic guidance and the distance between the splanchnic nerve or celiac axis and the spinal canal, the most important mechanism of neurologic injury is postulated to relate to spinal cord ischemia or infarct as a consequence of disruption of small nutrient vessels by spasm, direct injury, or accidental intravascular injection. Mechanical or chemical disruption of the nutrient vessels to the spinal cord with the development of spinal cord infarction has been invoked to explain most occurrences of major neurologic morbidity after celiac and splanchnic block. Adamkiewicz's arteries (arteria radicularis magna), the largest of the cord's ventral radicular arteries, provide nutrient blood flow to the lower two-thirds of the spinal cord. After leaving the aorta, they run laterally, about 80 % of the time on the left, and typically reach the cord between T8 and L4, making them vulnerable to injury during the splanchnic block.

- Neuritis

Neuritis may develop due to the neurolytic agents. The incidence seems to be higher with alcohol; thus, phenol in saline is preferred.

- Inadvertent. Epidural or intrathecal puncture

If the entry point is more than 7.5 cm from the midline and the angle of insertion is less than 45°, there is a risk of inadvertent epidural or intrathecal puncture. However, this complication is nearly impossible if the splanchnic block is performed under fluoroscopy.

- Chylothorax

Inadvertent puncture of the thoracic ducts may cause chylothorax. However, it is a very rare complication.

- Inadvertent. Vascular injection

As with all techniques, there is a risk of intravascular injection. The contrast material should be administered under live imaging and an aspiration test is mandatory.

- Hemi-diaphragmatic paralysis

The spread of the neurolytic solution on the diaphragm may cause paralysis of the diaphragm.

Helpful Hints

The fluoroscopic oblique view ensures the medial direction of the needle, and the lateral view ensures that the needle stays posterior to the aorta and anterior to the foramen.

Before lesioning, the injection of the local anesthetic helps in reducing the discomfort due to the RF lesioning and decreases pain postoperatively. Steroids help in treating the occasional occurrence of neuritis by reducing edema and inflammation of the lesioned structures.

The incidence of pneumothorax related to splanchnic nerve block is higher than the celiac plexus block. The incidence of pneumothorax can be decreased if the needles are kept dose to the vertebral bodies during needle placement.

There is a recognition among pain physicians, that in a subset of patients who fail to obtain relief from bilateral celiac plexus block, splanchnic nerve block may provide relief. There is also further rationale for this block, since the splanchnic nerves are in a definable compartment they are easy to block. Unilateral blocking of splanchnic nerves also helps unilateral pain

Efficacy and Outcome

Since the definition of splanchnic nerve blockade, various techniques and drugs have been evaluated for complications, quality of life, and drug consumption. Garcia studied ten patients with RF of splanchnic nerves taking into consideration of the pain levels, anxiety, quality of life, and mood [5]. Although the patient number is small, all the parameters associated with long-term debilitating chronic pain were improved. Ozyalcin et al. compared the survival rate and quality of life in patients with pancreatic cancer treated either with celiac plexus blockade or splanchnic nerve blockade [6]. They found splanchnic nerve blockade with neurolytic superior to celiac plexus blockade on the basis of survival rates, quality of life, and side effects. Phan et al. [7] studied the correlation of splanchnic nerve block efficacy and cancer staging. They found that splanchnic nerve block effectively helped control pain in patients with pancreatic and GI malignancies, producing significant decreases in pain and MEDD. However, staging of cancer did not significantly predict procedure efficacy.

Plancarte-Sanchez used percutaneous transdiscal splanchnic nerve blockade under tomographic control in 64 patients, aiming to reduce possible complications due to nerve blockade. Side effects included dyspnea, 5; hypotension, 26.7; nausea, 31.7; and diarrhea, 83.3 [8].

Neither morbidity (which was minor) nor efficacy (70–80 immediate success and 60–75 persistence of effect until death) correlated with anatomic technique. Splanchnic nerve block maintains a deservedly meaningful role in the armamentarium of the contemporary pain specialist. Despite a dearth of scientifically determined outcome data, even the most critical observer is nearly certain to acknowledge the therapeutic value of these techniques in patients with viscerally mediated abdominal and/or back pain or neoplastic origin, especially early in the course of established disease. For patients with longer life expectancies, the role of celiac/splanchnic neural blockade is increasingly recognized as modest, on other than a diagnostic basis. Despite daunting logistic and ethical methodological barriers, there is a pressing need to design and undertake collaborative controlled trials aimed at better determining the relative value of various technical approaches.

In our study of 69 patients, there were 18 males and 55 females with a mean age of 55 years. Of the 69 patients who had splanchnic procedures performed, 44 (73 %) had bilateral procedures and 29 of 69 required only onetime unilateral procedure, and repeat splanchnic procedures were performed in 31 of 69 patients (Fig. 5.11).

Acknowledgment The author appreciates and acknowledges that the major portion of excerpts in the text and some figures were taken from "Pain-Relieving Procedures: The Illustrated Guide" edited by P. Prithvi Raj and Serdar Erdine, published 2012. A smaller portion of excerpts and a few figures were also taken from "Interventional Pain Management Image Guided Procedures, Edited by P. Prithvi Raj, Leland Lou, Serdar Erdine, Peter S. Staats et al.

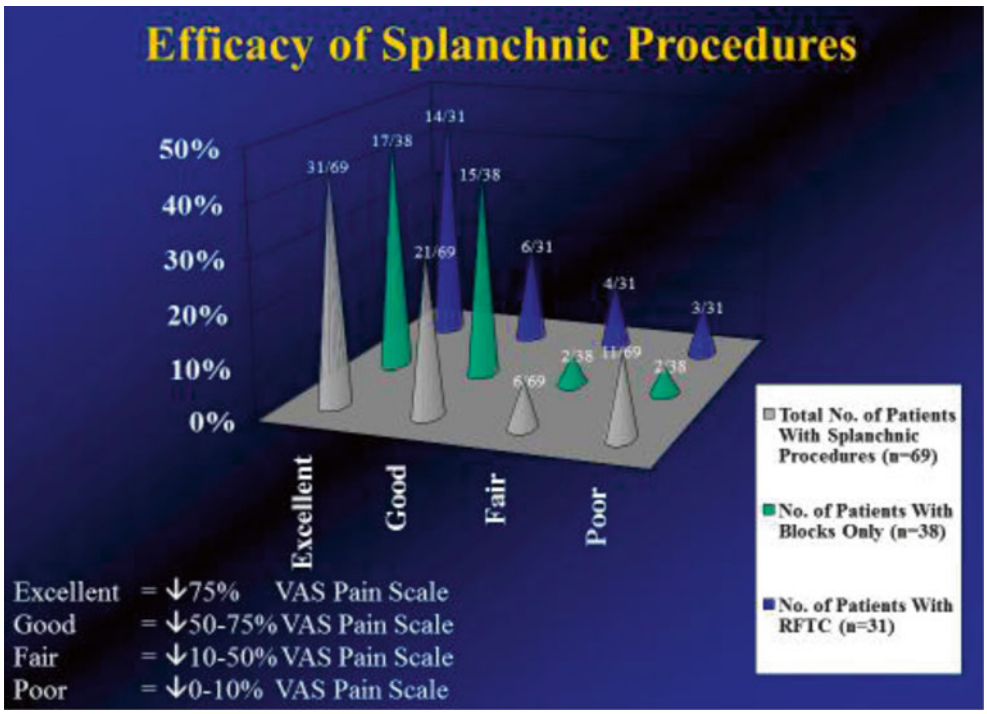


Fig. 5.11 This graph shows the efficacy of splanchnic procedures with blocks only and with RFTC in a total number of 69 patients. The pain scores were considered excellent or good or fair or poor based on the improvement of the percentage of the VAS pain scale.

References

1. Kappis M. Erfahrungen mit lokalanasrhesie bei bauchoperationen. Verbaud D Deutscb Gesellscb F Cir. 1914;43:87.
2. Kappis IvI. Die anasthesierung des nervus splanchnicus. Zentnlb. 1918;45:709.
3. Abram SE, Boas RA. Sympathetic and viscera nerve blocks. In: Benumof JL, editor. Clinical procedures ill anesthesia and intensive care. Philadelphia: JB Lippincott; 1993. p. 787–805.
4. Raj PP, Thomas J, Heavner JE, Racz GB, Lou L, Day M, Shaw BC. The development of a technique for radiofrequency lesioning of splanchnic nerves. Curr Rev Pain Curr Sci Inc. 1999;3:377–87.
5. Garcia G. Percutaneous splanchnic nerve radiofrequency ablation for chronic abdominal pain. Anst N Z J Surg. 2005;75:640–4.
6. Ozyalcin SN, Talu GK, Camlica H, et al. Efficacy of celiac plexus and splanchnic nerve blockades in body and tail located pancreatic cancer pain. Eur J Pain. 2004;8:539–45.
7. Phan P, Warneke C, Shah H, et al. Correlation of splanchnic nerve block efficacy and cancer staging. J Pain. 2004;5(Suppl l):S51.
8. Plancarte-Sanchez R. Transdiscal percutaneous approach of splanchnic nerves. Cir Cir. 2003;71:192–203.
9. Labat G. L'anesthesie splanchique dans les interventions chirurgicales et dans affections douloureuses de la cavite abdominal. Gazd'Hop. 1920; Vol xv111:93–112.

Sympathetic and Celiac Plexus Blocks

6

Octavio Calvillo, Gabor B. Racz, and Carl Noe

Sympathetic Blocks

Introduction

Pain and the Sympathetic Nervous System

Silas Weir Mitchell reported in 1864 about gunshot and other injuries of peripheral nerves [44]. This is probably the first detailed description of complex regional syndrome [CRPS]. Since then, many attempts have been made to explain the clinical features of CRPS, in particular pain and sympathetic disturbances, to define diagnostic criteria and to find an adequate name for this disease. Still the most common ones, among a variety of others, are "reflex sympathetic dystrophy and causalgia."

The involvement of the sympathetic nervous system is not always demonstrable thus sympathetic blockade does not consistently resolve the pain.

According to the Orlando consensus conference, the following diagnostic criteria were proposed [57]:

1. Preceding noxious event [CRPS I] or with apparent nerve lesion [CRPS II]
2. Spontaneous pain or hyperalgesia not limited to a single nerve territory and disproportionate to the inciting event; involvement of the distal part of the affected limb
3. Evidence of edema, discoloration, or other signs
4. Exclusion of other diagnoses

O. Calvillo, MD, PhD, FIPP, ABIPP (✉)
Department of Anesthesiology, Methodist Hospital Houston, Houston, TX, USA
e-mail: octaviocalvillo@yahoo.com

G.B. Racz, MD, ABA, FIPP, ABIPP
Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX, USA

C. Noe, MD
Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

Sympathetic blockade [SB] has been the first line of treatment for complex regional pain syndrome [CRPS]. This concept has been challenged and the benefits considered being due to placebo [48]. Since then, examination of the available evidence has heightened the controversy resulting from the scarcity of double-blind placebo-controlled studies with adequate sample size and follow-up, in support of the idea that the placebo effect is the predominant underlying mechanism of pain relief [10]. However, Rocha demonstrated a positive response compared to placebo in their study [18].

Pathophysiology of CRPS

CRPS is the current diagnostic label for the syndrome historically known as reflex sympathetic dystrophy causalgia and a variety of other names. It can be neuropathic pain, acute or chronic, without any clear anatomical or electrophysiological abnormality. In addition to classic neuropathic pain features (i.e., intense burning pain, hyperalgesia, allodynia, and specific localized pain generators), CRPS is associated edema and changes suggestive of autonomic involvement (i.e., altered sweating, skin color, and skin temperature in the affected region) (Fig. 6.1).

Trophic changes to the skin, hair, nails, and abnormal motor function (i.e., weakness, decreased active range of motion, tremor, spasms, and flexion contractures) may occur.

CRPS is subdivided into CRPS I (reflex sympathetic dystrophy) and CRPS II.

The results of two studies indicate that at least 50,000 new cases of CRPS I occur annually in the United States [17, 54]. Attempts have been made to explain CRPS with a single pathophysiological mechanism (e.g., sympatho-afferent coupling) [52]; however, it has become evident that there are multiple mechanisms to explain the disease.

Initial nerve trauma is usually the trigger for the development of CRPS [47], suggesting a significant loss of C fibers and delta fibers in the affected area; however, no evidence has been put forward to support the notion that the reduced density of nociceptive fibers is related to expression of the signs and symptoms of CRPS.

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_6

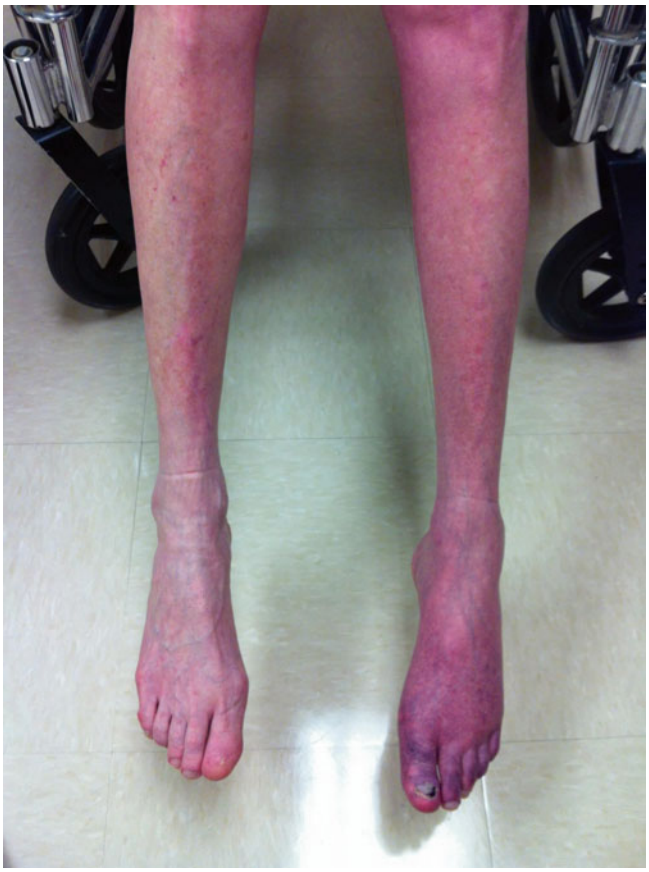


Fig. 6.1 Patient with a history of causalgia with recurrent pain after another injury (above). Left lower extremity discoloration, calf atrophy, foot edema, and allodynia are prominent features

Persistent noxious input from the inciting injury to the dorsal horn leads to central sensitization [35, 65]. CRPS patients display significantly greater windup to repeated stimuli to the affected extremity [33].

Peripheral sensitization likewise occurs after tissue trauma thus contributing to the pain in CRPS [12].

Altered Sympathetic Nervous System

Traditionally it was assumed that the features such as discoloration were the result of excessive sympathetic outflow therefore the pain was sympathetically maintained. The presumed increase in sympathetic outflow and the pain in CRPS was the traditional rationale for sympathetic blocks.

Changes in the pattern of CRPS signs and symptoms may in fact reflect at least partly a progression in catecholaminergic mechanisms. Despite evidence that chronic CRPS patients often display exaggerated vasoconstriction to cold challenge on the affected side, they nonetheless have lower norepinephrine levels compared with the unaffected side [20, 66].

Inflammatory Factors

There are some reports that at least in the acute phase of CRPS, anti-inflammatory corticosteroids significantly improve symptoms in some patients [13].

There is evidence that classic inflammatory mechanisms can contribute through actions of immune cells such as lymphocytes and mast cells, which after trauma, secrete pro-inflammatory cytokines such as interleukin 1b-2–1b-3 and tumor necrosis factor [TNF]-alpha 40. One effect of these substances is to increase plasma extravasation in tissue thus producing edema similar to that observed in CRPS.

Plasticity

Neuroimaging studies suggest one consistent alteration in the brain of patients with CRPS: a reorganization of somatotopic maps, with reduction in size of the representation of the CRPS affected limb in the somatosensory cortex [37, 45]. Studies have demonstrated reversal of these with pain reduction [40].

Psychological Factors

Psychological factors have historically been blamed for CRPS since the pain is out of proportion to the inciting event in a non-dermatomal distribution. This continues to be supported by some [64].

A pure psychogenic model is neither tenable nor supported by the available evidence. However, the contribution a psychophysiology link to CRPS is theoretically possible, taking into consideration it is conceivable that any psychological factor that causes catecholamine release could exacerbate signs and symptoms of CRPS.

In support of this idea, it has been proposed that increased depression levels are a predictor of greater pain intensity [23] and that the pain aggravating effects of emotional distress are greater in CRPS patients compared to non-CRPS patients [6].

No evidence was produced of catecholamine levels in this study; however, other studies indicate greater depression and stress in CRPS associated with significant levels of epinephrine and norepinephrine, in support of this concept [30].

Genetic Factors

Genetic factors may play a role in CRPS. In a study of 31 families, with familial CRPS, the families with CRPS had more frequent CRPS than comparable nonfamilial CRPS cases [19].

The pathophysiology in CRPS seems to be multifactorial. These factors probably include peripheral and central sensitization, inflammation, altered sympathetic and catecholaminergic activity, reduced representation of the affected limb in the somatosensory cortex, genetic factors, and a psychological contribution. The degree to which individual mechanisms contribute to CRPS differs among patients.

Recently, four patterns of allodynia have been described [28]. Some patients have either cold allodynia or warm allodynia. Others have allodynia to both cold and warm and some have no allodynia to either cold or warm.

Sympathetic Blocks

Blocks of the cervical, thoracic, and lumbar sympathetic ganglia have been used to treat pain. Neoplastic and vascular disease as well as neuropathic pain and visceral pain have been successfully treated with blocks using local anesthetic, neurolytic agents such as phenol and alcohol, and neurolytic techniques using radiofrequency thermocoagulation and surgical ablation.

History

Cross reported the superiority of phenol lumbar sympathetic blocks versus bupivacaine in a randomized trial for ischemic rest pain [15].

Wilkinson pioneered the radiofrequency thermocoagulation technique for the thoracic sympathetic chain for hyperhidrosis and reflex sympathetic dystrophy [67]. Haynsworth and Noe reported results with lumbar radiofrequency sympatholysis using a 5 mm exposed tip probe versus phenol and, later, a modified technique with multiple lesions 5 mm tip probe lesions for better results [31, 46].

Technical Aspects and Equipment

Patients should be evaluated prior to scheduling these procedures and then evaluated again immediately prior to the procedure to verify that anticoagulant medications have been properly withheld and allergies, informed consent, affected side, and other pertinent information are taken. Patients should be educated about reasonable expectations for pain relief, keeping a log after the block and follow-up instructions. Intravenous fluid administration and monitoring with EKG, pulse oximetry, and blood pressure should be performed. Resuscitative equipment and personnel should be available in case of complications. Patients should be monitored following the procedure in a monitored nursing area and ideally in a recovery room unit.

Lumbar Sympathetic Block

Indications for lumbar sympathetic block include complex regional pain syndrome, neuropathic pain, vascular disease, hyperhidrosis, and other conditions where the risk/benefit warrants the cost and risk of the procedure. Local anesthetic blocks are used to confirm sympathetically maintained pain and as prognostic tests for sympathectomy or lytic procedures. Local anesthetic blocks have a therapeutic role in some patients.

Contraindications include a lack of a trial of conservative care, local or systemic infection, local tumor, bleeding abnormality, unstable psychiatric or medical status, and unreasonable expectations.

Informed consent should include risk of kidney and other organ puncture, retroperitoneal hematoma, lymphatic injury and edema, post sympathectomy neuralgia, impotence, nerve damage including paralysis, seizures, infection, persistent or worsening pain, cardiac arrest, and death. Bilateral blocks should not routinely be performed on the same day.

Lumbar sympathetic blocks are best performed in the prone position with the use of fluoroscopy. Patients with knee pain should have the L2 level blocked. Patients with foot pain should have the L5 level blocked. Patients with widespread pain should have multiple levels blocked especially if contrast spread is not consistent with blockade of several lumbar levels of the lumbar sympathetic chain.

Twenty-two gauge, 15 cm curved, blunt needles with an introducer are recommended to potentially reduce the risk of puncturing vessels and other structures. For radiofrequency neurolytic blocks, curved tip radiofrequency probes are used with 10 mm exposed tips. The use of a cannula is necessary to puncture the skin and place the blunt tip probe posterior to the neural foramen prior to advancement toward the final position.

The patient is positioned in the prone position and the C-arm is rotated obliquely to have the effect of moving the transverse process to the other side of the image. Small patients may need a more medial entry point to avoid kidney puncture. Local anesthetic should be infiltrated along the needle path to the level of the transverse process.

Once the skin entry has been made, an oblique fluoroscopic view should be made to align the skin entry point and anterolateral edge of the vertebral body. This allows for a single pass to the target and minimal discomfort for the patient. The needle should pass just inferior to the transverse process, which will lead to the needle passing superior to the neural foramen on lateral view. This results in rare paresthesias from other nerve roots that require redirection. The needle should be advanced slowly toward the anterolateral vertebral body while using the lateral view to prevent placement anterior to the vertebral body (Fig. 6.2).

The sympathetic ganglion at L2 is approximately 12 mm form the anterior border of the vertebral body on the lateral fluoroscopic image, so the tip of the probe should be posterior to the anterior border.

For lumbar sympathetic radiofrequency procedures, final needle tip placement is thought to be most effective at the junction of the upper 2/3 and lower 1/3 of the vertebral body at the L2 level according to lateral fluoroscopic imaging. At L3, the junction of the upper 1/3 and lower 2/3 is the final target. At L4, the mid vertebral body is the optimal target.

Aspiration should be negative for blood or other fluid. Contrast injection should show spread in the area of the sympathetic chain along the anterolateral vertebral bodies.

For local anesthetic lumbar sympathetic blocks, 5–10 ml of local anesthetic may be injected in 3 ml increments.

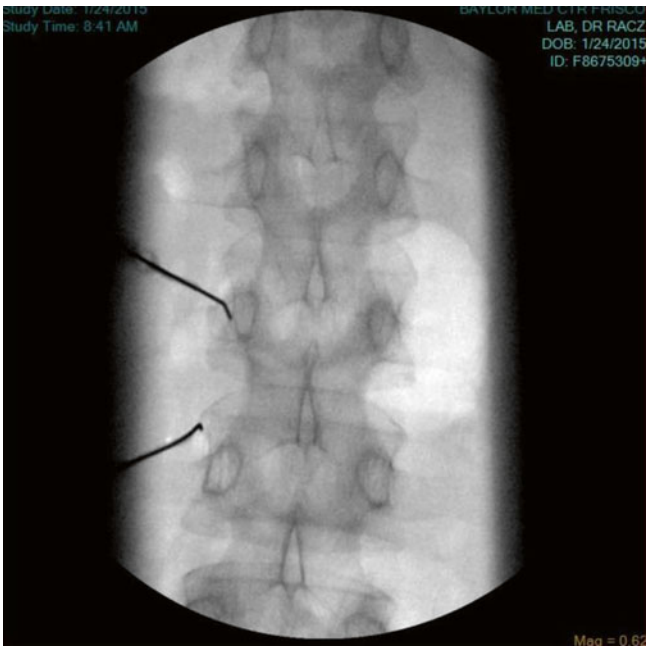


Fig. 6.2 Anterior–posterior fluoroscopic image of radiofrequency probe placement for sympathetic block at lumbar levels 2 and 3 (above)

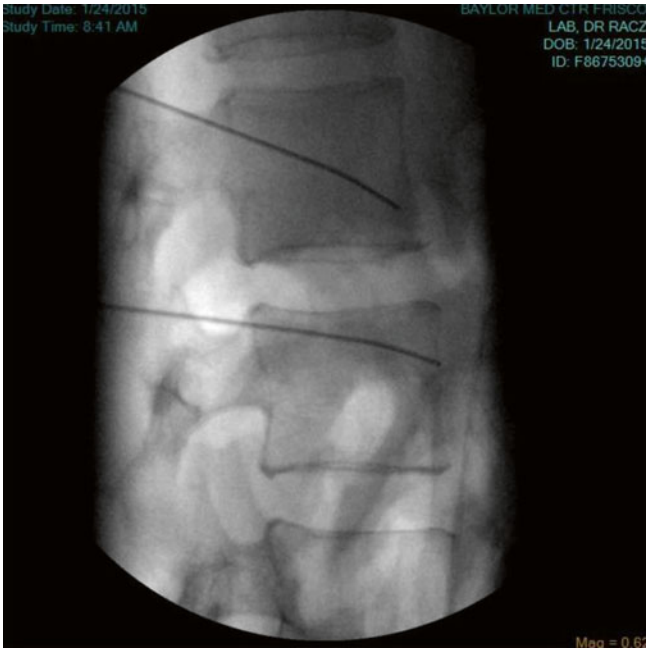


Fig. 6.3 Lateral fluoroscopic image of inferior rotation of curved radiofrequency probe for lesion placement at the junction of the superior two-thirds and inferior one-third at the second lumbar vertebra and at the junction of the superior one-third and inferior two-thirds at the third lumbar vertebra (above)

For radiofrequency thermocoagulation, stimulation on a motor nerve frequency (2–5 Hz) and graded voltage from 1 V, increasing at 1 V increments to 4 V. Cracks in probe insulation and misplacement may produce neuromuscular activity that necessitate replacement of the probe or repositioning.

One milliliter of lidocaine should be injected for anesthesia before thermocoagulation. A lesion may be made at 80° centigrade for 90 s. The curved needles can be rotated to place additional lesions along the sympathetic chain without an additional needle placement (Figs. 6.3 and 6.4).

Following thermocoagulation, the needles may be injected with 1 ml of bupivacaine and 10 mg methylprednisolone. This may reduce discomfort in the immediate post procedure period including post sympathectomy neuralgia.

Patients should be monitored following the procedure and evaluated for signs of sympathetic block such as increased temperature, hypohidrosis, pain relief, and increased blood flow. Sensory examination is important in patients with allodynia. In the case of neuropathic pain, patients should be prescribed exercises to improve range of motion within the block duration. Patients should keep logs of pain and extremity skin temperature for 24 h after local anesthetic blocks to document any correlation between pain relief and the duration of the local anesthetic used.

Patients should be followed in the clinic for reevaluation and further treatment planning and should be able to contact a physician on call for problems after hours.

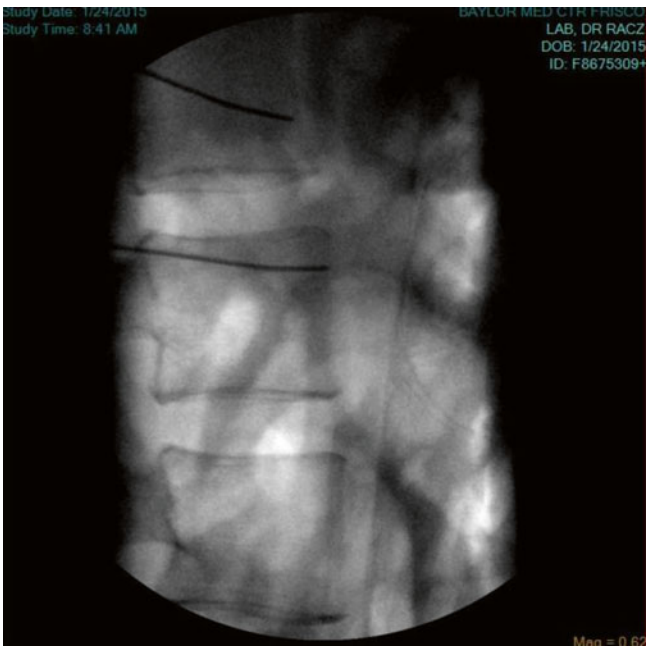


Fig. 6.4 Lateral fluoroscopic image of superior rotation of radiofrequency probe to place a second lesion and increase the length of the lesion (above)

Thoracic Sympathetic Blocks

Informed consent should include risks of pneumothorax, paralysis, vascular injury, and post sympathectomy neuralgia.

Thoracic sympathetic radiofrequency procedures are performed at T2 and T3. The patient is positioned in the prone position with the C-arm rotated to have the effect of moving the transverse process to the other side in the fluoroscopy image, with the image intensifier toward the operative side and above the patient. The C-arm is rotated 20° in a second plane with the image intensifier rotating cephalad to allow for a tunnel view of the upper thoracic spine that is in kyphosis. Local anesthetic is used along the initial path of the needle or radiofrequency probe. The introducer for a curved blunt needle is placed just superior to where the rib and transverse process articulate. The skin entry is made over the lateral border of the spine on the fluoroscopic view and small incremental advances are made, and lateral deviations are avoided to prevent lung puncture. Lateral fluoroscopic views are obtained to monitor needle depth, and the final needle tip position is so the proximal end of the active tip is at the junction of the posterior 1/3 and anterior 2/3 of the vertebral body on lateral views and very close to the lateral border of the vertebral body on AP views [24]. Stimulation should not produce sensation in the axilla or anterior chest and repositioning may be necessary to avoid this.

Cervical Sympathetic Blocks

Informed consent should include risks of Horner's syndrome, recurrent laryngeal nerve block, phrenic nerve block, pneumothorax, vertebral artery injection, nerve root injection, and total spinal block.

The patient is positioned in the supine position with the neck slightly extended to expose the cricoid cartilage area. Placing a thin pillow or folded towel under the patient's shoulders may improve the positioning. The nondominant index finger is used to locate the cricoid cartilage and lateral trachea on the side to be blocked. Palpation one fingerbreadth inferior to the cricoid cartilage is performed to identify a space between the trachea and the muscles and carotid artery.

Local anesthetic is used for analgesia and a Bella-D needle is inserted to the anterolateral aspect of the C7 vertebral body. The Bella-D needle has an injection port 1.5–2 mm proximal to the sealed distal tip. When bony contact is made with the tip, the injection port will be superficial to the longus colli muscle. Fluoroscopy is used to confirm needle position while holding the Bella-D needle with an instrument. The side port direction is marked on the proximal needle to allow for directional injections away from the recurrent laryngeal nerve. After A/P and lateral fluoroscopic views are made to confirm placement, the needle is rotated so the opening is lateral, and contrast is injected to confirm tissue plane spread on the surface of the longus colli muscle prior to injection of local anesthetic. The needle is then rotated 45° to place the opening in an infero-lateral position. Local anesthetic injection spread can be monitored with fluoroscopy. Five milliliters of local anesthetic may be injected to spread to the T2–T3 level that is necessary for ulnar distribution pain (Figs. 6.5, 6.6, 6.7, and 6.8).

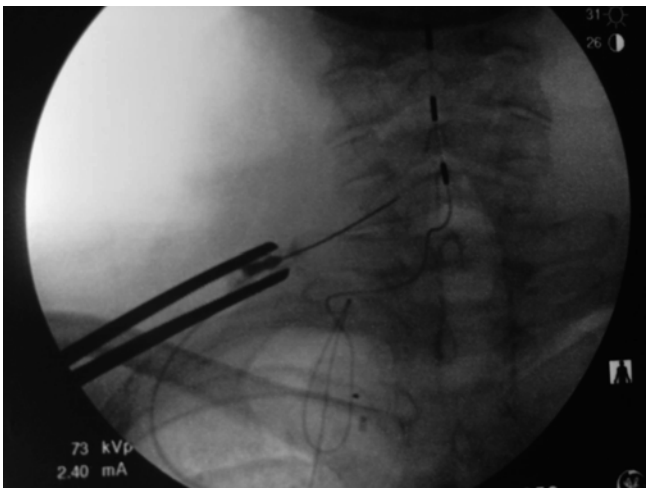


Fig. 6.5 Cervical sympathetic block with Bella-D needle (below). Contrast spread is directed by the side port and is away from the recurrent laryngeal nerve. First image Fig. 6.5 is anterior–posterior image of Bella-D needle placement with forceps grasping the hub

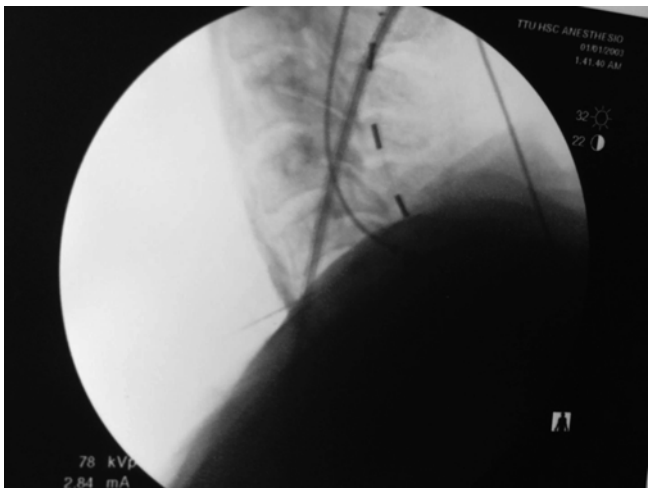


Fig. 6.6 Second image is the lateral image

Outcome Data

Several studies have demonstrated pain relief following sympathetic block [43, 49, 64]. A crossover study of local anesthetic versus saline reported prolonged return to baseline pain for local anesthetics compared to saline. The average time of return to baseline pain in this study was 6 h for saline versus 5 days and 12 h for local anesthetics [49]. Another crossover study reported 12/16 patients responded to local anesthetic versus 8/16 in the control group [64]. Twenty-three pediatric patients were studied using lumbar sympathetic blocks and intravenous lidocaine. Allodynia was improved in the lumbar sympathetic block group [43].

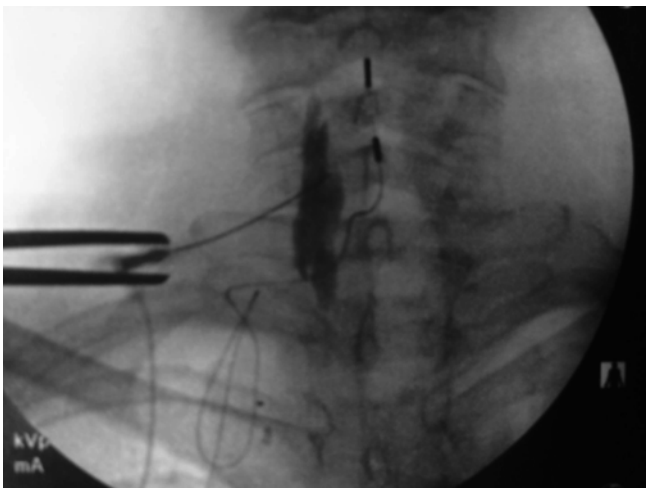


Fig. 6.7 Third image is anterior–posterior image with contrast injection demonstrating spread in a safe distribution

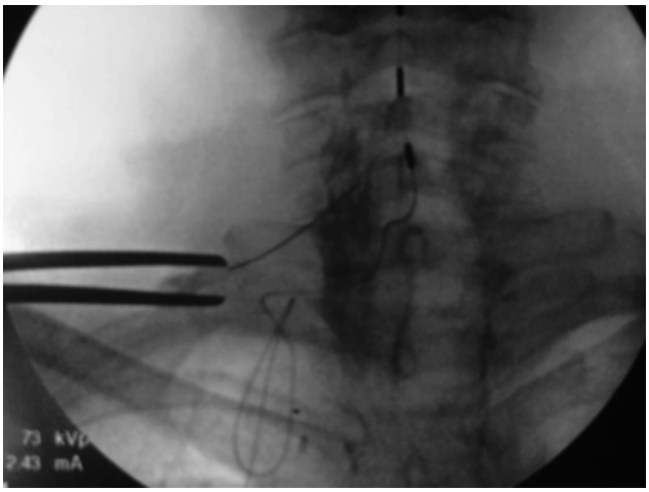


Fig. 6.8 Fourth image is after local anesthetic demonstrating contrast and local anesthetic spread for cervical sympathetic block

Manjunath reported similar results between lumbar sympathetic radiofrequency thermocoagulation and phenol in a randomized double-blind study [42].

A trial of thoracic sympathetic radiofrequency thermocoagulation at T2 and T3 compared to a single level lesion at T2 followed by a phenol injection, showed no difference between the two techniques other than longer procedure time with the two-level procedure in patients with Raynaud's. Pain was reduced by 2/3 in both groups at 90 days follow-up but interestingly vasospasm with cold was not improved [24].

However, large randomized controlled trials have not been performed and some consider sympathetic blocks to be unproven [16, 56].

Surgical sympathectomy for neuropathic pain has fallen out of favor [41].

Certainly malpractice cases based on delayed administration of sympathetic blocks are unfounded.

Complications

Post sympathectomy neuralgia is a complication characterized by pain in the groin and thigh area following lumbar sympatholysis. It is frequently self-limited but may be severe and permanent. It was once thought to be related to genitofemoral nerve injury, but it is probably related to sympathectomy itself [39].

Post sympathectomy neuralgia is treated with medications for neuropathic pain such as topical lidocaine for allodynia, gabapentin, tricyclic antidepressants, and duloxetine. Tramadol may be used with gabapentinoids but may be best avoided with serotonin reuptake inhibitor antidepressants. Opioids should be limited but used if necessary.

Following radiofrequency thermocoagulation techniques, injection of local anesthetic and corticosteroid at the lesion site, through the probe, may reduce the incidence and severity of this complication. Patients should be warned about this complication since it can be severe and permanent.

Retroperitoneal hematoma may occur as a result of venous perforation during the procedure. Guidelines for regional anesthesia and anticoagulation management have been described.

The American Society of Regional Anesthesia has issued 2015 guidelines for anticoagulation management that are more restrictive, as are the institutional guidelines at Stanford University and the University of Washington [34]. These guidelines are publically available with internet service.

A report of a segmental artery laceration and uncontrolled bleeding has been reported. This case required embolization and resulted in spinal cord infarction. Blunt needles are recommended to reduce this type of complication as well as reduce the risk of nerve and kidney laceration.

Lymphatic injury and leg edema has been reported and can be significant.

Impotence has occurred in males and bilateral procedures should be avoided on the same day and if necessary an interval of weeks in between procedures should be considered.

Cervical and thoracic sympathectomy may produce pain in the anterior upper chest near the shoulder. Complications from cervical sympathetic block include Horner's syndrome, recurrent laryngeal nerve block, phrenic nerve block, pneumothorax, vertebral artery injection, nerve root injection, and total spinal block. The use of blunt needles can reduce the risk of complications related to puncturing or lacerating structure unintentionally.

Discussion and Conclusions

The Role of Lumbar Sympathetic Blocks in Complex Regional Pain Syndrome

Complex regional pain syndromes (CRPS) are pain syndromes characterized by pain out of proportion to an inciting injury or

stimulus, swelling, discoloration, stiffness, hyperhidrosis (sudomotor), temperature (vasomotor), and trophic changes. Also commonly seen are fine tremor and less often spasms involving upper and lower extremities. Dr. Silas Weir Mitchell described CRPS II, or causalgia, during the American Civil War. CRPS I was described about the end of the nineteenth century by Sudeck (Sudeck's atrophy). Evans described reflex sympathetic dystrophy (RSD). Numerous other terms used to describe similar syndromes include algodystrophy and shoulder-hand syndrome. Bonica described three stages of RSD. Roberts described sympathetically maintained pain.

Diagnostic Criteria

Specific inclusion criteria are needed for research studies, but from a clinical perspective, many patients seem to have a constellation of signs and symptoms of CRPS without meeting strict criteria. The diagnosis is made by the process of exclusion. While avoiding overdiagnosing and overtreatment, the patients with this spectrum of symptoms need to be treated even if they do not meet strict criteria because they have pain and dysfunction. Perhaps dysfunction should be included in future renditions of diagnostic criteria. Patients with localized pain, swelling, stiffness, discoloration, temperature changes, skin, nail, or hair changes may be candidates for sympathetic blocks. The critical point is to avoid sympathetic blocks on patients who have these findings but have an underlying diagnosis of osteomyelitis, fracture, deep venous thrombosis, or a self-inflicted injury syndrome.

The International Association for the Study of Pain (IASP) proposed clinical criteria (Budapest)

A clinical diagnosis of CRPS can be made when the following criteria are met:

- Continuing pain that is disproportionate to any inciting event
- At least one symptom reported in at least three of the following categories:
  - Sensory: Hyperesthesia or allodynia
  - Vasomotor: Temperature asymmetry, skin color changes, and skin color asymmetry
  - Sudomotor/edema: Edema, sweating changes, or sweating asymmetry
  - Motor/trophic: Decreased range of motion, motor dysfunction (e.g., weakness, tremor, dystonia), or trophic changes (e.g., hair, nail, skin)
- At least one sign at time of evaluation in at least two of the following categories:
  - Sensory: Evidence of hyperalgesia (to pinprick) and allodynia (to light touch, temperature sensation, deep somatic pressure, or joint movement)
  - Vasomotor: Evidence of temperature asymmetry (>1 °C), skin color changes, or asymmetry
  - Sudomotor/edema: Evidence of edema, sweating changes, or sweating asymmetry
  - Motor/trophic: Evidence of decreased range of motion, motor dysfunction (e.g., weakness, tremor, dystonia), or trophic changes (e.g., hair, nail, skin)
- No other diagnosis better explaining the signs and symptoms

Prognosis

The prognosis for CRPS is highly variable and to a large extent is influenced by the treatment. Functional restoration and involving the patient in ongoing range of motion and resistive exercises is helpful. Timely pain relief and interventional pain procedures, as well as psychological support, are important. Patients often need to be followed closely and treatments adjusted accordingly. Timely and appropriate referral to experienced pain physicians that are able to offer multimodal therapies may prevent costly delays and complications.

Theories of Mechanisms

The mechanism for CRPS is unknown. Multiple theories exist for CRPS mechanisms including psychological, inflammatory, vascular, neurogenic, and combinations of several mechanisms.

Neuropathic pain has been defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system." Debate regarding definitions of neuropathic pain has led to the notion that CRPS may not be neuropathic pain since a demonstrable nerve lesion is not present in CRPS 1. Psychogenic pain can be construed as "pain arising as a direct consequence…of (psychological) disease" but few would think of psychogenic pain as a neuropathic pain that should be treated with anticonvulsants.

CRPS II is caused by, or associated with, an injury to a peripheral nerve. It is difficult to accept that CRPS 1 is not neuropathic pain since it resembles CRPS II so closely. CRPS 1 is likely caused by a lesion in or injury to a small nerve or multiple small nerves.

Denial of care based on psychological explanations is neither reasonable nor justifiable yet in rare instances pain can be of psychological origin. Commonly the onset of CRPS is 1–3 months after the injury.

History

The diagnosis is made by process of exclusion following history of pain that is out of proportion to an injury or period of immobilization. Swelling; temperature asymmetry; stiffness; sweat function changes; atrophy; hair, skin, nail, and bone changes; tremors or spasms; and asymmetry in sweat function are important symptoms to review while taking a history. It is important to remember that many injuries are associated with pain, discoloration, and swelling without being CRPS. Infection and other causes of inflammation are sometimes mistakenly thought to be CRPS. A number of patients have CRPS symptoms following stroke and classifying this as central pain or CRPS is problematic.

Physical Exam

Observation of upper extremity guarding, flexed posturing, or antalgic gait for lower extremity is important. Range of motion of affected joints is particularly important as many patients develop permanent stiffness if they are not treated with analgesic treatments for specific range of motion therapy. Discoloration or asymmetrical coloration, swelling, atrophy, and allodynia are other physical findings. The allodynia may be tactile or cold induced.

Diagnostic Tests

Bone scans, sweat tests, and sympathetic blocks have been used, but the diagnosis is a clinical one and can be made without confirmatory tests. Thermography has been used, but more commonly, the documentation of temperature differences is adequate. Early on in the evolution of the condition, there may be increased temperature in the painful area and, later, temperature reduction with vasoconstriction, possibly related to increased sympathetic activity. Three-phase bone scan often shows corresponding changes.

Comparing contralateral X-ray images can show osteopenia in the involved area. Electromyography (EMG) usually does not change secondarily to CRPS, but nerve conduction velocity testing (NCV) may show nerve injury.

Differential Diagnosis

While it is important to be vigilant in diagnosing CRPS, it also is important to avoid misdiagnosis and overdiagnosis. Many patients have "pain out of proportion," swelling, and discoloration after injuries and will improve within a month with usual therapeutic interventions.

Infection is always a concern after surgery or other penetrating trauma. Other causes of acute inflammation, swelling, and discoloration need to be considered such as malignancy, deep venous thrombosis as well as peripheral nerve entrapment, peripheral neuropathy, and other neuropathic pains.

Stages

Three stages of RSD have been described; however it is unclear that staging has much value regarding treatment planning. Early erythema and increased temperature are followed by cyanosis and decreased skin temperature in this classification.

Timing

Much has been made about early sympathetic blocks and failure to diagnose early. There is no data to support "emergent" sympathetic blocks and some patients have a favorable natural history.

Spreading

Pain from CRPS can spread, in rare instances, proximally and contralaterally [55]. Lower extremity pain can spread to upper extremities and vice versa.

Recurrent CRPS

Patients with a history of CRPS are thought to be at higher risk for developing recurrent CRPS or an exacerbation of CRPS. Elective surgery in an area of CRPS is thought to be a risk factor for a "flare up," and an injury to a normal limb may trigger CRPS in a new area. In these situations, reviewing treatments that seemed to be effective in the past for an individual patient is important as patients tend to respond favorably to the same modalities.

Bone Loss

Osteopenia and fractures can occur in severe cases and aquatic therapy is useful to rehabilitate these patients. Osteomyelitis may mimic CRPS on bone scans.

Natural History

The natural history of CRPS 1 is variable but in an interesting report, approximately 25 % of patients that had Colles' fractures developed signs of CRPS [2]. Approximately 40 % of these patients improved in 6 months. This suggests that mild cases may not require extensive treatment. Patients need to be followed frequently to monitor progress and adjust treatment. Also, patients obtain information on the Internet that is usually about catastrophic cases. This needs to be dealt with by educating patients in an appropriate and caring manner such that therapy is timely yet one can avoid catastrophizing based on inaccurate or overly pessimistic information.

Dogma

Much of "standard care" is not "evidence based" but based on following patients toward a good outcome. Additionally, it is based on physician experience and the outcomes are superior in the hands of better-trained physicians. As new information becomes available, dogma can be weeded out, and treatments based on randomized controlled trails can be incorporated into treatment guidelines.

Cases

One lady had not worn high-heeled shoes for a long time and then wore a pair for several hours at an event. She developed classic signs and symptoms of RSD. She experienced profound analgesia with sympathetic blockade and the condition resolved completely.

Another case was a woman who had a paper cut on her distal index finger on the job. She had classic signs and symptoms of CRPS, which resolved with a series of blocks. Insurance companies challenged both of these cases since the inciting injury was so minor but both patients were legitimate. The point is that physicians caring for these patients must be willing to serve as advocates for the patient even in an environment of cost containment. We have to be mindful of our "report cards" but not at the expense of a patient's outcome.

In 1994, the International Association for the Study of Pain (IASP) revised the terminology from RSD and causalgia to CRPS type I and II. Fifteen years ago we proposed an analgesic ladder for CRPS/RSD which included three steps [50]. Since then, well-respected groups have advanced other guidelines [29, 57, 60].

Our current analgesic ladder promotes several concepts:

1. Interdisciplinary pain treatment is recommended rather than multidisciplinary care that tends to be fragmented. Interdisciplinary treatment specifically provides coordinated medical care, education, and cognitive behavioral therapy for pain, physical therapy, and outcome documentation by the interdisciplinary team. Patients who receive care at different clinics for each component of care by a group of providers who do not meet on a weekly basis nor document comprehensive outcomes are not receiving interdisciplinary pain management.
2. Interdisciplinary care is not isolated from medical pain management. Analgesic treatments are necessary to provide pain relief and allow functional restoration.
3. The course of an individual patient is highly variable and adjustments to the treatment plan should be made in a highly flexible manner.
4. Limiting opioid doses to below 200 mg/day morphine equivalents.
5. If there is treatment failure and functional restoration failure, the patient should be referred to centers or individuals with recognized experience to be specialists in the field.
6. Epidural infusion of local anesthetic and fentanyl has been observed to rapidly resolve allodynia in CRPS. For lower extremity CRPS, placing the catheter tip at the area of the L4 dorsal root ganglion is important to suppress allodynia. The infused solution consists of 0.1 % ropivacaine and fentanyl 5 mcg/ml at 6 ml/h for 5 days. The infusion may require a bolus in the morning and at night for additional effect. The allodynia resolves after several hours of infusion and the CRPS picture typically improves after 4–4.5 days of infusion. Brachial plexus infusions are used for upper extremity CPRS allodynia. Some patients may have a residual sympathetic component requiring specific sympathetic block, and some patients may have a component of muscle spasm requiring muscle injection with Botox. Following this, peripheral pain generators are identified by palpation and marked for injection with local anesthetic and hyaluronidase. These targets may respond to cryoneurolysis for long-term relief from neuromas or other peripheral pain generator.

Sympathetic blocks have been recommended early on in the management of the disorder but little data exists to support this practice. Only recently has any data from a randomized controlled trial been published to demonstrate efficacy of sympathetic blockade [43]. Allodynia and hypoesthesia are negative predictors of treatment response [60, 61].

Spinal cord stimulation has been shown to produce significant analgesia even after 5 years of treatment [38]. However, many patients with acute CRPS improve with physical therapy, topical DMSO, analgesics, transcutaneous stimulation and sympathetic blocks, and spinal cord stimulation should be reserved for patients who fail more conservative modalities [60, 61].

Cortical stimulation has been shown to have some benefit [63]. Deep brain stimulation has been shown to be ineffective.

Vitamin C has been studied by multiple investigators for the prevention of CRPS and has some effect. [5] Intravenous magnesium has been reported to be effective in an initial study [14]. Clodronate has been shown to be partially effective [62]. Mirror therapy has been reported to have benefit in stroke patients with CRPS [7]. Multicenter comparison of spinal cord stimulation and peripheral nerve stimulation showed that PNS is more effective than SCS, but the best outcome was where both modalities were utilized [8].

Intravenous regional anesthesia with the addition of vasodilators such as phentolamine, reserpine, and bretylium allow manipulation of hands without post procedure edema and speed up functional restoration without the pain associated with physical therapy [8, 32, 50]. Gabapentin has been shown to have a positive analgesic effect in patients with CRPS type 1 [59]. Patients with neuropathic pain may respond to gabapentin, but careful titration is necessary to reach an effective dose and to avoid discontinuation of the drug at a subtherapeutic dose due to side effects from rapid dose increases.

An evidenced-based review endorses bisphosphonates (alendronate, pamidronate, clodronate), corticosteroid, gabapentin, physiotherapy, and psychotherapy/relaxation techniques as treatments [3]. Additionally intrathecal baclofen for associated dystonia and spinal cord stimulation for refractory case are recommended. Topical DMSO and sympathetic blocks are not strongly recommended. Intravenous regional blocks with guanethidine are not recommended as specific treatment [60, 61].

Treatments to Avoid

Amputation is less common nowadays because it was rarely effective and usually resulted in a phantom pain plus different pain of greater severity

IV regional with guanethidine has been shown to be ineffective in several studies as sole agent.

Deep brain stimulation has been shown to be ineffective.

High-dose opioid should be avoided if possible due to possible opioid-induced hyperalgesia, addiction, diversion risk, and overdosage [21, 58].

Treatment

Stepwise care may be used to treat CRPS in most cases (Fig. 6.1). Step care is outlined below with three steps. Step 1 is the initial step. Each patient should be considered for each evaluation or treatment on each step, but many patients do not need all of the treatments listed for each step.

Step 1

Screening for substance abuse, affective disorders, and disability
Education
Physical therapy with a focus on preservation of range of motion
Occupational therapy
Vocational rehabilitation
Topical lidocaine for allodynia
Tricyclic antidepressants
Vitamin C
Gabapentin
Tramadol
Opioid doses limited to less than 200 mg morphine equivalents per day and below 50 mg/day if possible
Corticosteroid

Step 2

Interdisciplinary pain evaluation including psychological testing (MMPI-RF) and treatment (cognitive behavioral therapy, group psychoeducational therapy and psychotropic medication management, addictionology, physical and occupational therapy, in a coordinated goal-directed, outcome documenting rehabilitation program)
Sympathetic block
IV regional block
Peripheral block
Other drug trials – bisphosphonates, baclofen
Local anesthetic infusion – epidural or brachial plexus
Muscle injection with botulinum toxin

Step 3

Spinal cord stimulation
Sympathectomy/sympatholysis
Peripheral nerve stimulation
Peripheral nerve decompression/lysis
Intrathecal/epidural analgesia
Cryoneurolysis of peripheral generators (Fig. 6.9)

However, in some cases, a stratified care approach may be needed. Stratified care is based on severity of the condition. For example, a patient with severe pain and CRPS may need to progress to a treatment in step 2 or 3 sooner than expected based on a lack of response to initial measures. The step care model is a general recommendation as a conservative approach and is not intended to limit, for example, a patient from proceeding to a psychological evaluation or a trial of spinal cord stimulation.

Interdisciplinary pain management is a term that is poorly understood. It is best reserved to describe a team of healthcare professionals led by a physician and including a psychologist and physical therapist at a minimum. A care team of multiple physicians from different specialties is not an interdisciplinary pain management team nor is a psychologically based treatment program in isolation from medical pain management. Cognitive behavioral therapy, education, and functional rehabilitation must be provided in an interdisciplinary pain care model in addition to medical pain management therapies. Case management, psychiatry, outcome database management, nursing, vocational rehabilitation, and occupational therapy are key disciplines to include in a mature pain program. Nutrition, chaplaincy, and other medical specialties are needed for tertiary programs. Medical direction, program direction, and administrative support are also very important for program growth and stability.

CRPS has a sensory component of pain, an emotional component, and an associated functional impairment. Each factor needs evaluation and treatment simultaneously in a coordinated fashion. Clearly, the relative size of each component varies from patient to patient and responses to treatment vary as well (Fig. 6.10).

Complex regional pain syndrome is a challenging pain problem that frequently requires a comprehensive interdisciplinary assessment and treatment plan. Until a mechanism is discovered and a specific treatment for the syndrome is developed, an interdisciplinary approach, including pharmacologic and interventional pain management in a stepwise fashion, will likely remain as the best route to follow.

Treating CRPS does not lend itself well to a uniform care path and the decision-making is largely determined by the individual patient's responses to individual modalities and the patient's individual natural history. Next steps follow as needed on an individual basis. For example, one patient may seem to respond to occupational therapy treatments and oral medication and not need interventions at all. Another patient may not respond to anything except interventions. This individualized medicine approach has been advocated for other treatments such as opioid therapy, but opioid doses should be limited and other analgesic treatments used as alternatives to opioid escalation, as a sole treatment, beyond 50 mg per day of oral morphine equivalents. Similarly, some patients may not respond to cognitive behavioral therapy and may need other psychological interventions, such as hypnosis, in order to make gains. Patients who are unable to progress with occupational therapy may make progress with a different physical therapist that is more experienced with these patients or is better able to connect with the patient in

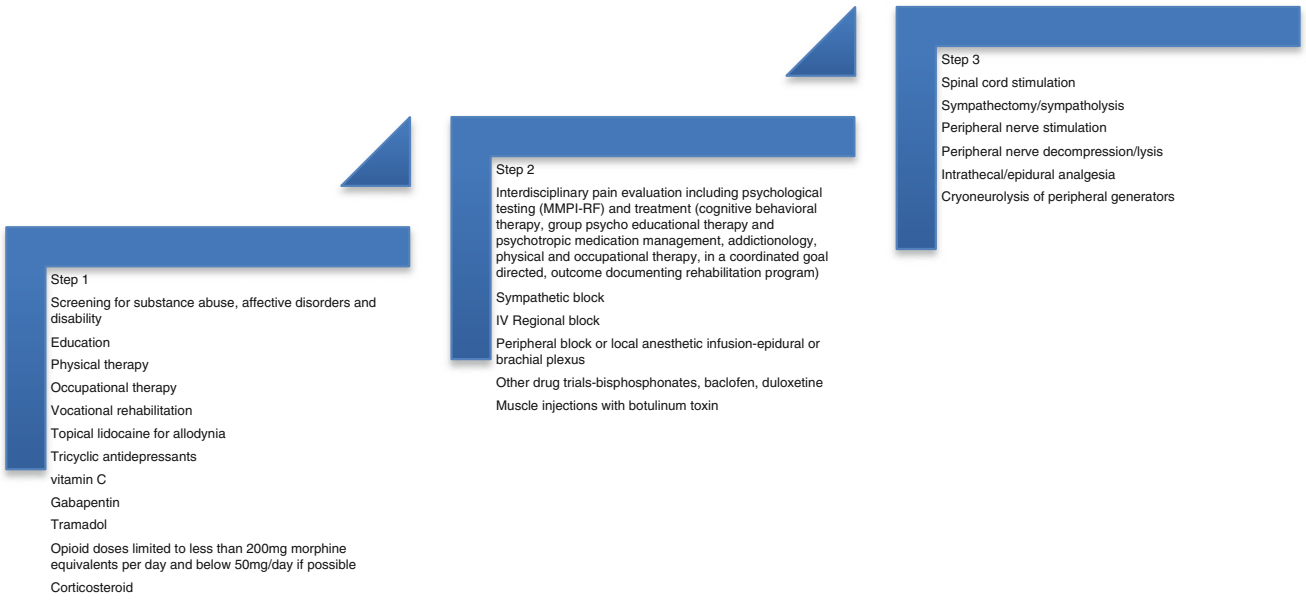


Fig. 6.9 Step care for CRPS

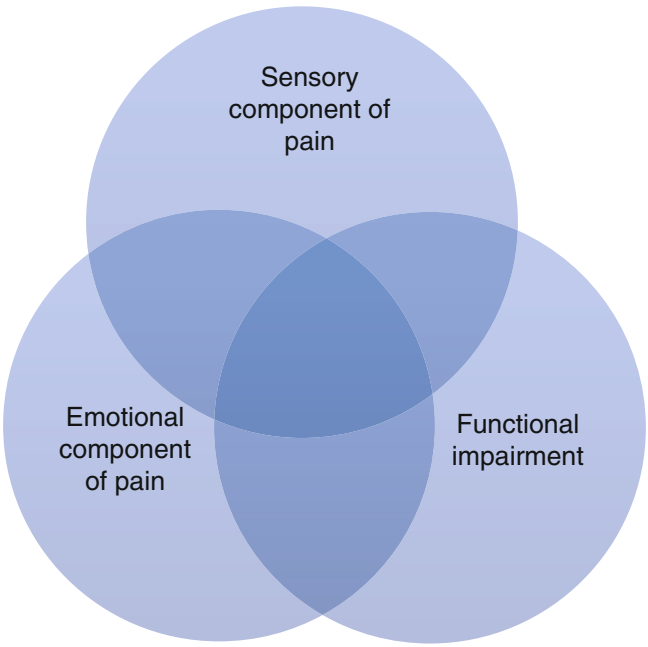


Fig. 6.10 CRPS has a sensory component of pain, an emotional component, and an associated functional impairment

a therapeutic way. Allowing patients to split the interdisciplinary team is not advocated at all, but neither is a rigid approach to managing these patients. Each member of the interdisciplinary team has to understand that the patient is presenting with their best adaptation to their pain syndrome, and providers need to meet patients halfway between where they are and where they need to be.

The UK guidelines provide a comprehensive differential diagnosis and list of treatment modalities [25]. The information below is directly from the guidelines:

"Differential diagnosis infection (bone, soft tissue, joint, or skin)

- orthopedic malfixation
- joint instability
- arthritis or arthrosis
- bone or soft tissue injury (including stress fracture, instability, or ligament damage)
- compartment syndrome
- neural injury (peripheral nerve damage, including compression or entrapment neuropathy, or central nervous system or spinal lesions)
- thoracic outlet syndrome (due to nerve or vascular compression)
- arterial insufficiency (usually after preceding trauma, atherosclerosis in the elderly, or thromboangiitis obliterans (Buerger's disease))
- Raynaud's disease
- lymphatic or venous obstruction
- Gardner-Diamond syndrome (see the list of differential diagnoses in the "rheumatology, neurology, and neurosurgery" section)
- brachial neuritis or plexitis (Parsonage–Turner syndrome or neuralgic amyotrophy)
- erythromelalgia (may include all limbs)
- self-harm bone or soft tissue injury (including stress fracture, ligament damage, and instability)
- compartment syndrome

- neuropathic pain (e.g., due to peripheral nerve damage including compression or entrapment neuropathy or due to central nervous system or spinal lesions)
- arthritis or arthrosis
- thoracic outlet syndrome (due to nerve or vascular compression)
- infection (bone, soft tissue, joint, or skin)
- arterial insufficiency (usually due to atherosclerosis in the elderly, trauma, or thromboangiitis obliterans (Buerger's disease))
- lymphatic or venous obstruction
- Raynaud's disease
- Gardner-Diamond syndrome
- brachial neuritis or plexitis (Parsonage–Turner syndrome or neuralgic amyotrophy)
- erythromelalgia (may include all limbs)
- self-harm

Skin differential diagnosis:

- erythema
- skin atrophy
- edema
- hypohidrosis
- warmth
- hyperhidrosis
- pallor
- Beau's lines in nails
- cyanosis
- factious ulcers
- hypertrichosis
- bullae
- hypotrichosis
- leukonychia
- nail ridging
- onychodystrophy

Yellow flags iatrogenic factors, i.e., previous negative experiences with health professionals:

- poor coping strategies, e.g., ongoing "guarding" of the limb despite education
- involved in litigation, which is affecting willingness to progress with treatment (note that this is not the case for all patients involved in litigation)
- overuse of appliances
- distress
- anxiety/depression
- lack of willingness to set goals
- passive in treatment sessions
- inappropriate beliefs despite education
- negative family influences

Treatment approaches patient education and support:

- desensitization
- general exercises and strengthening
- functional activities
- mirror visual feedback
- gait reeducation
- transcutaneous electrical nerve stimulation (TENS)
- postural control
- pacing, prioritizing, and planning activities 46
- goal setting
- relaxation techniques
- coping skills
- hydrotherapy
- sleep hygiene
- edema control strategies
- vocational support
- facilitating self-management of condition
- splinting
- modalities
- graded motor imagery
- self-administered tactile and thermal desensitization with the aim of normalizing touch perception
- mirror visual feedback
- strategies to correct body perception disturbance, involving looking, touching, and thinking about the affected body part
- mental visualization to normalize altered size and form perception of affected body part
- functional movement techniques to improve motor control and awareness of affected limb position
- principles of stress loading
- conflict allodynia reeducation to reduce fear of physical contact with others in community settings
- management of CRPS-related dystonia"

Conclusion

Sympathetic blocks are an important treatment for pain. Gabapentin, interdisciplinary pain rehabilitation, and spinal cord stimulation are important options for patients with sympathetically maintained pain.

Future developments may include refinement of minimally invasive sympathectomy techniques or blocks with new agents. Thoracoscopic thoracic sympathectomy has increased in usage due to less morbidity compared to open surgical sympathectomy. A similar technique has been developed for lumbar sympathectomy [51]. Carroll reported prolonged blockade using botulinum toxin [9]. Lumbar sympathetic blocks with liposomal bupivacaine have not been reported.

Sympathectomy at specific levels are recommended for hyperhidrosis and similar specificity with regard to pain is needed as well [11]. Ulnar distribution pain seems to respond better to T2 blockade while radial with median distribution pain responds better to a C7 block. Knee pain responds better to L2 blockade and foot pain responds better to L4 and L5 blocks.

Sympathetically maintained pain, complex regional pain syndrome, vascular disease hyperhidrosis, and other conditions will continue to be treated with sympathetic blocks, but most patients require additional treatment in conjunction with blocks.

Celiac Plexus Blocks

Introduction

Celiac plexus block has been successfully used to treat pain in the upper abdomen related to carcinoma of the pancreas. Many patients are able to limit or reduce their opioid requirement and opioid-related side effects, thus improving their quality of life and pain management. The development of the splanchnic radiofrequency technique by Dr. Raj has led many to employ his approach as an alternative to celiac block. Dr. Raj's technique is described in another chapter.

History

Celiac blocks were initially tried for surgical anesthesia but were ineffective. A two-needle technique was used for bilateral blocks in the retrocrural space using large volumes of local anesthetic or alcohol 50 %. The use of imaging techniques, such as fluoroscopy and computerized tomography, has led to other techniques. A two-needle technique into the periaortic area has been used as well as a single-needle transaortic approach. Radiologists have used anterior approaches using ultrasonography, and gastroenterologists have used endoscopic approaches for blocks.

Technical Aspects and Equipment

The results seem to be related to responses to local anesthetic blocks performed on a prognostic basis, and the replication of placement and contrast spread with a subsequent lytic block. As with many procedures of this type, the operator's technique and skill are critical for a successful block.

The celiac ganglia and plexus are clustered around the junction of the celiac artery and aorta. This is frequently at the level of the first lumbar level or 12th thoracic level. The plexus may be diffuse and may require large volumes of local anesthetic or lytic agents to cover the distribution of fibers.

Lidocaine may be used for prognostic blocks and analgesia prior to an alcohol block.

For a single-needle transaortic block, 7–10 ml may be used. For two-needle retrocrural blocks, larger volumes are required to produce spread around the aorta and superiorly toward the splanchnic nerves. Bupivacaine is preferred for diagnostic blocks if no lytic agent is used at the same procedure. Liposomal bupivacaine has been used with good results but no data has been reported to substantiate this.

Alcohol 50 % is generally used for two-needle techniques where large volumes (20 ml or more) are used on each side. Absolute alcohol is used for transaortic techniques where 7 ml may be adequate. Alcohol is painful upon injection and local anesthetic must be used to provide surgical levels of anesthesia before injecting alcohol. Patients will writhe with pain after an unanaesthetized alcohol injection, and gross movement with a needle placed in the periaortic position is to be avoided.

Alcohol vials should be kept off the sterile field to avoid a medication error and opened immediately prior to use. Alcohol and water are completely miscible, and absolute alcohol will extract water from the air in the room to dilute its final concentration.

For transaortic approaches, 20 or 22 gauge 15 cm needles may be used. For periaortic blocks, blunt needles may be used via an introducer to reduce the risk of vena cava, thoracic duct, or other injury.

C-arm fluoroscopy is used for most blocks and most outcome data is with fluoroscopy-guided procedures.

Techniques

Informed consent including risks of paralysis, pneumothorax, kidney perforation, retroperitoneal hematoma, orthostatic hypotension, diarrhea, and lack of pain relief or recurrent pain should be explained to the patient prior to scheduling the procedure.

Intravenous fluids should be infusing during the procedure in case of hypotension and for sedative administration. The patient is positioned in the prone position and the skin is prepped and draped in a sterile fashion. Anterior–posterior fluoroscopy is used to locate the second lumbar level at the transverse process. A skin wheel is made with local anesthetic approximately 8 cm lateral of the midline. In smaller patients, a skin entry point may be 6–7 cm lateral to midline.

The two-needle technique requires oblique fluoroscopy at an angle that aligns the skin puncture site with the lateral

aspect of the first lumbar vertebra. The needle tract is infiltrated with additional local anesthetic to the level of the transverse process. The needle is advanced medially and superiorly toward the lateral aspect of the upper L1 vertebral body while monitoring needle direction using the oblique view to avoid a path too medially into the vertebral body or spinal canal or too lateral into the kidney or lung. Lateral fluoroscopy is used to check depth and to avoid placement more than several centimeters anterior to the vertebral body at the superior end of first lumbar level.

Once the needles are in an acceptable location, aspiration test are performed to rule out intravascular placement. Radiopaque contrast is injected to detect vascular run off and also to observe adequate spread in the area of the celiac plexus anterior and lateral to the aorta.

Local anesthetic is then injected and pain relief is noted. Fifteen to twenty milliliters of alcohol 50 % is injected on each side. The needles are flushed with saline before removal to prevent any residual alcohol from leaking from the needle as the needle is withdrawn past the nerve roots and skin. The volume of local anesthetic will dilute the concentration of injected alcohol and if 50 % alcohol is used after a large volume of local anesthetic, the alcohol may be diluted and affect the quality of the neurolytic block. The block may be repeated but scarring can occur especially if phenol is used. A lytic block may provide analgesia for 6 months.

The one-needle transaortic technique is performed from the left side but the needle is advanced more anteriorly. The stylet is removed and bright red blood will drain from the hub until resistance is met on the anterior aortic wall. The needle should be advanced through the wall so that blood stops draining and contrast injection is neither painful nor met with resistance. Contrast will accumulate anterior to the aorta and the pulsations will be seen on fluoroscopy.

Seven to ten milliliters of lidocaine 1 % is injected for anesthesia. A volume of absolute alcohol that is slightly less than the volume of local anesthetic used is slowly injected after the local anesthetic has taken effect. As with the two-needle technique, the needle is flushed prior to removal to avoid alcohol damaging nerve roots or skin as the needle is removed.

Outcome Data

One randomized trial showed improved pain relief with celiac block using 20 ml of alcohol. However, no improvement in survival or quality of life was associated with the improvement in pain [68]. Another trial also reported improvement in pain and opioid sparing but no difference in quality of life. [71] A meta-analysis of seven trials of celiac blocks reported improved pain and reduced medications with celiac block but pain relief was not permanent [72]. However, an open trial comparing opioid management, celiac block, and resection of the splanchnic nerves showed no difference between the groups of patients with upper abdominal cancer-related pain [36].

The timing of a celiac block is an important consideration. A 1-year follow-up study compared the timing of celiac block for patients with carcinoma of the pancreas. Patients were treated with 40 ml of absolute alcohol. The authors concluded that celiac blocks were more effective if performed after medication treatment as opposed to initially as pain treatment [1].

A study of tumor location showed a higher rate of successful celiac blocks in patients with carcinoma of the head of the pancreas as opposed to other locations in the pancreas [53].

Endoscopic ultrasound-guided celiac blocks have been reported to be superior to CT-guided blocks [27].

Complications

Reversible anterior spinal artery syndrome has been reported with celiac plexus block [22]. This is a possible mechanism for rare cases of paralysis. Injury or injection in the artery of Adamkiewicz or segmental arteries is another possible mechanism for paralysis. Alcohol tracking posteriorly to nerve roots is another possible mechanism for neurological deficits after alcohol injection. Maintaining the patient in a prone position following the procedure may help mitigate this when it is a concern based on posterior contrast spread during the procedure.

Celiac artery runoff may occur with contrast injection. The celiac artery originates from the aorta most commonly at T12 (34 %), the T12–L1 junction (31 %), and L1 (28 %) [69]. Injection of alcohol into the celiac artery could result in bowel infarction.

Kidney injury may occur if needles are placed at a skin entry point too lateral from the midline or if needles are directed too laterally. Eight centimeters lateral to midline may be a reasonable maximum distance from the midline to make a skin entry. The transaortic approach may be made more medial since the needle is advanced more anteriorly and less medially compared to the classic approach.

Pneumothorax may occur with transcrural techniques.

Diarrhea may occur after autonomic block and opioid reduction but this is usually transient.

Skin sloughing may occur if alcohol is not flushed from needles before removing. Usually 1 ml of additional lidocaine or contrast is used to flush each needle.

Conclusions and Discussion

Celiac plexus block is used for pain related to pancreatic cancer and may be helpful for pain related to other upper

abdominal cancers [4]. Neurolytic celiac blocks should be avoided in noncancer patients. Splanchnic nerve radiofrequency thermocoagulation is favored over lytic celiac blocks in patients with noncancer pain, such as pancreatitis.

Cryoneurolysis may be developed as a technique as an alternative to lytic solutions [70].

Splanchnic neuromodulation may have a role in some patients as an alternative to lytic procedures [26].

References

1. Amr YM, Makharita MY. Comparative study between 2 protocols for management of severe pain in patients with unresectable pancreatic cancer; one- year follow-Up. Clini J Pain. 2013;29:807–13.
2. Atkins RM, Duckworth T, Kanis JA. Algodystrophy following Colles' fracture. J Hand Surg Br. 1989;14:161–4.
3. Baron R, Naleschinski D, Hullemann P, Mahn F. Complex regional pain syndrome: a neuropathic disorder? In: Pain 2010 – an updated review: refresher course syllabus. Seattle: IASP Press; 2010. p. 109–17.
4. Bektas M, Atiq M, Bhutani MS. First report of celiac plexus block for refractory abdominal pain secondary to peripancreatic colon cancer metastasis. Gastrointest Endosc. 2012;76(3):692–3.
5. Besse J, Gadeyene S, Galand-Desme S, et al. Effect of vitamin C on prevention of complex regional pain syndrome in foot and ankle surgery. Foot Ankle Surg. 2009;15:179–82.
6. Bruehl S, Chung OY, Burns JW. Differential effects expressive anger regulation on chronic pain in CRPS and non-CRPS limb pain patients. Pain. 2003;104:647–54.
7. Cacchio A, De Blasis E, De Blasis V, et al. Mirror therapy in complex regional pain syndrome type 1 of the upper limb in stroke patients. Neurorehabil Neural Repair. 2009;23:792–9.
8. Calvillo O, Racz GB, Diede J, Smith K. Neuroaugmentation in the treatment of complex *Syst Rev* regional pain syndrome of the upper extremity. Acta Orthop Belg. 1998;64–1:57–63.
9. Carroll I, Clark JD, Mackey S. Sympathetic block with botulinum toxin to treat complex regional pain syndrome. Annals of Neurology. 2009;65(3):348–51.
10. Cepeda MS, Carr DB, Lau J. Local anesthetic sympathetic blockade for complex regional pain syndrome. Cochrane Syst Rev. 2005;(4):CD004598.
11. Cerfolio RJ, De Campos JR, Bryant AS, Connery CP, Miller DL, DeCamp MM, McKenna RJ, Krasna MJ. The society of thoracic surgeons expert consensus for the surgical treatment of hyperhidrosis. Ann Thorac Surg. 2011;91(5):1642–8.
12. Cheng JK, Ji RR. Intracellular signaling in primary sensory neurons and persistent pain. Neurochem Res. 2008;33:1970–8.
13. Christensen K, Jensen EM, Noer I. The eflex sympathetic dystrophy syndrome response to treatment with systemic corticosteroids. Acta Chir Scand. 1982;148:653–5.
14. Collins S, Zuurmond WWA, de Lange JJ, et al. Intravenous magnesium for Complex Regional Pain Syndrome Type 1 (CRPS1) patients: a Pilot Study. Pain Med. 2009;10:930–40.
15. Cross FW, Cotton LT. Chemical lumbar sympathectomy for ischemic rest pain: a randomized prospective controlled clinical trial. Am J Surg. 1985;150(3):341–5.
16. Day M. Sympathetic blocks. The evidence. Pain Prac. 2008;8:98–109.
17. de Mos M, de Bruijn AG. The incidence of complex regional pain syndrome: a population-based. Pain. 2007;129:12.
18. de Olivera RR, Exira MJ. Thoracic sympathetic block for the treatment of complex regional pain syndrome type 1: a double-blind randomized controlled study. Pain. 2014;155:2274–81.
19. de Rooij AM, de Mos M, Stukernboom MC, Marinus J, Van den Magdenberg AM, van Hilten JJ. Family occurrence of complex regional pain syndrome. Eur J Pain. 2009;13:171–7.
20. Drummond PD, Finch PM, Skipwork S, Blockey P. Pain increases during sympathetic arousal in patients with complex regional pain syndrome. Neurology. 2001;57:1296–303.
21. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med. 2010;152:85–92.
22. Elahi F, Wu WY, Callahan D, Bhandary AK, Beutler BC. Lassalle, CA, Hemmings Jr HC, editors. Schwartz AJ, associate editor. Images in anesthesiology: reversible anterior spinal artery syndrome during celiac plexus block. Anesthesiology. 2013;118:187.
23. Feldman SI, Downey G. Schafer-Neitz: pain negative mood and perceived social support in chronic pain patients: a daily diary study of people with reflex sympathetic dystrophy. J Consult Clin Psychol. 1999;67:776–85.
24. Gabrhelik T, Michalek P, Adamus M, Berta E. Percutaneous upper thoracic radiofrequency sympathectomy in Raynaud's phenomenon – a comparison of T2/T3 procedure versus T2 lesion with phenol application. Reg Anesth Pain Med. 2009;34:425–9.
25. Goebel A, Barker CH, Turner SL, et al. Complex regional pain syndrome in adults: UK guidelines for diagnosis, referral and management in primary and secondary care. London: RCP; 2012.
26. Goroszeniuk T, Warsaw LM, Riaz K. Permanent percutaneous splanchnic nerve neuromodulation for management of pain due to chronic pancreatitis: a case report. Neuromodulation. 2011;14:253–7.
27. Gress F, Schmitt C, Sherman S, Ikenberry S, Lehman G. A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain. Am J Gastroenterol. 1999;94:900–5.
28. Grothusen JR, Alexander G, Erwin K, Schwartzman R. Thermal pain in complex regional pain syndrome. Pain Physician. 2014;17:71–9.
29. Harden RN, Oaklander AL, Burton AW, Perez RS, Richardson K, Swan M, Barthel J, Costa B, Graciosa JR, Bruehl S. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. Pain Med. 2013;14(2):180–229.
30. Harden RN, Rudin NJ, Buehl S, Kee W, Parik DK, Kooch J, Duc T, Gracely RH. Increased systemic catecholamine in complex regional pain syndrome and relationship to psychological factors. Anesth Analg. 2004;99:1478–85.
31. Haynsworth Jr RF, Noe CE. Percutaneous lumbar sympathectomy: a comparison of radiofrequency denervation versus phenol neurolysis. Anesthesiology. 1991;74(3):459–63.
32. Heavner JE, Calvillo O, Racz GB. Thermal grill illusion and complex regional pain syndrome-type I reflex sympathetic dystrophy. Reg Anesth. 1997;22(3):257–9.
33. Herrero JF, Laird JM, Lopez Garcia JA. Windup of spinal neurons and pain sensation: much ado about something? Prog Neurobiol. 2000;61:169–203.
34. Horlocker T, Wedel D, Rowlingson D, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Guidelines (3rd ed.). Reg Anesth Pain Med. 2010;35:64–101.
35. Ji RR, Woolf CJ. Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. Neurobiol Dis. 2001;8:1–10.
36. Johnson CD, Berry DP, Harris S, Pickering RM, Davis C, George S, Imrie CW, Neoptlemos JP, Sutton R. An open randomized comparison of clinical effectiveness of protocol-driven opioid analgesia, celiac plexus block or thoracoscopic splanchnicectomy for pain

management in patients with pancreatic and other abdominal malignancies. Pancreatology. 2009;9(6):755–63.
37. Juottonen K, Gockel M, Sillen T, Hurri H, Fors N. Altered central sensory motor processing in patients with complex regional pain syndrome. Pain. 2002;98:315–23.
38. Klemer MA, deVet HC, Barendse GAM, et al. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five–year follow-up of patients in a randomized controlled trial. J Neurosurg. 2008;108:292–8.
39. Kramis RC, Roberts WJ, Gillette RG. Post–sympathectomy neuralgia: hypotheses on peripheral and central neuronal mechanisms. Pain. 1996;64(1):1–9.
40. Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Cortical reorganization during recovery from complex regional pain syndrome. Neurology. 2004;63(4):693–701.
41. Mailis A, Furlan A. Sympathectomy for neuropathic pain. [Review] [18 refs] [Update in Cochrane Database Syst Rev. 2010;(7):CD002918; PMID: 20614432].
42. Manjunath PS, Jayalakshmi TS, Dureja GP, Prevost AT. Management of lower limb complex regional pain syndrome type 1: an evaluation of percutaneous radiofrequency thermal lumbar sympathectomy versus phenol lumbar sympathetic neurolysis-a pilot study. Anesth Analg. 2008;106(2):647–9. Table of Contents, 2008 Feb.
43. Meier PM, Zurakowski D, Berde CB, Sethna NF. Lumbar sympathetic blockade in children with complex regional pain syndromes: a double blind placebo-controlled crossover trial. Anesthesiology. 2009;111(2):372–80.
44. Mitchel SW, Morehouse GR, Keen WW. Gunshot wounds and other injuries to nerves. Philadelphia: JB Lippincott & Co; 1864.
45. Moiset X, Boiusharia D. Brain imaging of neuropathic pain. Neuroimage. 2007;37(suppl):S80–8.
46. Noe CE, Haynsworth Jr RF. Lumbar radiofrequency sympatholysis. J Vasc Surg. 1993;17(4):801–6.
47. Oaklander AL, Rissmiller JG, Gelman LB, Zheng L, Chang Y, Gott R. Evidence of small- fiber axonal degeneration in complex regional pain syndrome type 1 [reflex sympathetic dystrophy]. Pain. 2006;120:244–66.
48. Ochoa JL. Truths, errors and lies around "reflex sympathetic dystrophy". J Neurol. 1999;246:875–9.
49. Price DD, Long S, Wilsey B, Rafti A. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. Clin J Pain. 1998;14(3):216–26.
50. Racz Gabor B, Heavner, James E, Noe, Carl E. Definitions, classification and taxonomy: an overview. Sympathetic pain syndromes: reflex sympathetic dystrophy and causalgia. Physical medicine and rehabilitation: State of the art reviews, vol. 10, no. 2. Philadelphia: Hanley and Belfus; 1996.
51. Rieger R, Loureiro Mde P, Pedevilla S, de Oliveira RA. Endoscopic lumbar sympathectomy following thoracic sympathectomy in patients with palmoplantar hyperhidrosis. World Journal of Surgery. 2011;35(1):49–53.
52. Roberts WJ. A hypothesis on the physiological basis for causalgia and related pains. Pain. 1986;24:297–311.
53. Rykowski Jan J, Hilgier M. Efficacy of neurolytic celiac plexus block in varying locations of pancreatic cancer; influence on pain relief. Anesthesiology. 2000;92(2):347–54. 92547–54 0 2000, American Society of Anesthesiologists, Inc Lippincott Williams & Wilkins, Inc.
54. Sandroni P. Benrud-Larson: complex regional pain syndrome type 1: incidence and prevalence in Olmstead county, a population-based study. Pain. 2003;109:199–207.
55. Shah RV, Racz GB. Recurrence and spread of complex regional pain syndrome due to distant site surgery: a case report. Am J Orthop (Belle Mead NJ). 2006;35(11):523–6.
56. Stanton TR, Wand BM, et al. Local anesthetic sympathetic blockade for complex regional pain syndrome. Cochrane Database Syst Rev. 2013;(8):CD0004598.
57. Stanton-Hicks M, Baron R, Boa R, et al. Complex regional pain syndromes: guidelines for therapy. Clini J Pain. 1998;14:155–66.
58. Sullivan MD. Who gets high dose opioid therapy for chronic non-cancer pain? Pain. 2010;151:567–8.
59. Van de Vusse AC, Stomp-van den Berg SGM, Kessels AHF, Weber WEJ. Randomized controlled trial of gabapentin in complex regional pain syndrome type 1. BMC Neurol. 2004;4:13. doi:10.1186/1471-4-13.
60. van Eijs F, Stanton-Hicks M, Van Zundert J, Faber CG, Lubenow TR, Mekhail N, van Kleef M, Huygen F. Evidence-based interventional pain medicine according to clinical diagnoses. 16. Complex regional pain syndrome. Pain Practice. 2011;11(1):70–87. Jan/Feb 2011.
61. van Eijs F, Geurts JW, Van Zundert J, Faber CG, Kessels AG, Joosten EA, van Kleef M. Spinal cord stimulation in complex regional pain syndrome type I of less than 12 month duration. Neuromodulation. 2012;15(2):144–50. March/April 2012.
62. Varenna M, Zucchi F, Ghiringhelli D, et al. Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. J Rheumatol. 2000;27:1477–83.
63. Velasco F, Carrillo-Ruiz JD, Castro G, et al. Motor cortex stimulation applied to patients with complex regional pain syndrome. Pain. 2009;147:91–8.
64. Verdugo RJ, Moya MF, Cea JG, Salinas HA, Bilbeny CJ. Stellate ganglion block in reflex sympathetic dystrophy: a double-blind crossover study. Program and abstracts of the 1st scientific meeting of the European Federation of IASP chapters, Verona: IASP; 1995.
65. Wang H, Kohno T, Amaya F, Brenner GJ, Ito N, Allchorne W. Bradykinin produces pain hypersensitivity by potentiating spinal cord glutaminergic synaptic transmission. J Neurosci. 2005;25:7986–92.
66. Wassr G, Schattschneider J, Heckman K, Maier C, Baron R. Vascular abnormalities in reflex sympathetic dystrophy [CRPS1]: mechanisms and diagnostic value. Brain. 2001;124:587–99.
67. Wilkinson HA. Percutaneous radiofrequency upper thoracic sympthectomy. Neurosurgery. 1996;38(4):715–25.
68. Wong GY, Schroeder DR, Carns PE, Wilson JL, Martin DP, Kinney MO, Mantilla CB, Warner DO. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA. 2004;291:1092–9.
69. Yang IY, Oraee S, Viejo C, Stern H. Computed tomography celiac trunk topography relating to celiac plexus block. Reg Anesth Pain Med. 2011;36:21–5.
70. Yarmohammadi H, Nakamoto DA, Azar N, Hayek SM, Haaga JR. Percutaneous computed tomography guided cryoablation of the celiac plexus as an alternative treatment for intractable pain caused by pancreatic cancer. J Cancer Res Ther. 2011;7(4):481–3.
71. Zhang CL, Zhang TJ, Guo YN, Yang LQ, He MW, Shi JZ, Ni JX. Effect of neurolytic celiac plexus block guided by computerized tomography on pancreatic cancer pain. Dig Dis Sci. 2008;53(3):856–60.
72. Zhong WA, Yu Z, Zeng J-X, Lin Y, Yu T, Min X-H, Yuan Y-H, Chen Q-K. Celiac plexus block for treatment of pain associated with pancreatic cancer: a meta-analysis. Pain Pract. 2014;14(1):43–5.

Hypogastric Plexus Block and Neurolysis

7

Michelle Smith and Miles Day

The hypogastric plexus is a retroperitoneal structure that is a continuation of the paravertebral sympathetic chain, located near the bifurcation of the abdominal aorta. It contains visceral, sympathetic, and parasympathetic efferents as well as parasympathetic and visceral afferents to pelvic structures including the uterus, urethra, prostate, lower 1/3rd of the colon, and perineum. It has been targeted in patients with pelvic cancer, endometriosis, post-prostatectomy penile pain, urethral pain, and post-uterine artery embolization pain.

History

In 1990, Plancarte described the classic posterior approach for superior hypogastric plexus block to treat pelvic pain following reports of pain relief after cordotomy [1]. This approach has been used routinely to treat pelvic pain of benign and malignant origin [2]. A transdiscal approach for the superior hypogastric plexus was described by Ina in 1992 [3] and further refined by Erdine [4] and Turker [5]. More recently, a transsacral approach for inferior hypogastric block [6] and a coccygeal transverse approach [7] for the same have been described.

Anatomy

The hypogastric plexus is a mixture of adrenergic and cholinergic nerve fibers and relays sympathetic, parasympathetic, and visceral impulses from the pelvic viscera [8]. The superior hypogastric plexus (SHP) contains sympathetic efferents from L1–L5, and the inferior hypogastric plexus (IHP) receives contributions from parasympathetic and somatic efferents from S2–S4. The IHP also contains visceral and sympathetic afferents. Visceral pelvic pain fibers travel with the sympathetic supply. The SHP is located anterior to the lower third of the L5 vertebral body and extends to the upper third of the sacrum. It is situated mostly to the left. It lies anteromedial to the psoas muscle and positioned anterior to the aortic bifurcation, left common iliac vein, and medial sacral vessels. It is in close proximity to the roof of the sigmoid colon mesentery with the attachment point of the mesocolon left of the plexus. The SHP gives rise to the right and left hypogastric nerves which join the right and left pelvic splanchnic nerves from S2-4 to form the inferior hypogastric plexus. The inferior hypogastric plexus forms a triangular structure with the following landmarks: the cephalad edge runs parallel to the hypogastric artery; the caudal edge stretches from the fourth sacral root to the ureter entry point at the broad ligament; and the dorsal edge runs along the ventral surface of the sacrum close to the S2-S4 nerve roots. Parasympathetic nerves ascend from the IHP to the sigmoid colon, descending colon, and left colic flexure. The IHP gives rise to peripheral nerves including the pelvic, middle rectal, vesicle, prostatic, and uterovaginal plexus. The pudendal nerve also has connections to the IHP.

Technical Aspects and Equipment

When performing the superior or inferior hypogastric plexus block, radiological guidance is required to increase efficacy and decrease complications. This can be computerized tomography (CT) or fluoroscopy. CT will expose the patient and practitioner to more radiation.

Either sharp- or blunt-tipped needles can be used. A blunt needle requires that an introducer needle two sizes larger is placed first. The 15 cm length is preferred given the location of the superior hypogastric plexus. The transsacral approach

M. Smith, MD (✉) • M. Day, MD, DABA, DABIPP, FIPP
Department of Anesthesiology, Texas Tech University Health Sciences Center, 3601 4th Street, Lubbock, TX, 79430, USA
e-mail: michelle.smith10@gmail.com; miles.day@ttuhsc.edu

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_7

for the inferior hypogastric plexus may allow a 10 cm length to be used.

Indications

Indications for hypogastric plexus block and neurolysis include benign and malignant pain thought to arise from pelvic visceral structures including uterus, urethra, distal colon, bladder, vagina, prostate, and perineum. Benign conditions include endometriosis, pelvic adhesions, pelvic inflammation, interstitial cystitis, irritable bowel syndrome, proctalgia fugax, and vulvodynia.

Contraindications

Relative contraindications are allergies to the medications used for the block, anticoagulant medications, and history of previous surgery leading to altered anatomy. Absolute contraindications include coagulopathy, infection, sepsis, and patient refusal.

Pre-procedure Considerations

Preoperative evaluation should include review of the patient's medical problems including cardiac history, allergies, and recent or active infection. Evaluate patient for anticoagulant or antiplatelet therapy prior to any interventional pain management procedure. The benefit of the patient receiving the procedure must outweigh the risk of withholding anticoagulation to justify the procedure. Communication with the patient's primary care physician (PCP) or cardiologist is a necessity to ensure patient safety and to protect the pain physician. General guidelines for stopping anticoagulants are based on the individual drug's effect on platelets or coagulation factors:

- Nonsteroidal anti-inflammatory drugs (NSAIDS) are withheld for 4 days.
- Aspirin is withheld for 7–10 days.
- Clopidogrel is withheld for 7–10 days.
- Ticlopidine is withheld for 10–14 days.
- Coumadin should be withheld according to PCP's or cardiologist's recommendations and a prothrombin time (PT) should be evaluated prior to the procedure.
- Heparin use should receive the same precautions as Coumadin use, although a partial thromboplastin time (PTT) should be evaluated instead.
- For newer anticoagulants such as rivaroxaban, dabigatran etexilate, apixaban, and argatroban, review the package insert for guidelines.

Technique

Local anesthetic nerve blocks as well as neurolytic blocks to the hypogastric plexus have been described in several different approaches including "classic," paravertebral, transdiscal, lateral, trans-spinal, and via the S1 foramen. This chapter will focus on the classic, paravertebral, and transdiscal approaches. Common to all techniques is the need for standard ABA-recommended monitoring during the procedure. Intravenous fluids should be administered 30 min prior to initiation of procedure due to the risk of hypotension with sympathetic blockade. A 500 ml volume of a balanced salt solution should suffice. Perioperative antibiotics are recommended for the transdiscal approach to prevent discitis. The hypogastric plexus block needs to be performed with fluoroscopic or CT guidance. A 15 cm, 20- or 22-gauge, curved, sharp, or blunt needle is used. When using a blunt needle, a cannula two sizes larger needs to be inserted first, i.e., 16-gauge cannula for a 20-gauge needle. The patient is placed in the prone position with pillows placed under the lower abdomen to reverse the lumbar lordosis.

Classic

The lower lumbar and sacral region is sterilely prepped and draped. Identify the L4–L5 interspace and tilt the C-arm in the cephalocaudal direction to square the inferior endplate of L4 and the superior endplate of L5. Raise a skin wheal with local anesthetic approximately 5–7 cm lateral to the L4–L5 interspace. Insert an introducer cannula through the skin wheal, angling 30–45° medially and caudally. If using a sharp needle, this step is omitted. Insert the block needle through the cannula and advance toward the inferior, anterolateral aspect of the L_5 vertebral body. Check the depth of the needle with a lateral image. Adjust the angle of the needle until the tip walks off the anterior edge of the L5–S1 interspace. The transverse process of L5 may sometimes be encountered and requires the initial angle of the needle to be steeper. On the A-P image, the needle tip should be medial to an imaginary line drawn through the medial aspect of the lumbar pedicle shadows and extending caudally through the sacrum. Repeat the procedure on the opposite side using the same technique. Utilizing continuous lateral fluoroscopic imagining and after negative aspiration for blood and CSF, inject 2–3 mL of nonionic, water-soluble contrast through each needle. The contrast should spread caudally in a curvilinear fashion over the L5–S1 disc and sacral promontory. The A-P view should show contrast over the upper portion of the sacrum extending caudally. Perform the block with 8–10 mL of 1–2 % lidocaine, 0.2 % ropivicaine, or 0.25 % bupivacaine.

Paravertebral

This approach is very similar to blockade of the L5 sympathetic ganglion, except the target is the inferior aspect of the L5 vertebral body at the L5–S1 disc. Sterilely prep and drape the lower lumbar and sacral region. Square the inferior endplate of L5 and the superior aspect of the sacrum. Oblique the C-arm ipsilaterally, stopping just before the shadow of the iliac crest slightly overlaps the inferior, lateral aspect of the L5 vertebral body. Raise a skin wheal with local anesthetic over the inferior, lateral aspect of L5. Insert the introducer cannula in a coaxial fashion and check the depth with a lateral image. Insert the curved, blunt block needle through the introducer. Return to the oblique view and advance the block needle, checking its direction with spot images. Once bone is touched, turn the tip caudally and advance the needle on a lateral image. As the needle is advanced, turn the tip medially to confirm that the needle is still on the bone. Advance the needle until the tip is just past the inferior, anterolateral edge of the L5 vertebral body (Fig. 7.1). Obtain an A-P image. Repeat the procedure on the opposite side using the same technique (Fig. 7.2). Under continuous lateral fluoroscopy and after negative aspiration for blood and CSF, inject 2–3 mL of nonionic, water-soluble contrast through each needle (Fig. 7.3). The contrast should spread in the same fashion as described for the classic approach (Fig. 7.4). The type and volume of medication is the same as previously described.

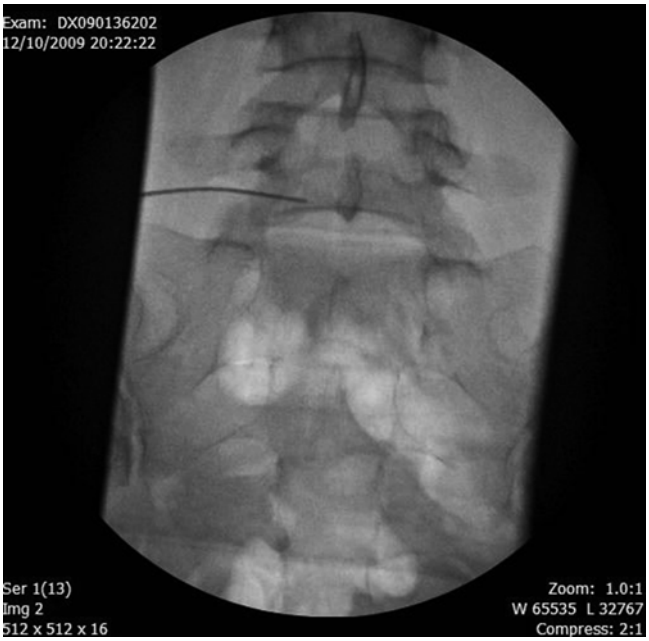


Fig. 7.1 Anterior-posterior fluoroscopic image with needle placed for hypogastric plexus block

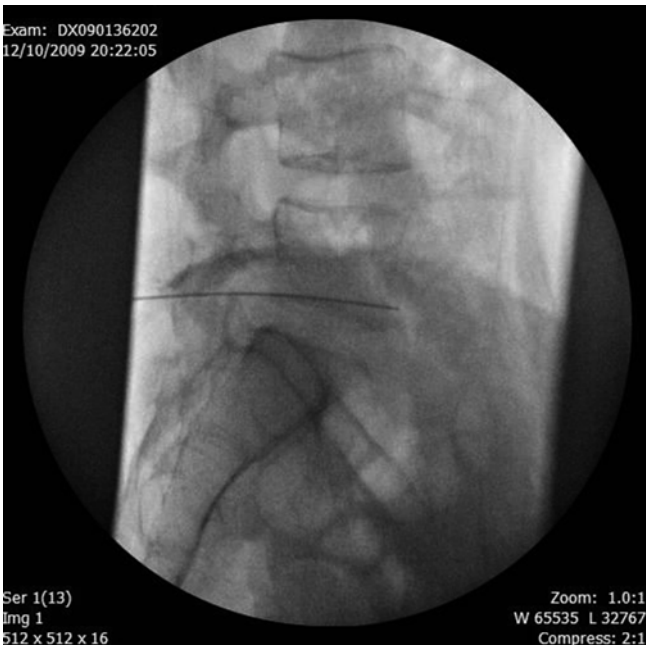


Fig. 7.2 Lateral fluoroscopic image with needle placed for hypogastric plexus block

Transdiscal

The posterior transdiscal approach targets the SHP anterior to the L5/S1 intervertebral disc. The patient is placed prone on the fluoroscopy table. This is a one-sided (left) approach and a double-needle technique is used to decrease the chance of discitis. Prophylactic, intravenous antibiotic is given within 1 h of the procedure.

Square the inferior endplate of L_5 and the superior aspect of the sacrum with a cephalocaudal tilt of the C-arm. Oblique the C-arm toward the left until an inverted triangle is created with the shadows of the superior endplate of L5, the lateral aspect of the superior articular process of the sacrum, and the iliac crest. Raise a skin wheal over the shadow of the lateral aspect of the superior articular process of the sacrum. Insert the introducer cannula in a coaxial fashion at the midpoint of the lateral aspect of the superior articular process of the sacrum. Insert the curved, sharp, or blunt block needle through the introducer cannula and advance in a coaxial fashion toward the disc using spot images. Check a lateral image and advance until the tip of the needle is posterior to the L5–S1 foramen. Return to the oblique view and check to make sure the needle is coaxial. If not, withdraw the needle slightly and redirect medially. On a lateral view, advance the needle into and through the disc until the needle tip just exits the anterior portion of the disc. Try to stay in the middle of the disc. Check an A-P image. The needle tip should be in the same position as described in the aforementioned techniques,

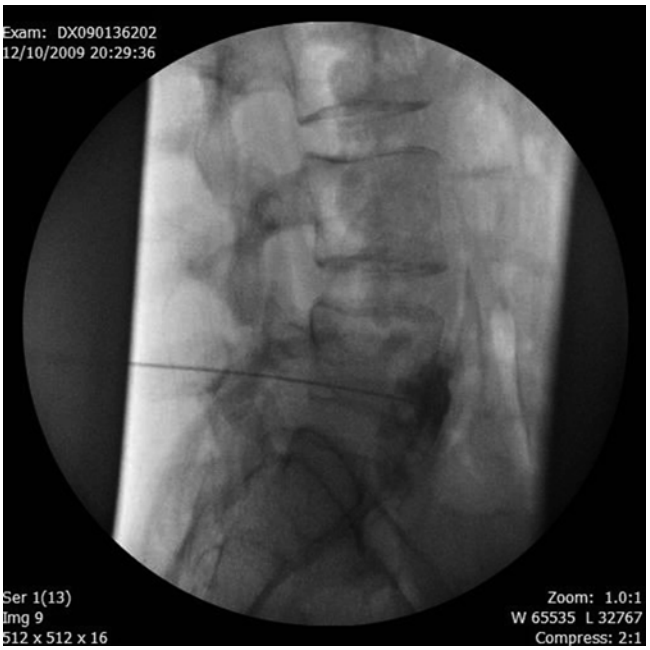


Fig. 7.3 Lateral fluoroscopic image with needle placed for hypogastric plexus block after contrast injection

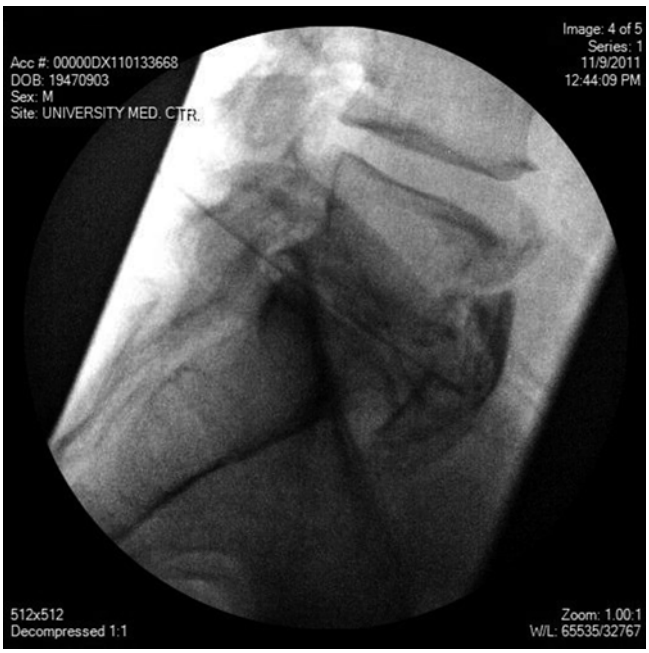


Fig. 7.5 Lateral fluoroscopic image of hypogastric plexus block after injection of local anesthetic

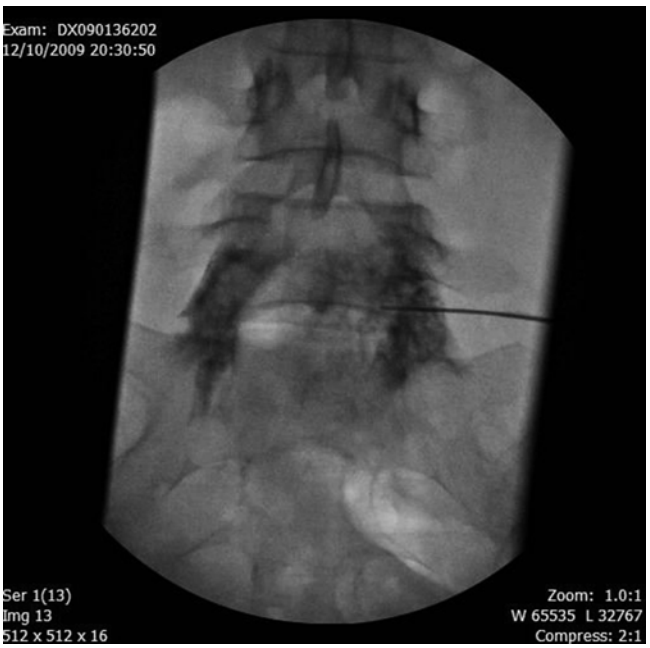


Fig. 7.4 Anterior-posterior fluoroscopic image with needle placed for hypogastric plexus block after contrast injection

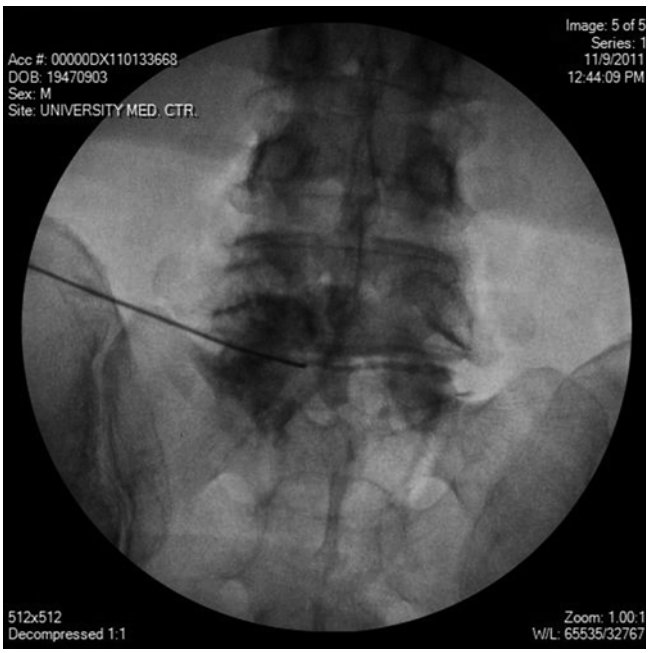


Fig. 7.6 Anterior-posterior fluoroscopic image of hypogastric plexus block after local anesthetic injection

but is typically more medial. Inject nonionic, water-soluble contrast on a lateral image and observe for proper spread as described previously (Fig. 7.5). Check the A-P (Fig. 7.6). The block is performed with 8–10 mL of 1–2 % lidocaine, 0.2 % ropivacaine, or 0.25 % bupivacaine. As the needle is withdrawn, inject antibiotic into the disc to decrease the possibility of discitis.

Neurolytic Hypogastric Plexus Block

Chemical neurolysis can be accomplished with 5–8 mL of 6–10 % phenol or 50–100 % anhydrous alcohol. Confirm proper needle placement as described in the aforementioned techniques prior to the injection of any neurolytic. Prior to

removal of the needle/s, 2–3 mL of preservative-free normal saline should be used to flush the needle/s. Failure to flush the needle/s could result in tissue injury along the path of the withdrawn needle.

Other Techniques

The transsacral and coccygeal transverse approaches for inferior hypogastric block will not be discussed in this chapter. Please refer to the articles for these approaches.

Literature

A review of the available literature revealed 15 research articles concerning hypogastric plexus block and neurolysis for pelvic pain, 12 of which targeted SHP and three of which targeted IHP.

Inferior Hypogastric Plexus

The literature for IHP block and neurolysis consists of one case report [7], one case series [6], and one observational study [9]. All of the prospective studies address SHP blockade/neurolysis, and there are no higher-quality research studies in the literature on IHP blockade/neurolysis.

Superior Hypogastric Plexus

The literature for SHP block and neurolysis consists of four case reports [10–13], four case series [1, 4, 14, 15], two observational studies [2, 16], and two prospective, randomized trials [17, 18]. The articles published by Plancarte in 1990 [1] and 1997 [2] are the earliest publications that describe SHP blockade and neurolysis, respectively. The first article described SHP blockade in 28 patients with refractory pelvic pain related to malignancy. The block was performed after an L4/L5 epidural was placed for anesthesia. Mean numerical pain-rating scores were recorded before and after the procedure and monthly until patient death. The results indicated that patients received 70 % pain relief after the block, and the residual pain was thought to be secondary to somatic pain. In two patients, CT-guided SHP blockade was required when retroperitoneal spread of tumor made fluoroscopic guidance difficult. Plancarte's second article described SHP neurolysis following diagnostic blockade in 227 patients with pelvic pain related to malignancy [2]. Of the 227 patients who underwent blockade with 0.25 % bupivacaine, 159 had a positive response and went on to receive neurolysis with 10 % phenol. Of these, 115 patients had a significant reduction in pain. Oral opioid usage decreased by 43 % and 72 % of patients had sustained pain relief following neurolysis. In 2004, de Oliveira [17] et al. performed a comparison study of three arms in which they attempted to identify if cancer patients would benefit from early versus late sympathetic blocks compared with pharmacologic treatment alone. However, this study included celiac and lumbar sympathetic blocks as well as superior hypogastric plexus blocks. The patients had diagnoses other than pelvic pain. They showed that those cancer patients receiving a nerve block, whether early or late in their course, had decreased side effects from oral opioids and improved quality of life measures compared with pharmacotherapy alone. In 2006, Gamal et al. [18] performed a comparison study of patients with pelvic cancer who received the classic approach for SHP block versus the posterior transdiscal approach for pain. They showed that the transdiscal approach was safer than the classic approach; however, there was no significant difference in pain scores or change in morphine consumption between the two groups.

Complications

Potential complications of hypogastric plexus block include infection, intravascular injection due to the proximity of the iliac vessels, neuraxial injection, nerve injury, discitis, ureter injury, bladder/bowel incontinence, sexual dysfunction, and bowel perforation.

Conclusion

The hypogastric plexus block is an important part of the interventional pain practitioner's armamentarium. Knowledge of the relevant anatomy is key to improve the success of the block and to decrease potential complications. Various techniques have been described, and the choice will depend on the experience of the practitioner, pros and cons of each technique, and relevant anatomy which can vary depending on the current cancer or previous surgery. Efficacy has been established with decreased pain and opiate consumption.

References

1. Plancarte R, Amescua C, Patt R, Aldrete J. Superior hypogastric plexus block for pelvic cancer pain. Anesthesiology. 1990;73:236–9.
2. Plancarte R, de Leon-Casasola O, El-Helaly M, et al. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Reg Anesth. 1997;22(6):562–8.

3. Ina H, Kobayashi M, Imai S, et al. A new approach to superior hypogastric plexus block: trans-intervertebral disc (L5-S1 disc) technique. Reg Anesth. 1992;17(35):123.
4. Erdine S, Yucel A, Celik M, Talu G. Transdiscal approach for hypogastric plexus block. Reg Anesth Pain Med. 2003;28(4):304–8.
5. Turker G, Basagen-Mogol E, Gurbet A, et al. A new technique for hypogastric plexus block: the posteromedian transdiscal approach. Tohoku J Experi Med. 2005;206(3):277–81.
6. Schultz D. Inferior hypogastric plexus blockade: a transsacral approach. Pain Physician. 2007;10:757–63.
7. Choi H, Kim Y, Han J, Moon D. A new technique for inferior hypogastric plexus blockade: a coccygeal transverse approach. Korean J Pain. 2012;25(1):38–42.
8. Alsaid B, et al. Coexistence of adrenergic and cholinergic nerves in the inferior hypogastric plexus: anatomical and immunohistochemical study with 3D reconstruction in human male fetus. J Anat. 2009;214(5):645–54.
9. Mohamed S, Ahmed D, Mohamad M. Chemical neurolysis of the inferior hypogastric plexus for the treatment of cancer-related pelvic and perineal pain. Pain Res Manag. 2013;18(5):249–52.
10. Baik J, Choi E, Lee P, Nahm F. Unilateral, single needle approach using an epidural catheter for bilateral superior hypogastric plexus block. Korean J Pain. 2012;25(1):43–6.
11. Kanazi G, Perkins F, Thakur R, Dotson E. New technique for superior hypogastric plexus block. Reg Anesth Pain Med. 1999;24(5):473–6.
12. Michalek P, Dutka J. Computed tomography-guided anterior approach to the superior hypogastric plexus for noncancer pelvic pain: a report of two cases. Clin J Pain. 2005;21(6):553–6.
13. Rosenberg S, Tewari R, Boswell M, et al. Superior hypogastric plexus block successfully treats severe penile pain after transurethral resection of the prostate. Reg Anesth Pain Med. 1998;23(6):618–20.
14. De Leon-Casasola O, Kent E, Lema M. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Pain. 1993;54:145–51.
15. Wechsler R, Maurer P, Halpern E, Frank E. Superior hypogastric plexus block for chronic pelvic pain in the presence of endometriosis: CT techniques and results. Radiology. 1995;196(1):103–6.
16. Mercadante S, Fulfaro F, Casuccio A. Pain mechanisms involved and outcome in advanced cancer patients with possible indications for celiac plexus block and superior hypogastric plexus block. Tumori. 2002;88(3):243–5.
17. de Oliveira R, dos Reis M, Prado W. The effects of early or late neurolytic sympathetic plexus block on the management of abdominal or pelvic cancer pain. Pain. 2004;110(1-2):400–8.
18. Gamal G, Helaly M, Labib Y. Superior hypogastric block: transdiscal versus classic posterior approach in pelvic cancer pain. Clin J Pain. 2006;22(6):544–7.

Epidural Lysis of Adhesions and Percutaneous Neuroplasty

8

Gabor B. Racz, James E. Heavner, Carl E. Noe, Adnan Al-Kaisy, Tomikichi Matsumoto, Sang Chul Lee, and Laszlo Nagy

Introduction

Chances are relatively high that each of us will experience acute low back pain and/or sciatica at some point in our lives. The usual course is gradual improvement with 5–10 % having persistent symptoms [1]. In the 1990s, the estimated cost of low back pain to the healthcare system was in the billions of dollars annually, and with an aging population, this number can only be expected to increase [2, 3]. Treatment typically begins with conservative measures such as medication and physical therapy and may include invasive pain management interventions. Surgery is sometimes required in patients who have progressive neurologic deficits or persistent pain. Recurrent pain after surgery is a quandary. The question is whether repeat surgery or another alternative technique should be tried. This is the exact scenario that the epidural adhesiolysis procedure was developed to address. Failed back surgery or postlaminectomy syndrome is common, and this led to the development of the epidural adhesiolysis procedure. Epidural adhesiolysis was shown to be effective in many patients with chronic pain after back surgery presumably by freeing up nerves and breaking down scar formation, delivering site-specific corticosteroids and local anesthetics and reducing edema with the use of hyaluronidase and hypertonic saline. Epidural adhesiolysis has resulted in a reduction in pain and neurologic symptoms without the expense and occasional long recovery period associated with repeat surgery and it often prevents the need for surgical intervention. Epidural adhesiolysis was given an evidence rating of strong, in the most recent American Society of Interventional Pain Physicians evidence-based guidelines, correlating to a 1B or 1C evidence level for postlumbar surgery syndrome. The therapy is supported by observational studies and case series and more recently with randomized-control trials. The recommendation has also been made that this therapy could apply to most patients with postlaminectomy syndrome or failed back syndrome in many circumstances with informed consent (Van Zundert J, 2005, personal communication). Additionally, two procedural terminology (CPT) codes have been assigned to the two different kinds of adhesiolysis: CPT 62263 for the three-time injections over 2–3 days, which has recently changed to three injections 6–8 h apart within 24 h, usually done in an inpatient hospital setting, and CPT 62264 for the one-time injection series surgery-center model that may need to be repeated 3–3.5 times in a 12-month period.

G.B. Racz, MD, ABA, FIPP, ABIPP (✉)
Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Advanced Pain Medicine Associates, Wichita, KS, USA
e-mail: gbracz@yahoo.com

J.E. Heavner, MD, PhD, DVM
Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX, USA

C.E. Noe, MD
Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

A. Al-Kaisy, MB, ChB, FRCA, FPMRCA, FIPP
London Bridge Hospital, London, UK

T. Matsumoto, MD, FIPP
Jikei University School of Medicine, Tokyo, Japan

Shiga University of Medical Science, Shiga, Japan

S.C. Lee, MD, PhD, FIPP
Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul, Korea

L. Nagy, MD
Department of Pediatric Neurosurgery, Texas Tech University Health Sciences Center and Covenant Medical Center, Lubbock, TX, USA

Pathophysiology of Epidural Fibrosis (Scar Tissue) as a Cause of Low Back Pain with Radiculopathy

The mechanism of chronic low back pain with radiculopathy after appropriate surgery is not well understood. Kuslich et al. [4] investigated this issue when they studied 193 patients who had undergone lumbar spine operations given

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_8

local anesthetic into the epidural space. These investigators postulated that sciatica could only be produced by stimulation of a swollen, stretched, restricted (i.e., scarred), or compressed nerve root [4]. Back pain could be produced by stimulation of several tissues, but most commonly the tissue of origin was the outer layer of the annulus fibrosis and the posterior longitudinal ligament. Additionally, stimulation for pain generation of the facet joint capsule rarely generated low back pain, and facet synovium and cartilage surfaces of the facet or muscles were never tender [5].

The importance of fibrosis to the etiology of low back pain has been debated [6–8]. There are multiple possible etiologies of epidural fibrosis, including surgical trauma, an annular tear, infection, hematoma, or intrathecal contrast material [9]. These etiologies are well documented in the literature. LaRocca and Macnab [10] demonstrated the invasion of fibrous connective tissue into postoperative hematomas as a cause of epidural fibrosis, and Cooper et al. [11] reported periradicular fibrosis and vascular abnormalities occurring with herniated intervertebral disks. McCarron et al. [12] reported the irritative effect of nucleus pulposus on the dural sac, adjacent nerve roots, and nerve root sleeves independent of the influence of direct compression on these structures. Evidence of an inflammatory reaction was seen by gross inspection and microscopic analysis of spinal cord sections after homogenized autogenous nucleus pulposus was injected into the lumbar epidural space of four dogs. In the control group of four dogs injected with normal saline, the spinal cord sections were grossly normal. Parke and Watanabe [13] showed significant evidence of adhesions in cadavers with lumbar disk herniation.

It is widely accepted that postoperative scar makes the nerve root susceptible to injury by a compressive phenomena [8]. It is natural for connective tissue or any kind of scar tissue to form fibrous layers (scar tissue) as a part of the process that occurs after disruption of the intact milieu [14]. Scar tissue is found in three components of the epidural space. Dorsal epidural scar tissue is formed by reabsorption of surgical hematomas and may be involved in pain generation [15]. In the ventral epidural space, dense scar tissue is formed by posterior defects in the disk, which may persist despite surgical treatment and continue to produce low back pain and radiculopathy past the surgical healing phase [16]. The lateral epidural space includes the epiradicular structures outside the nerve root canals, known as the lateral recesses or "sleeves," which are susceptible to lateral disk protrusions, facet hypertrophy, and neuroforaminal stenosis [17].

Although scar tissue itself is not painful, an entrapped nerve root is. Kuslich et al. [4] surmised that the presence of scar tissue compounded the pain associated with a painful nerve root by fixing it in one position and thus increasing the susceptibility of the nerve root to tension or compression. They also concluded that no other tissues in the spine are capable of producing radicular leg pain. In a study of the relationship between peridural scar and radicular pain after lumbar diskectomy, Ross et al. [18] demonstrated that subjects with extensive peridural scarring, evaluated by magnetic resonance imaging (MRI), were 3.2 times more likely to experience recurrent radicular pain.

This evidence also parallels a new study by Gilbert et al. [19] in which lumbosacral nerve roots were identified as undergoing less strain than previously thought during straight leg raise and in which hip motion greater than 60° was determined to cause displacement of the nerve root in the lateral recess.

Fluid Foraminotomy: Foraminal Adhesiolysis or Disentrapment

Relative or functional foraminal root entrapment syndrome secondary to epidural fibrosis with corresponding nerve root entrapment is frequently evident after an epidurogram (radiopaque contrast injected in the epidural space) and signified by lack of epidural contrast flow into epidural finger projections at those levels. The lysis procedure works in one way by serving as a fluid foraminotomy reducing foraminal stenosis caused by epidural fibrosis. In addition to increasing foraminal cross-sectional area, adhesiolysis serves to decompress distended epidural venous structures that may exert compression at nearby spinal levels (Figs. 8.1 and 8.2). These engorged veins are associated epidural hematomas following injection procedures. Adhesiolysis has led to the development of flexible epiduroscopy that continues to be pioneered by Dr. James Heavner [20, 21].

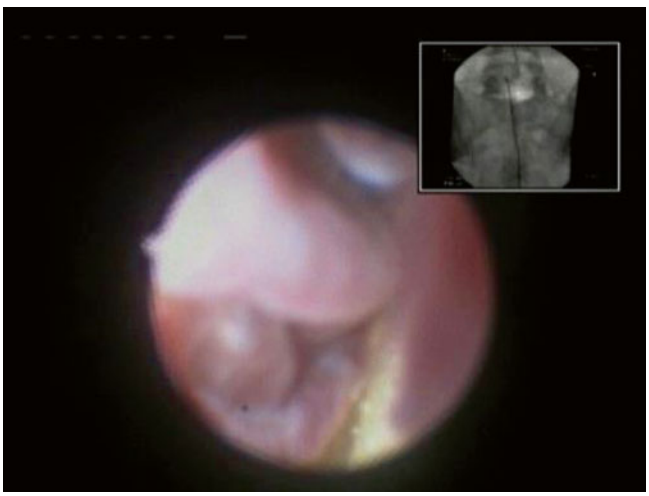


Fig. 8.1 Engorged blood vessels in the epidural cavity as observed during epiduroscopy. Insert in upper *right* corner is fluoroscopy showing location for epiduroscopy tip (left anterior border of L5)

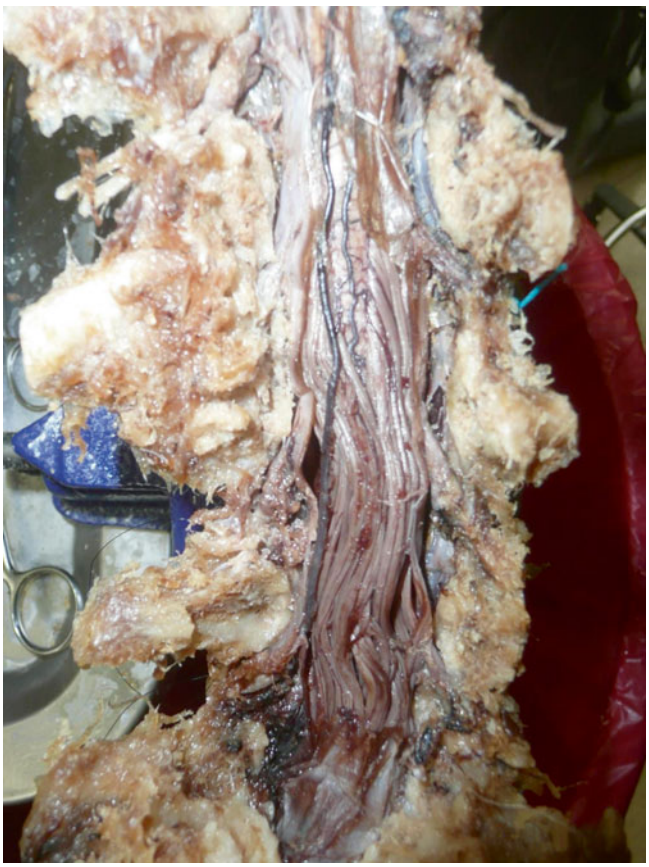


Fig. 8.2 Engorged blood vessels in the epidural cavity in cadaver

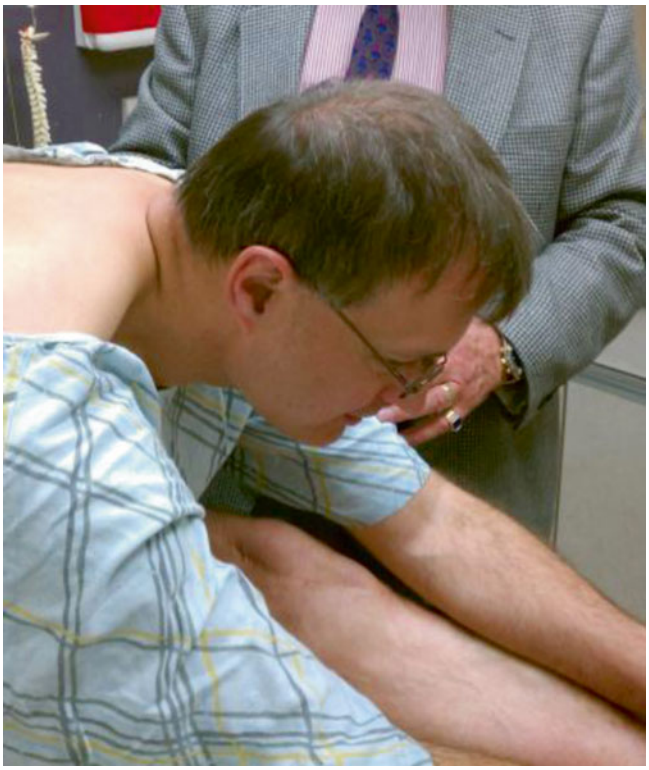


Fig. 8.3 The "dural tug" maneuver being performed prior to percutaneous neuroplasty

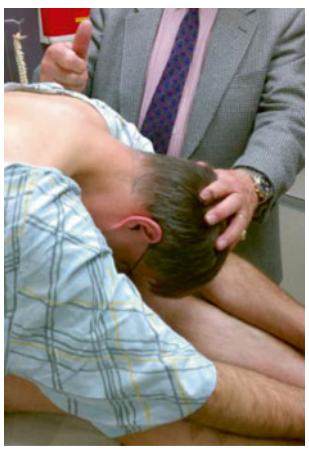


Fig. 8.4 Note pain reproduction prior to full neck flexion secondary to dural adhesions

Diagnosis and Radiologic Diagnosis of Epidural Fibrosis

As with any patient, a thorough history and musculoskeletal and neurologic examination should be performed. In addition to dural tension provocative tests, we recommend a provocative test called "dural tug." To perform the test, the patient should be instructed to sit up with a straight leg, bend forward flexing the lumbar spine until their back pain starts to become evident, and the head and neck flexed rapidly forward. During this maneuver, the dura is stretched cephalad and if adhered to structures such as the posterior longitudinal ligament, the most heavily innervated spinal canal structure, the movement of the dura will elicit back pain that is localized to the pain generator. A positive dural tug maneuver has been observed to resolve after percutaneous neuroplasty (Figs. 8.3, 8.4, 8.5, 8.6, and 8.7).

MRI and computed tomography (CT) are valuable diagnostic tools with a sensitivity and specificity of 50 % and 70 %, respectively [14]. CT myelography may also be helpful, although none of the aforementioned imaging techniques can identify epidural fibrosis with 100 % reliability. Epidurography is the "gold standard" technique used with considerable success, and it is believed that epidural fibrosis is best diagnosed by performing an epidurogram [22–25]. It can detect epidural filling defects in good correlation with a patient's symptoms in real time [25]. A combination of several of these techniques would likely increase the ability to identify and localize epidural fibrosis.

Current Procedural Terminology or CPT Codes

The American Medical Association has developed Current Procedural Terminology codes for epidural adhesiolysis, which include 62264 for a single infusion and 62263 for a staged three-series infusion.

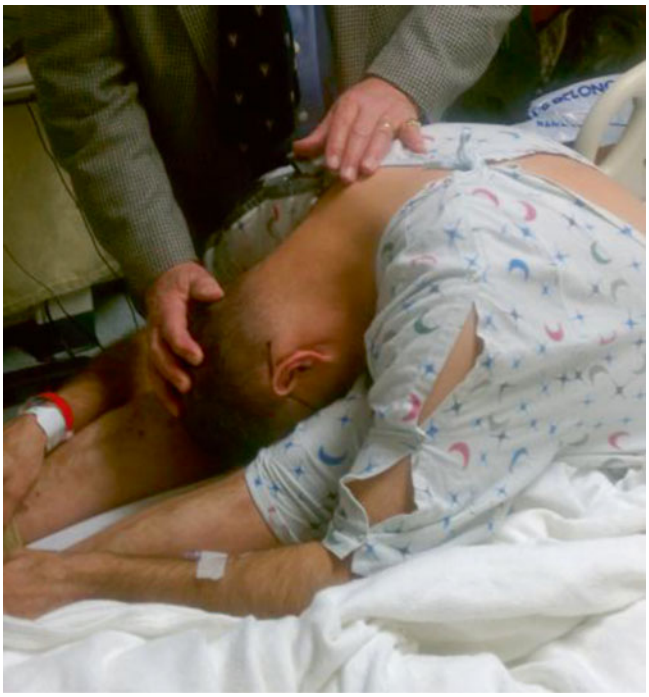


Fig. 8.5 Patient after percutaneous neuroplasty with pain-free neck and back flexion due to treatment of dural adhesions

Indications for Epidural Adhesiolysis

Although originally designed to treat radiculopathy secondary to epidural fibrosis following surgery, the use of epidural adhesiolysis has been expanded to treat a multitude of pain etiologies. These include the following [26]:

1. Failed back surgery syndrome
2. Postlaminectomy syndrome of the neck and back after surgery
3. Disk disruption
4. Metastatic carcinoma of the spine leading to compression fracture
5. Multilevel degenerative arthritis
6. Facet pain
7. Spinal stenosis
8. Pain unresponsive to spinal cord stimulation and spinal opioids
9. Thoracic disk-related chest wall and abdominal pain (after mapping)

Contraindications

The following are absolute contraindications for performing epidural adhesiolysis:

1. Sepsis
2. Chronic infection
3. Coagulopathy
4. Local infection at the procedure site
5. Patient refusal
6. Syrinx formation

A relative contraindication is arachnoiditis. With arachnoiditis, spinal tissue planes may be adherent to one another, increasing the chance of loculation of contrast or medication. Arachnoiditis may also increase the chance of spread of the medications to the subdural or subarachnoid space, which can increase the chance of complications. Practitioners with limited experience should consider referring these patients to a clinician with more training and experience with epidural adhesiolysis.

Patient Preparation

Before epidural adhesiolysis has been deemed an appropriate treatment modality, the risks and benefits of the procedure should be discussed with the patient and informed consent obtained. The benefits are analgesia, improved physical function, and possible reversal of neurologic symptoms. Risks include, but are not limited to, bruising, bleeding, infection, reaction to medications used (i.e., hyaluronidase, local anesthetic, corticosteroids, hypertonic saline), damage to nerves or blood vessels, no or little pain relief, bowel/bladder incontinence, worsening of pain, postdural puncture headache, seizure, and paralysis. Patients with a history of urinary retention or incontinence should have a urodynamic evaluation by a urologist before the procedure to document the preexisting urodynamic etiology and pathology.

Anticoagulant Medication

Medications, supplements, and foods that prolong bleeding and clotting parameters should be withheld before performing epidural adhesiolysis. The duration varies depending on the medication taken and the risk of holding anticoagulants. A consultation with the patient's primary physician should be obtained before stopping any of these medications, particularly in patients who require chronic anticoagulation such as those with drug-eluting coronary stents (especially within the first year) or mechanical prosthetic heart valves. Nonsteroidal anti-inflammatory drugs and aspirin, respectively, should be withheld 4 days and 7–10 days before the procedure. Although there is much debate regarding these medications and neuraxial procedures, we tend to be on the conservative side. New guidelines from ASRA are more restrictive than previous versions. Clopidogrel (Plavix) should be stopped 7 days before, whereas ticlopidine (Ticlid) is withheld 10–14 days before the adhesiolysis [27]. Warfarin (Coumadin) stoppage is variable, but 5 days is usually adequate [26] and an INR may be

Fig. 8.6 There is decreased spine flexion prior to treatment secondary to dural adhesions

Fig. 8.7 After treatment, the same patient demonstrates increased painless flexion of the spine

measured. Patients on subcutaneous heparin should have it withheld a minimum of 12 h before the procedure, whereas those on low-molecular-weight heparin require a minimum of 24 h [27]. Over- the-counter homeopathic medications that prolong bleeding parameters should also be withheld. These include fish oil, vitamin E, ginkgo biloba, garlic, ginseng, and St. John's Wort. Adequate coagulation status can be confirmed by the history, INR, prothrombin time, partial thromboplastin time, and a platelet function assay or bleeding time. The tests should be performed as close to the day of the procedure as possible. Tests performed only a few days after stopping the anticoagulant medication may return elevated because not enough time has elapsed to allow the anticoagulant effects of the medication to resolve. The benefits of the procedure must be weighed against the potential sequelae of stopping the anticoagulant medication, and this should be discussed thoroughly with the patient and communicated with their prescribing physician.

Preoperative Laboratory

Before the procedure, a complete blood count and a clean-catch urinalysis are obtained to screen for undiagnosed infections. An elevated white count and/or a positive urinalysis should prompt the physician to postpone the procedure and refer the patient to their primary care physician for further workup and treatment. A history of bleeding, abnormalities of prothrombin time, partial thromboplastin time, and platelet function assay or bleeding time are obtained to check

for coagulation abnormalities. Any abnormal value warrants further investigation and postponement of the procedure until those studies are complete.

Technique

This procedure is performed in the cervical, thoracic, lumbar, and caudal regions of the spine, depending on the spinal level involved with the pain syndrome. The caudal and lumbar transforaminal placement of catheters will be described in detail, whereas highlights and slight changes in protocol will be provided for cervical and thoracic catheters. Our practice is to perform this procedure under strict sterile conditions in the operating room. Prophylactic antibiotics are given before the procedure. Patients receive either ceftriaxone 1 g intravenously or Levaquin 500 mg orally if allergic to penicillin. The same dose is also given the day after the procedure. An anesthesiologist or supervised nurse anesthetist provides monitored anesthesia care.

Caudal Approach

The patient is placed in the prone position with a pillow under the abdomen to correct the lumbar lordosis and a pillow under the ankles for patient comfort. The patient is asked to internally rotate the legs to put his or her toes together and heels apart. This maneuver relaxes the gluteal muscles and facilitates identification of the sacral hiatus. After sterile preparation and draping, the sacral hiatus is identified by palpation just caudal to the sacral cornu or with fluoroscopic guidance. A skin wheal is placed with local anesthetic 1 in. lateral and 2 in. caudal to the sacral hiatus on the side opposite the documented radiculopathy. A distal subcutaneous approach theoretically provides some protection from meningitis. A local skin infection along a tunnel tract would be much preferred over infection closer to the caudal epidural space. The skin is incised with an 18-gauge cutting needle, and a 15-or 16-gauge RX Coudé (Epimed International) epidural needle is inserted through the nick at a 45° angle and guided fluoroscopically or by palpation to the sacral hiatus (Figs. 8.8 and 8.9).

As the needle is advanced through the hiatus, the angle of the needle is dropped to approximately 30° and advanced into the sacral epidural space. The advantages of the RX Coudé needle compared to other needles are the angled tip, which enables easier direction of the catheter, and the tip of the needle is less sharp. Also, the back edge of the distal opening of the needle is designed to be a noncutting surface that allows manipulation of the catheter in and out of the needle. A Tuohy needle has a cutting surface on the back edge of the distal opening and can more easily shear a catheter. A properly placed needle will be inside the caudal canal below the level of the S3 foramen on anteroposterior (AP) and lateral fluoroscopic images. Needle placement above the level of the S3 foramen could potentially puncture a low-lying dura. The needle tip should ideally cross the midline of the sacrum toward the side of the radiculopathy.

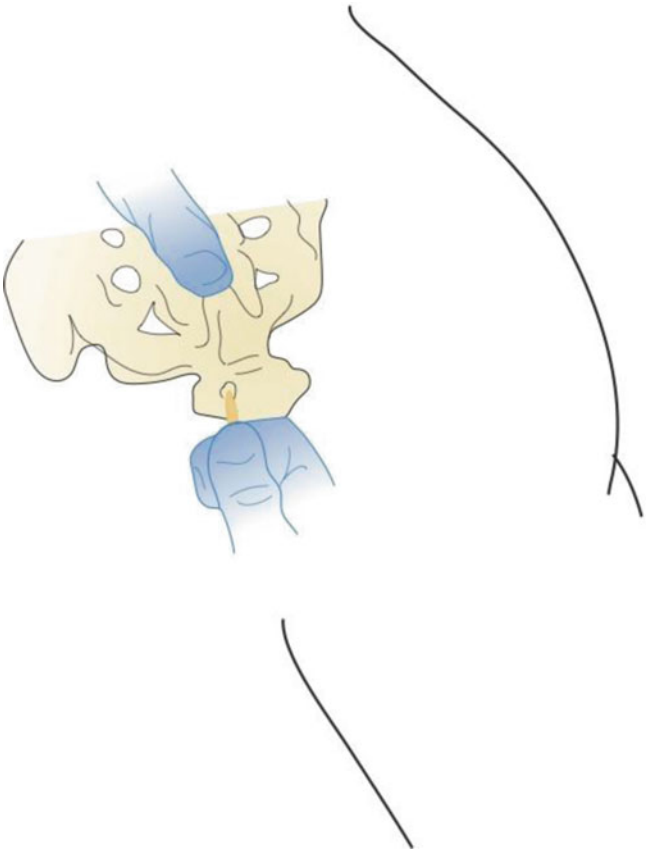


Fig. 8.8 Caudal lysis sequence—first find sacral hiatus and tip of coccyx

An epidurogram is performed using 10 mL of a myelogram grade, non-ionic, water-soluble contrast agent. Aspiration for blood or cerebrospinal fluid should be negative before any injection of the contrast or medication. Omnipaque 240 and Isovue M 300 are the two agents most frequently used and are suitable for myelography [28, 29]. Do not use ionic, water-insoluble agents such as Hypopaque or Renografin or ionic and water-soluble agents such as Conray [30, 31] as these agents are not indicated for myelography. Accidental subarachnoid injections of these agents can lead to serious untoward events such as seizure and possibly death. CSF lavage may be indicted if this occurs. Slowly inject the contrast agent and observe for filling defects using fluoroscopic imaging. A normal epidurogram will have a "Christmas tree" pattern with contrast in the central canal as the trunk and the outline of the nerve roots making up the branches. An abnormal epidurogram will have

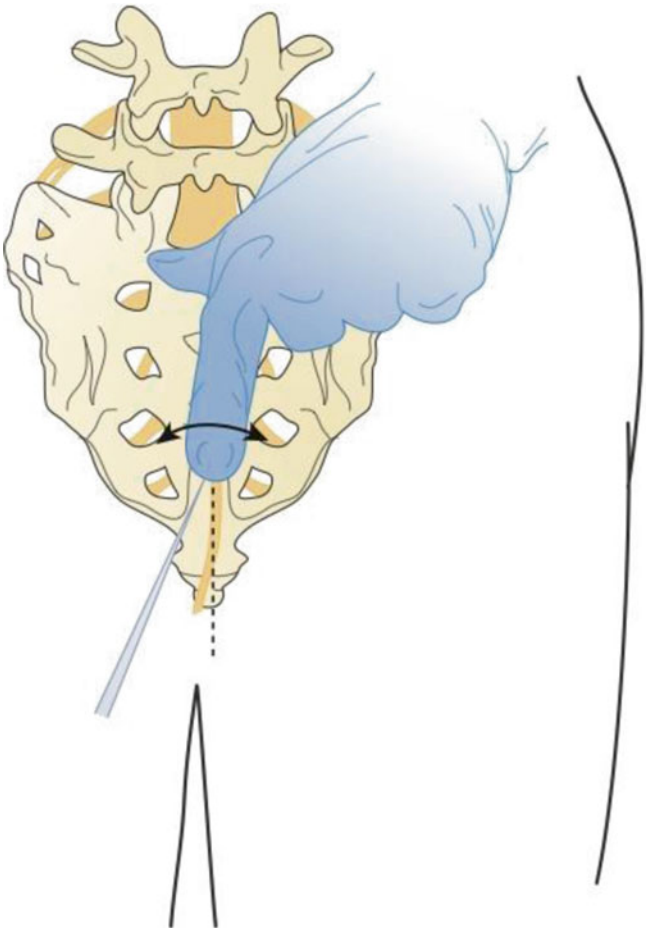


Fig. 8.9 Roll palpating index finger to identify the sacral cornu and thus the target sacral hiatus

areas where the contrast does not fill (Fig. 8.10) or fills asymmetrically. These are the areas of presumed scarring and typically correlate with the patient's radicular complaints. If vascular uptake is observed, the needle should be redirected.

After rotating the needle to position the distal opening of the needle toward a ventral lateral orientation, insert a TunL Kath or TunL-XL (stiffer) catheter (Epimed International) with a bend on the distal tip through the needle (Figs. 8.11 and 8.12). The bend should be 2.5 cm from the distal tip of the catheter and at a 30° angle. The bend allows the catheter to be steered to the target level (Fig. 8.13). Using continuous AP fluoroscopic guidance, advance the tip of the catheter toward the ventrolateral epidural space of the desired level. The catheter can be steered by gently rotating the catheter in a clockwise or counterclockwise direction. Avoid "propellering" the tip (i.e., twisting the tip in circles) because this makes it more difficult to direct the catheter. Do not advance the catheter superiorly in the middle of the sacrum because this makes guiding the catheter to the ventral- lateral epidural space more difficult. The ideal location of the tip of the

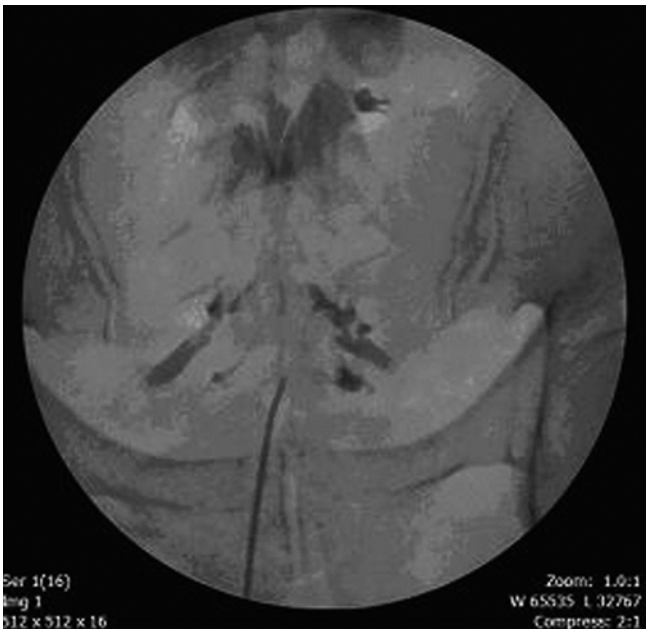


Fig. 8.10 Initial dye injection Omnipaque 240 (10 mL) showing sacral S3 runoff and filling defects at S2, S1, and right L5

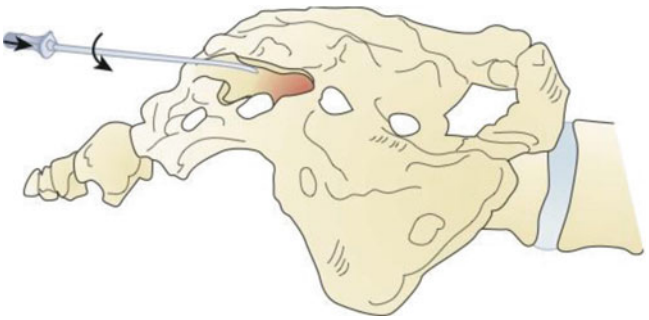


Fig. 8.11 The needle is placed through the sacral hiatus into the sacral canal and rotated in the direction of the target. Do not advance beyond the S3 foramen

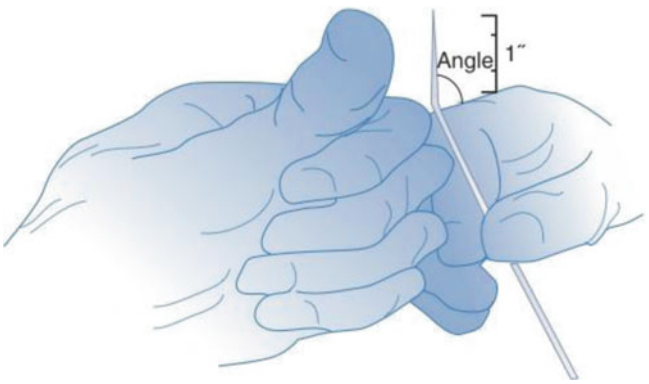


Fig. 8.12 The Epimed Racz catheter is marked for the location of the bend, or use the thumb as reference for the 15° angle bend

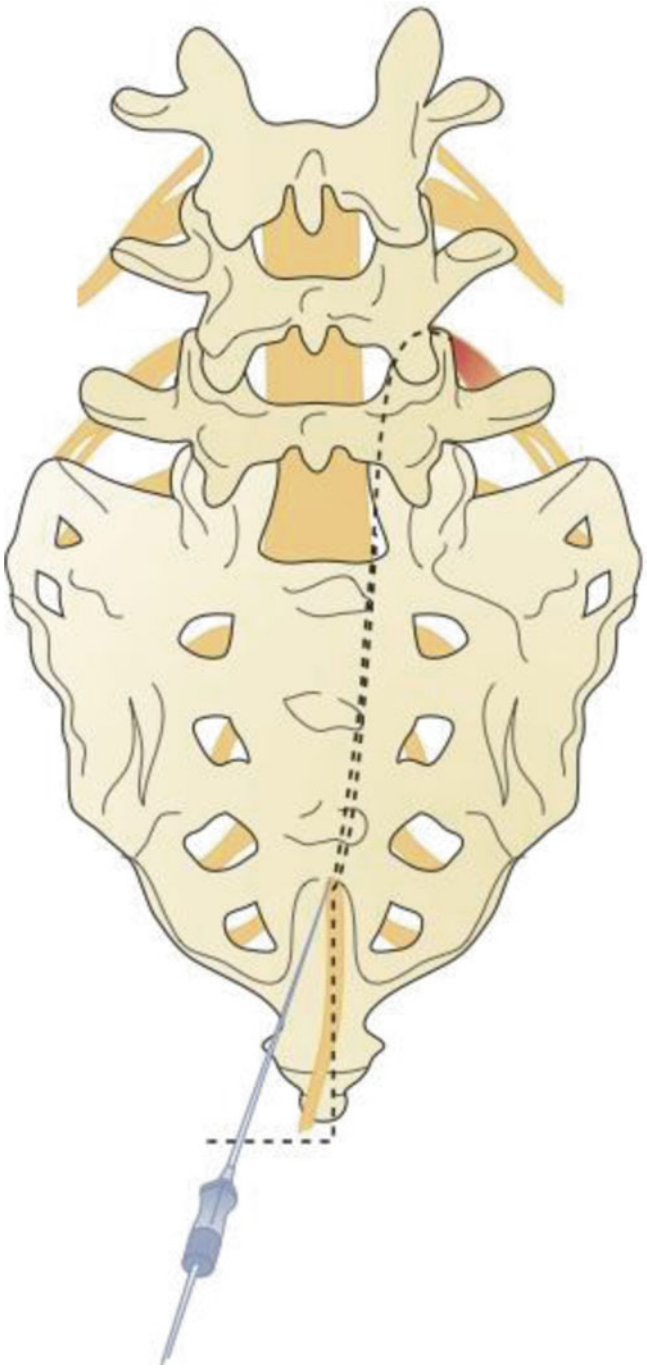


Fig. 8.13 The direction of the catheter is just near the midline; direct the curve under continuous fluoroscopic guidance to the ventral lateral target site. The needle rotation, as well as the catheter navigation, may need to be used to reach the target

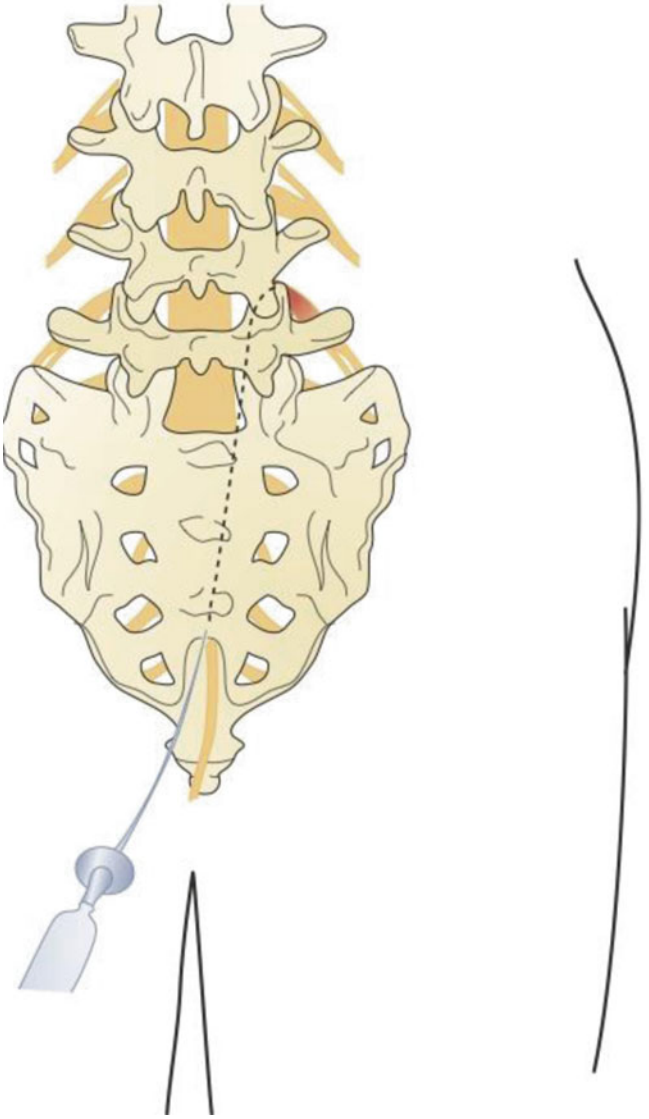


Fig. 8.14 The needle is removed, and the catheter is placed in the ventral lateral epidural space ventral to the nerve root

catheter in the AP projection is in the foramen just below the midportion of the pedicle shadow (Figs. 8.14 and 8.15). Check a lateral fluoroscopic projection to confirm that the catheter tip is in the ventral epidural space.

Using real-time fluoroscopy, inject 2–3 mL of additional contrast through the catheter in an attempt to outline the "scarred-in" nerve root (Fig. 8.16). If vascular uptake is seen, reposition the catheter and reinject contrast. Preferably, there should not be any vascular runoff, but infrequently secondary to venous congestion, an epidural pattern is seen with a small amount of vascular spread. This is acceptable as long as the vascular uptake is venous in nature and not arterial, but extra caution should be taken when injecting the local anesthetic to prevent local anesthetic toxicity. Toxicity is volume and dose related, and so far there have not been any reported complications from small-volume venous spread. Any arterial spread of contrast warrants repositioning of the catheter. We have not observed intra-arterial placement in 25 years of placing soft, spring-tipped catheters.

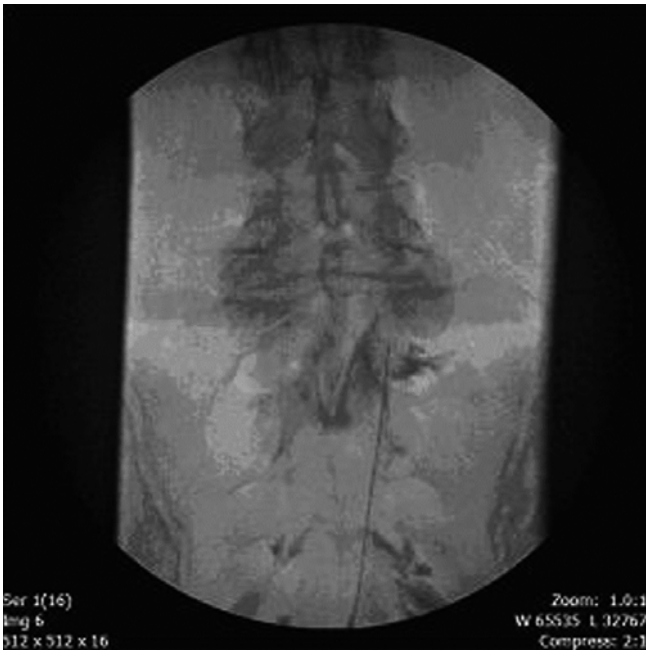


Fig. 8.15 Catheter (24xL) is threaded to lateral L5 neural foramen

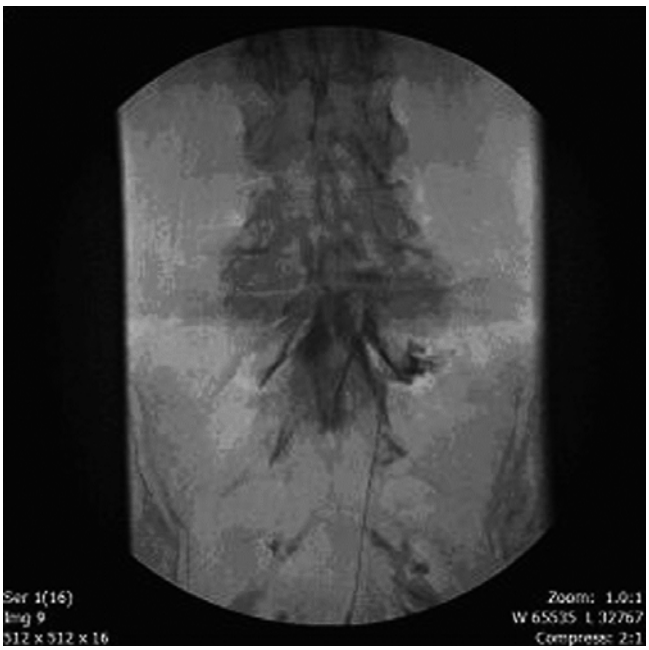


Fig. 8.16 Contrast injection Omnipaque 240, additional 5 mL opening right L5, S1, S2, and S3 perineural spaces; also left L5, S1, S2, and S3 in addition to right L4 spread in cephalad direction

Next, inject 1500 U of hyaluronidase dissolved in 10 mL of preservative-free normal saline. A newer development is the use of Hylenex or human-recombinant hyaluronidase, which has the advantage of a reportedly increased effectiveness at the body's normal pH compared to bovine-recombinant hyaluronidase [32]. This injection may cause some discomfort, so slow injection is preferable. Observe fluoroscopic images for "opening up" (i.e., visualization) of the "scarred-in" nerve root (Figs. 8.17 and 8.18, see also Fig. 8.16). A 3 mL test dose of a 10 mL local anesthetic/steroid (LA/S) solution is given. Our institution uses 4 mg of dexamethasone mixed with 9 mL of 0.2 % ropivacaine. Ropivacaine is used instead of bupivacaine for two reasons: the former produces a preferential sensory versus a motor block, and it is less cardiotoxic than a racemic bupivacaine. Doses for other commonly used corticosteroids are 40–80 mg of methylprednisolone (Depo-Medrol), 25–50 mg of triamcinolone diacetate (Aristocort), 40–80 mg of triamcinolone acetonide (Kenalog), and 6–12 mg of betamethasone (Celestone Soluspan). Five minutes after the test dose, if there is no evidence of intrathecal or intravascular injection of medication, inject the remaining 7 mL of the LA/S solution.

Remove the needle under continuous fluoroscopic guidance to ensure the catheter remains placed at the target level (Fig. 8.19). Secure the catheter to the skin using nonabsorbable suture and apply antimicrobial ointment to the skin puncture site. Apply a sterile dressing to the puncture site and attach a 0.2 μm filter to the end of the catheter. Affix the exposed portion of the catheter to the patient securely with tape and transport the patient to the recovery area.

Twenty to thirty minutes should elapse between the last injection of the LA/S solution and the start of the hypertonic saline (10 %) infusion. This is necessary to ensure that a subdural block of the LA/S solution has not occurred. A subdural block mimics a subarachnoid block, but a subdural block takes longer to establish, usually 16–18 min. Evidence for subdural or subarachnoid spread is the development of a motor block. If the patient develops signs of a subarachnoid or subdural block at any point during the procedure, the catheter should be removed and the remainder of the adhesiolysis canceled. The patient needs to be observed to document the expected resolution of the motor and sensory block and to document that 10 mL of the hypertonic saline is then infused through the catheter over 15–30 min. If the patient complains of discomfort with hypertonic saline, the infusion is stopped and an additional 2–3 mL of 0.2 % ropivacaine is injected for analgesia and the infusion is restarted. Alternatively, 50–75 mcg of fentanyl can be injected epidurally in lieu of local anesthetic for analgesia. After completion of the hypertonic saline infusion, the catheter is slowly flushed with 2 mL of preservative-free normal saline to clear the line and the catheter is capped.

Our practice is to admit the patient for 24-h observation status and do a second and a third hypertonic saline infusion the following day. On postcatheter insertion day 2, the catheter is injected twice (separated by 4 to 6-h increments) with 10 mL of 0.2 % ropivacaine without steroid and infused with 10 mL of hypertonic saline (10 %) using the

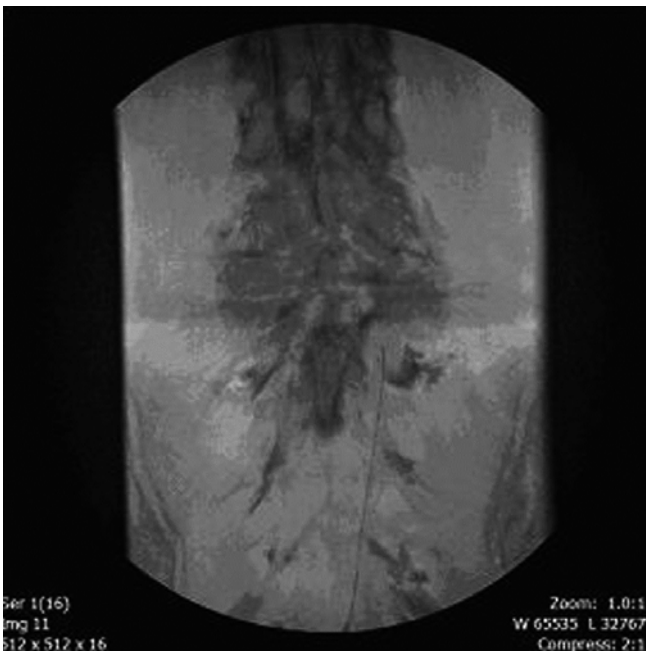


Fig 8.17 Additional contrast and hyaluronidase injection opens up bilaterally formerly scarred areas. The Christmas tree appearance is obvious

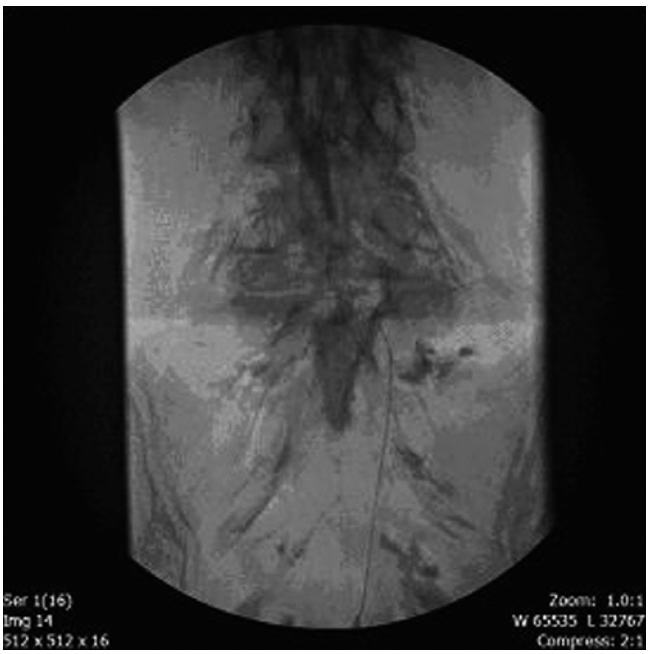


Fig. 8.18 Catheter advances to the desired symptomatic level of right L5 in the ventral lateral epidural space. Injection of contrast followed by 10-mL hyaluronidase 1,500 units opens up bilaterally L3–5, S1, S2, and S3 neural foramina

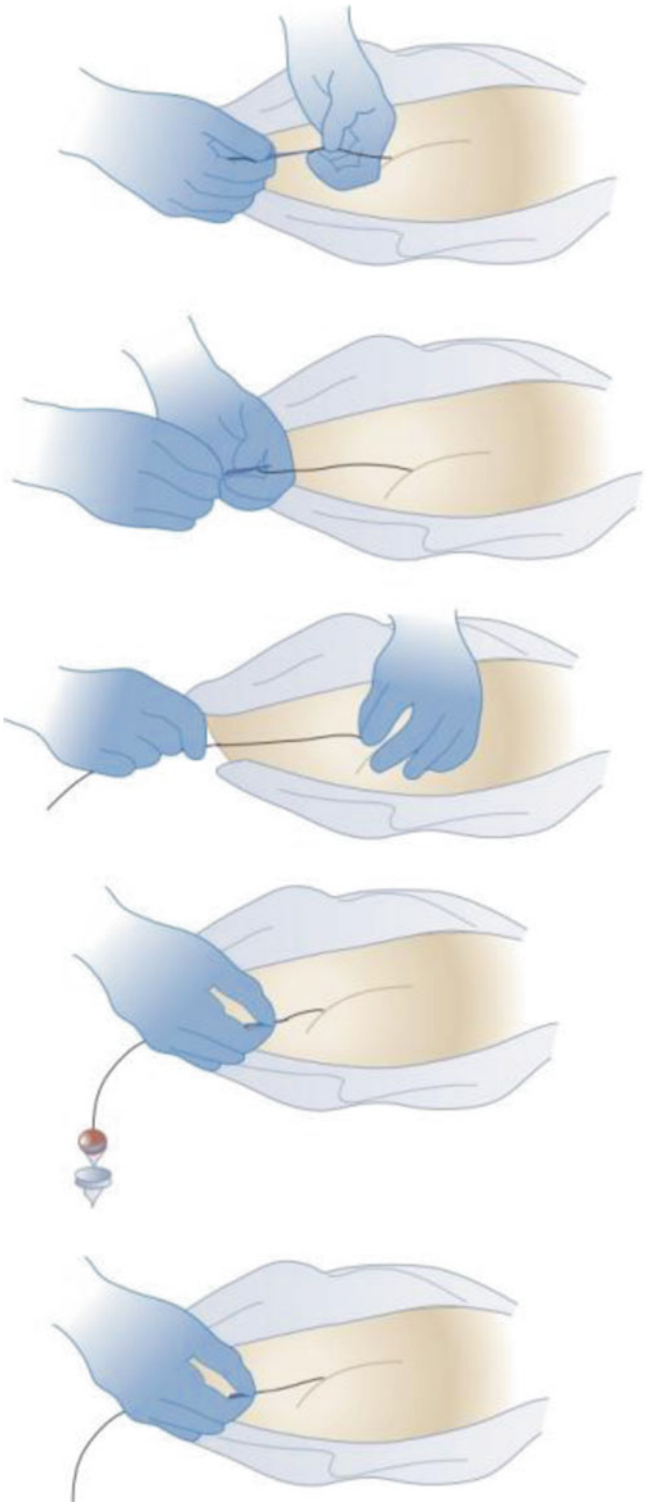


Fig. 8.19 Five-picture sequence of removal of the needle to prevent dislodging the catheter from target site before suturing and application of dressing

same technique and precautions as the day-1 infusion. After the third infusion, the catheter is removed and a sterile dressing applied. The patient is discharged with 5 days of oral cephalexin at 500 mg twice a day or oral levofloxacin (Levaquin) at 500 mg once a day for penicillin-allergic patients. Clinic follow-up is within 30 days.

Transforaminal Catheters

Patients with an additional level of radiculopathy or those in whom the target level cannot be reached by the caudal approach may require placement of a second catheter through the neural foramen. The second catheter is placed into the ventral epidural space via a transforaminal approach on the affected side and at the affected level.

After the target level is identified with an anteroposterior fluoroscopic image, the superior endplate of the vertebra that comprises the caudal portion of the foramina is "squared," that is, the anterior and posterior shadows of the vertebral endplate are superimposed. The angle of the c-arm is typically 15–20° in a caudocephalad direction. The fluoroscope is then rotated to an oblique position approximately 15° to the side of the radiculopathy and adjusted until the spinous process image is rotated to the opposite side. This fluoroscope positioning produces the best visualization of the superior articular process (SAP) that forms the inferoposterior portion of the targeted foramen. The image of the SAP should be superimposed over the image of the disk space on the oblique view. The superior tip of the SAP is the target for the needle placement (Fig. 8.20). A skin wheal is placed slightly lateral to the shadow of the tip of the SAP. Incise the skin with an 18-gauge needle and then insert a 15-or 16-gauge RX Coudé needle and advance using gun-barrel technique toward the tip of the SAP. Advance the needle medially toward the SAP until the tip contacts bone. Then rotate the tip of the needle 180° laterally and advance about 5 mm (Fig. 8.21). Next, rotate the needle back medially 180° (Fig. 8.22).

As the needle is slowly advanced, a clear "pop" is felt as the needle penetrates the intertransverse ligament. A lateral fluoroscopic image should show the tip of the needle just past the SAP in the posterior foramen. In the anteroposterior view with the tip of the needle under continuous AP fluoroscopy, insert the catheter slowly into the foramen and advance until the tip should be just short of the middle of the spinal canal (Figs. 8.23, 8.24, and 8.25).

Confirm that the catheter is in the anterior epidural space with a lateral fluoroscopic image (Fig. 8.26). Anatomically, the catheter is in the foramen superior or inferior to the exiting nerve root (Fig. 8.27). If the catheter cannot be advanced, it usually indicates that the needle is either too posterior or too lateral to the foramen. It may also indicate

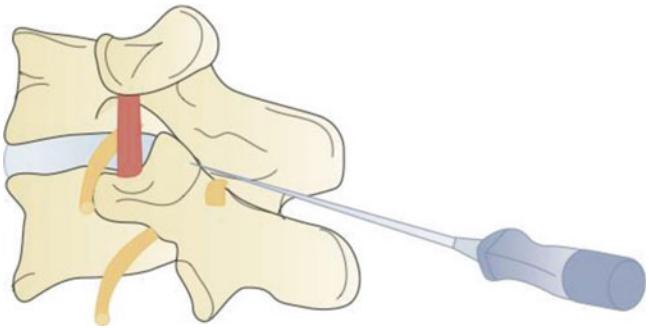


Fig. 8.20 Transforaminal lateral-oblique view. Target the SAP with the advancing RX Coudé needle

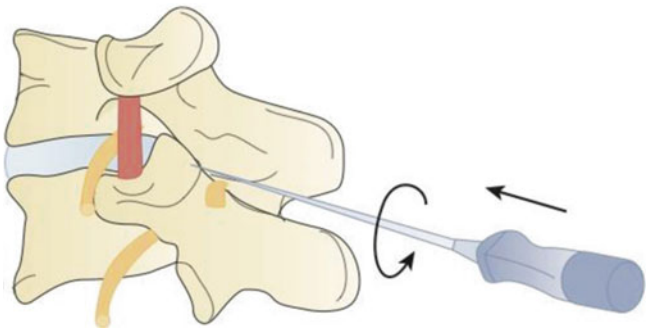


Fig. 8.21 Following bony contact with SAP. Lateral rotation of 180° to allow passage toward the target

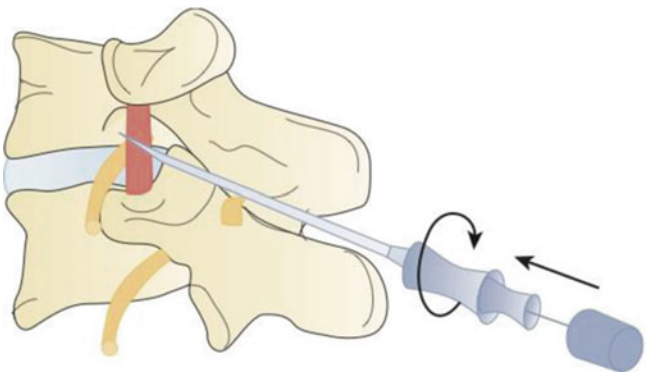


Fig. 8.22 Note the intertransverse ligament. The needle tip with the RX Coudé 2 that has 1-mm protruding blunt stylet will pass through the ligament and will be less likely to damage the nerve

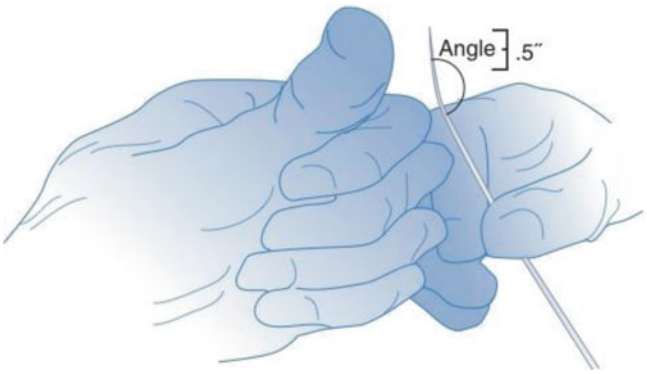


Fig. 8.23 The distal tip of the catheter may be bent 15°, 3/4 in. length

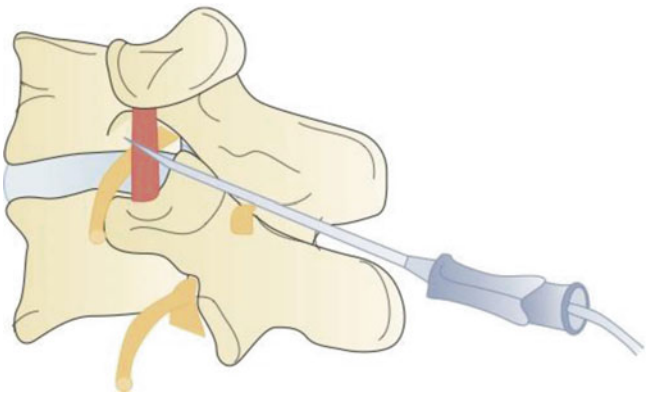


Fig. 8.24 Once the intertransverse ligament is perforated, the catheter is steered to the ventral lateral epidural space (lateral view)

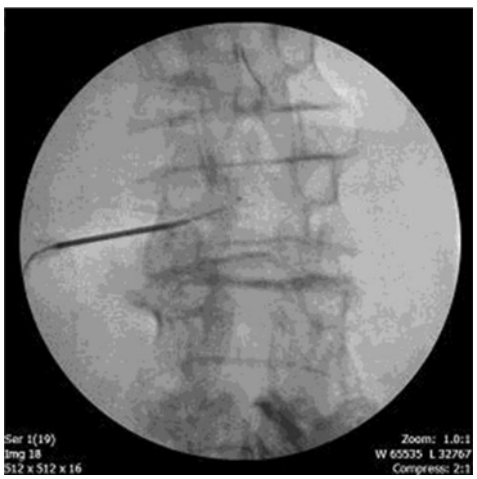


Fig. 8.25 Transforaminal 15-gauge RX-Coudé 2 (Epimed International, Johnstown, NY) catheter at left L3–4 threaded almost to near mid-canal position (anteroposterior view)

that the foramen is too stenotic to allow passage of the catheter. The needle can be advanced a few millimeters anteriorly in relation to the foramen, and that will also place it slightly more medial into the foramen. If the catheter still will not pass, the initial insertion of the needle will need to be more lateral to improve the angle of entry.

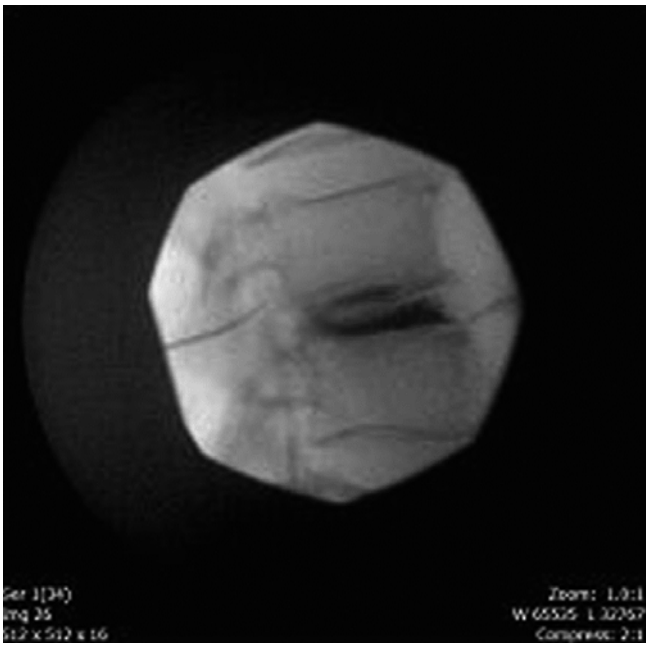


Fig. 8.26 Lateral view. Transforaminal-ventral-anterior catheter dye spread to epidural and L3–4 intradiskal area (through annular tear)

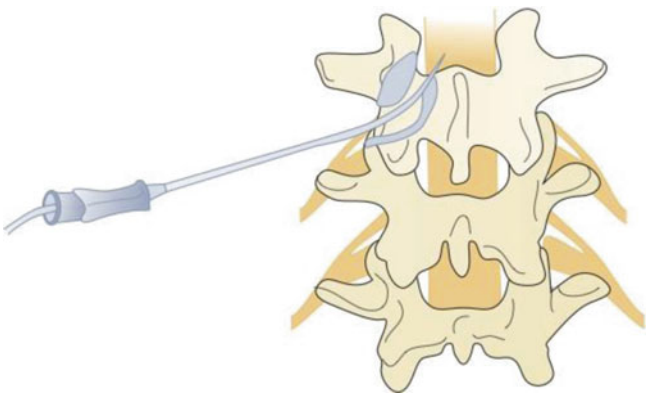


Fig. 8.27 Anteroposterior view. The catheter is in optimal position near midline via the transforaminal placement

Therefore, the fluoroscope oblique angle will be about 20° instead of 15°. The curve of the RX Coudé needle usually facilitates easy catheter placement. The target position of the catheter tip is just lateral to the midline.

Inject 1–2 mL of myelogram grade contrast to confirm epidural spread. When a combination of caudal and transforaminal catheters is placed, the 1500 U of hyaluronidase dose is divided equally between the two catheters (5 mL of the hyaluronidase/saline solution into each). The local anesthetic and steroid solution is also divided equally, but a volume of 15 mL (1 mL steroid and 14 mL 0.2 % ropivacaine; of the total volume, 5 mL is transforaminal and 10 mL is caudal) is used instead of 10 mL. Remove the needle under fluoroscopic guidance to be certain the catheter does not move from the original position in the epidural space. Secure and cover the catheter as described previously for

caudal catheters. The hypertonic saline solution is infused at a volume of 4–5 mL for transforaminal and 8–10 mL for caudal catheter over 30 min. The hypertonic saline injection volume should be less than or equal to the local anesthetic volume injected to avoid pain from injection by hypertonic saline spreading beyond the area of anesthesia. Check the position of the transforaminal catheter under fluoroscopy before performing the second and third infusions to ensure that the catheter has not become displaced. The catheter may become displaced and advanced across the epidural space into the contralateral foramen or paraspinous muscles or more commonly back out of the epidural space into the ipsilateral paraspinous muscles.

This will result in deposition of the medication in the paravertebral tissue rather than in the epidural space. As with the caudal approach, remove the transforaminal catheter after the third infusion. A recent development is the R-X Coudé 2 needle which has a second protruding stylet and may allow closer needle placement and less chance of nerve injury.

First Sacral Foramen Approach

The area at the L5–S1 anterolateral epidural space is frequently occupied with epidural adhesions that are associated with pain and a lack of contrast filling on epidurography. This volume of this space has been reported to be 1.1 ml anatomically and 0.9 ml surgically [33]. Catheter placement and lysis of adhesions via the caudal approach may be difficult in patients with epidural adhesions at this location, and the S1 foraminal approach may be used to achieve lysis and fluid foraminotomy at this level [34].

Matsumoto reported 36 cases with adhesive S-1 radiculopathy related to adhesions in this area. After the procedure, the patients were followed up for 12 months. A marked decrease in VAS and improvement in ADL (improvement in ODI scores) were reported [35].

http://www.paincast.com has video information regarding this procedure [36].

Cervical Lysis of Adhesions

The success of the caudal approach for lysis of lumbosacral adhesions led to the application of the same technique to the cervical epidural space. The indications and preprocedure workup are the same as those for the caudal lysis technique, but there are several important differences in technique and volumes of medication used.

The epidural space should be entered via the upper thoracic interspaces using a paramedian approach on the contralateral side in order to have an angle to advance a catheter to the affected side. The most common levels for needle placement are T1–2 and T2–3. Entry at these levels allows for a sufficient length of the catheter to be in the epidural space to stabilize the catheter placement. If the target is the lower cervical nerve roots, a more caudal interspace should be selected in order to have the same effect. We place the patient in the left lateral decubitus position for routine cases but use a prone approach in larger patients.

The "3-D technique" is used to facilitate entry into the epidural space. The "3-D" refers to direction, depth, and direction. Using an anteroposterior fluoroscopic image, the initial direction of the 15-or 16-gauge RX Coudé needle is determined. Using a modified paramedian approach with the skin entry one and a half levels below the target interlaminar space, advance and direct the needle toward the midpoint of the chosen interlaminar space with the opening of the needle oriented in the medial direction. Once the needle engages the deeper tissue planes (usually at 2–3 cm), check the depth of the needle with a lateral fluoroscopic image. Slowly advance the needle toward the epidural space and check repeat images to confirm the depth. The landmarks of the posterior border of the dorsal epidural space can be visualized by identifying the junction of the base of the spinous process of the vertebra with its lamina. This junction creates a distinct radiopaque "straight line" that can be visualized on fluoroscopy. Once the needle is close to the epidural space, obtain an AP fluoroscopic image to recheck the direction of the needle before advancing further. If the tip of the needle has crossed the midline as defined by the spinous processes of the vertebral bodies, withdraw the needle to allow redirection. The "3-D" process should be repeated as many times as is necessary to get the needle into the perfect position.

Using the loss-of-resistance technique, advance the needle into the epidural space with the tip of the RX-Coudé needle pointed caudally. Once a loss of resistance is obtained and the tip is in the epidural space, rotate the tip cephalad, and inject 1–2 mL of contrast to confirm entry. Rotation or movement of any needle in the epidural space can cut the dura and this technique has been improved with the advent of the RX Coudé two needle, which has a second interlocking stylet that protrudes slightly beyond the tip of the needle and functions to push the dura away from the needle tip as it is turned 180 degrees cephalad (Figs. 8.28, 8.29, 8.30, 8.31, and 8.32).

Inject an additional small volume of contrast as needed to complete the epidurogram. If there is no free flow of injected contrast in the epidural space, pressure may build up in the lateral epidural space. Characteristic contrast spread by the path of least resistance can be recognized as perivenous counter spread (PVCS). Presence of PVCS means pressure builds up in the lateral epidural space, and it is unable to spread laterally to decompress. The dye spread follows the path of least resistance to the opposite side. This pressure may build up and lead to ischemic spinal cord injury. Flexion and rotation of the head and neck can open up lateral runoff and release this pressure through the enlarged neural foramina (Fig. 8.33) [37].

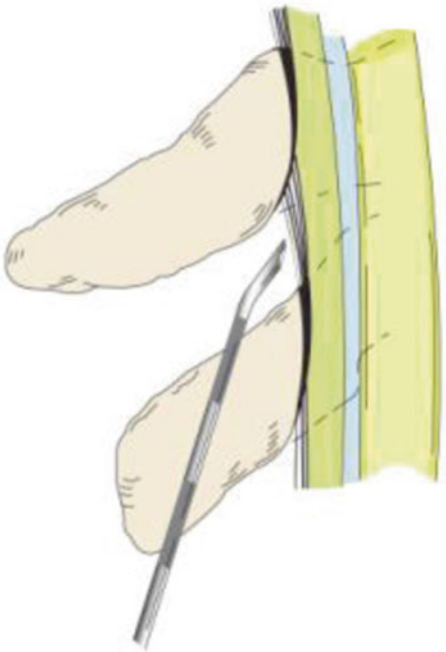


Fig. 8.28 Sequence of stages to place a catheter using the R-X Coudé

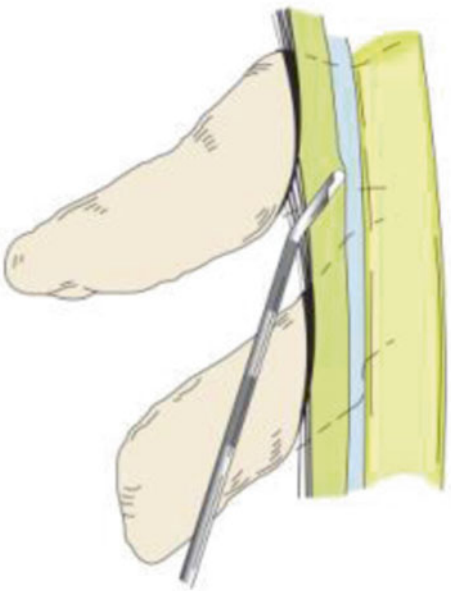


Fig. 8.30 The protruding stylet is inserted

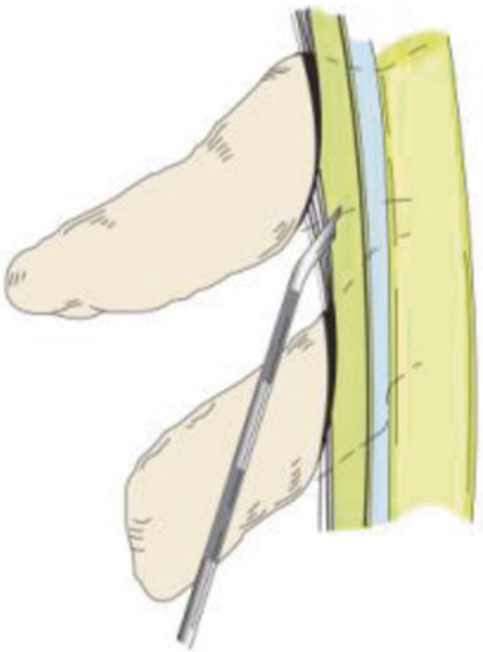


Fig. 8.29 The needle is inserted into the epidural space with the tip directed as shown

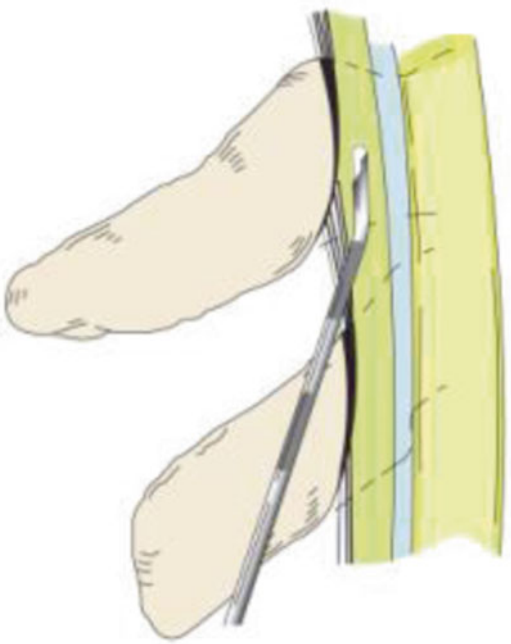


Fig. 8.31 Then the needle is rotated so the tip is parallel to the dura

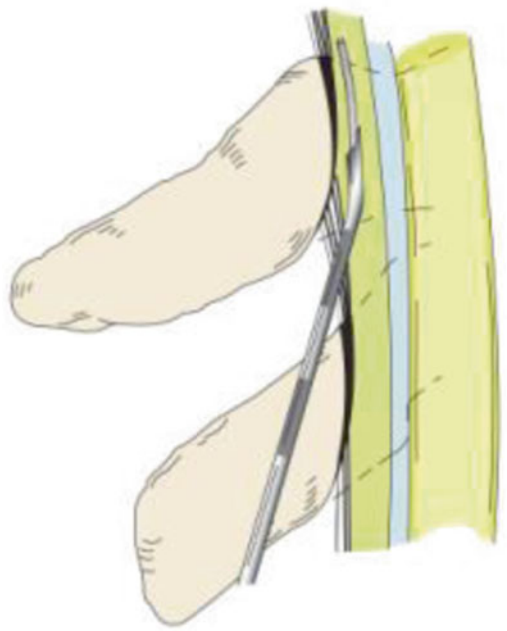


Fig. 8.32 The catheter is inserted

As with the caudal epidurogram, fluoroscopy will image for filling defects. It is extremely important to visualize spread of the contrast in both the cephalad and caudal directions. Loculation of contrast in a small localized area must be avoided as this can significantly increase the pressure in the epidural space and can compromise the already tenuous arterial blood supply to the spinal cord.

Place a bend on the catheter as previously described for the caudal approach and insert it through the needle while stabilizing the needle to prevent advancement of the needle (Fig. 8.32). The opening of the needle should be directed toward the symptomatic target side. Slowly advance the catheter to the lateral gutter of the epidural space and direct it cephalad. Redirect the catheter as needed and once the target level has been reached, rotate the catheter to place the tip of the catheter toward the foramen (Fig. 8.34). Inject 0.5–1 mL of contrast to visualize the target nerve root and foramen. Insure there is runoff of contrast out of the foramen (Fig. 8.35). Slowly instill 150 U of Hylenex dissolved in 5 mL of preservative-free normal saline through the catheter. Follow this with injecting 1–2 mL of additional contrast and

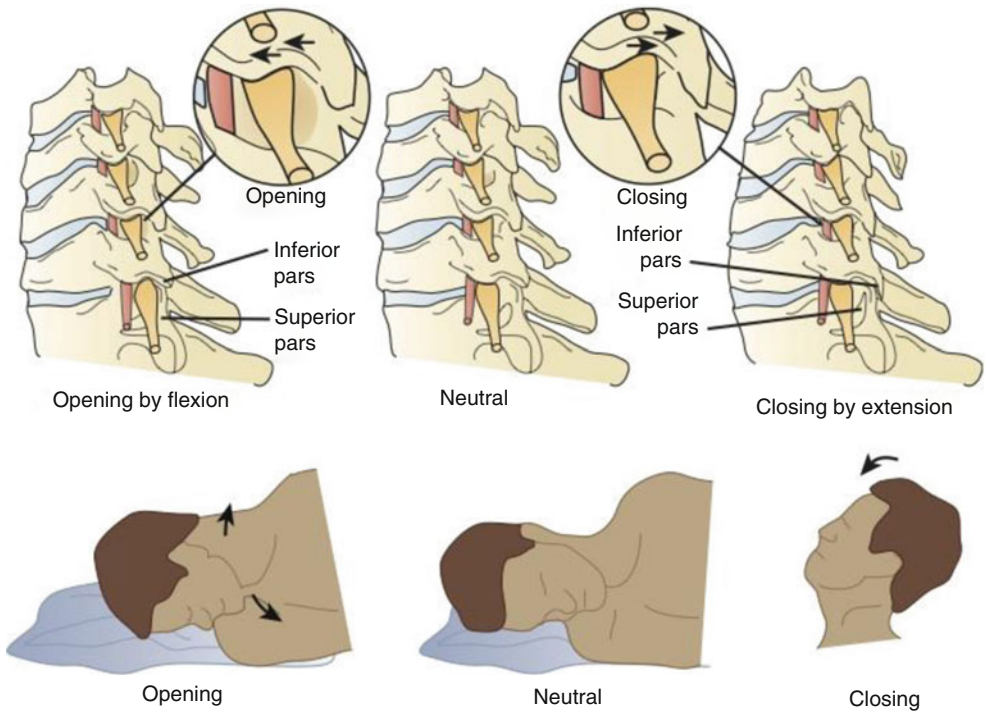


Fig. 8.33 Flexion rotation, left to right regardless patient position. The neural foramen enlarges on flexion rotation and gets smaller with extension. The inferior pars slides forward over the superior pars to enlarge the foramen. This allows lateral runoff and pressure release with PVCS

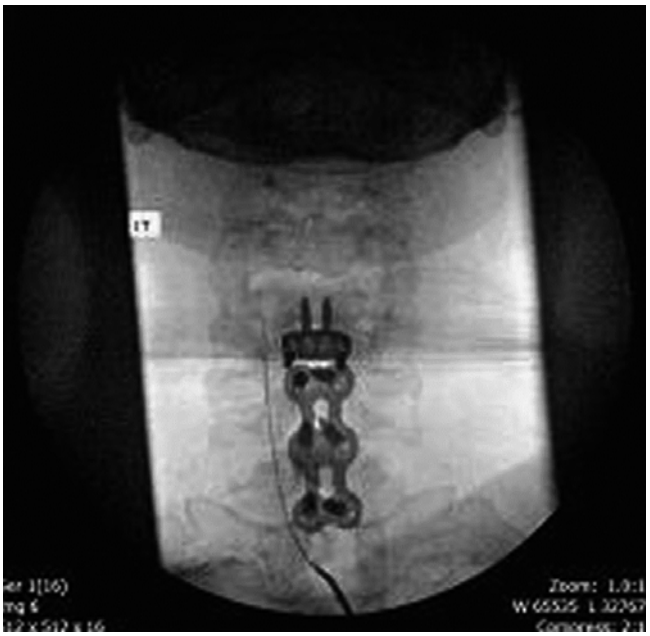


Fig. 8.34 Cervical left ventral lateral catheter to the upper level of fusion C5–7

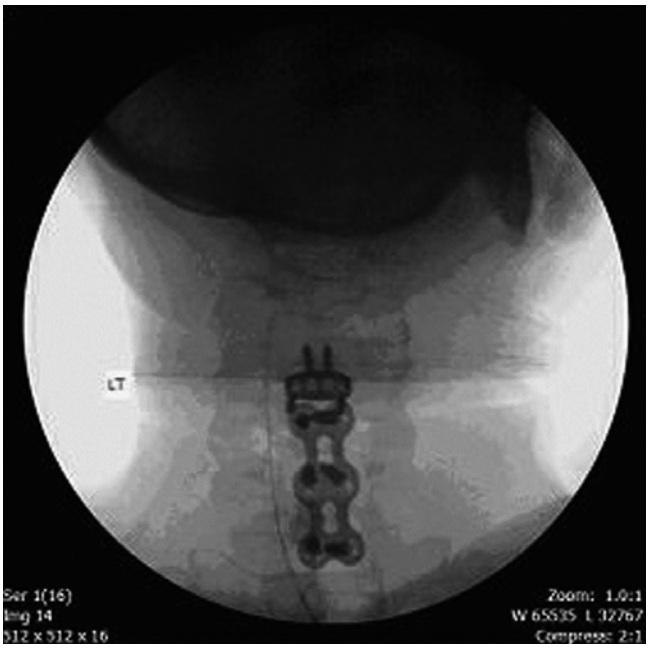


Fig. 8.35 Cervical left ventral lateral catheter threaded to above level of fusion of C4. The dye injection spreads cephalad and lateral

observe for "opening up" of the "scarred-in" nerve root. Give a 2-mL test dose of a 6-mL solution of local anesthetic and steroid (5 mL of 0.2 % ropivacaine and 1 ml–4 mg of dexamethasone). If after 5 minutes there is no evidence of intrathecal or intravascular spread, inject the remaining 4 mL of solution.

Remove the needle without changing the catheter placement, and secure and dress the catheter as previously described. Twenty minutes after the last dose of LA/S solution, if there is no evidence of a subarachnoid or subdural block, start an infusion of 5 mL of hypertonic saline over 30 min. Following the infusion, flush the catheter with 1–2 mL of preservative-free normal saline and cap the catheter.

The second and third infusions are performed on the next day with 6 mL of 0.2 % ropivacaine, monitoring for the absence of motor block and other signs of subdural block for 30 min, before administering 5 mL of hypertonic saline using the same technique and precautions described for the first infusion. The catheter is removed and prophylactic antibiotics are prescribed. Clinic follow-up is within 30 days.

Thoracic Lysis of Adhesions

The technique for entry into the thoracic epidural space for adhesiolysis is similar to that for the cervical region, using the 3-D technique. Be certain to get a true lateral when checking the depth of the needle. This is obtained by superimposing the rib shadows on one another. The target is the ventrolateral epidural space with the tip of the catheter in the foramen of the desired level. The major difference for thoracic lysis compared to the caudal and cervical techniques is the volumes of the various injectates. Volumes of 8 mL are used for the contrast, Hylenex, local anesthetic and steroid mixture, and hypertonic saline (Table 8.1).

Neural Flossing

The technique for epidural adhesiolysis has been aided by neural flossing exercises that were designed to mobilize nerve roots by "sliding" them in and out of the foramen (Fig. 8.36). These exercises break up scar tissue weakened from the procedure and prevent further scar tissue deposition. If these exercises are done effectively three to four times per day for a few months after the procedure, the formation of scar tissue will be significantly reduced (Figs. 8.37, 8.38, 8.39, 8.40, and 8.41).

Epidural Mapping

In patients with multilevel radiculopathy and complex pain, it can be difficult to determine where the majority of the pain is originating. Mapping is used to locate the most painful nerve root with stimulation and then carry out the adhesiolysis at that level. Larkin has reported the use of stimulation to confirm epidural placement of a catheter and for nerve root

Table 8.1 Typical infusion volumes for epidural adhesiolysis

	Contrast	Hyaluronidase and normal saline	Local anesthetic and steroid	10 % hypertonic saline infusion
Caudal	10 mL	10 mL	10 mL	10 mL
Caudal and transforaminal	5 mL in each catheter	5 mL in each catheter	5 mL in each catheter	8 mL in caudal catheter and 4 mL in transforaminal catheter
Thoracic	8 mL	8 mL	8 mL	8 mL
Cervical	5 mL	6 mL	6 mL	5 mL

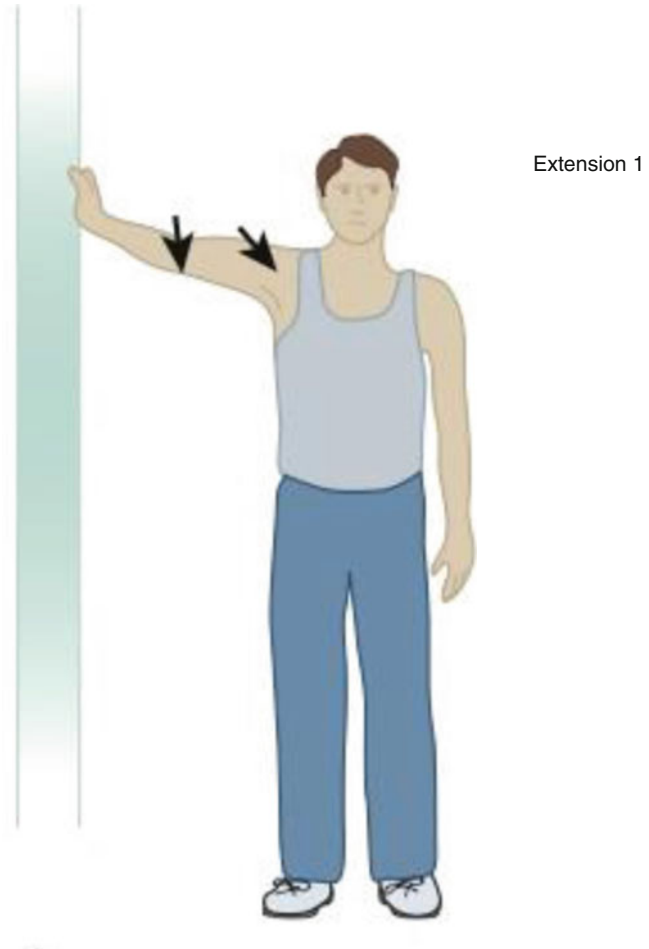


Fig 8.36 Neural flossing exercises. Standing erect, firmly grasp a stable surface (e.g., a door frame) with outstretched arm. Press elbow and shoulder forward

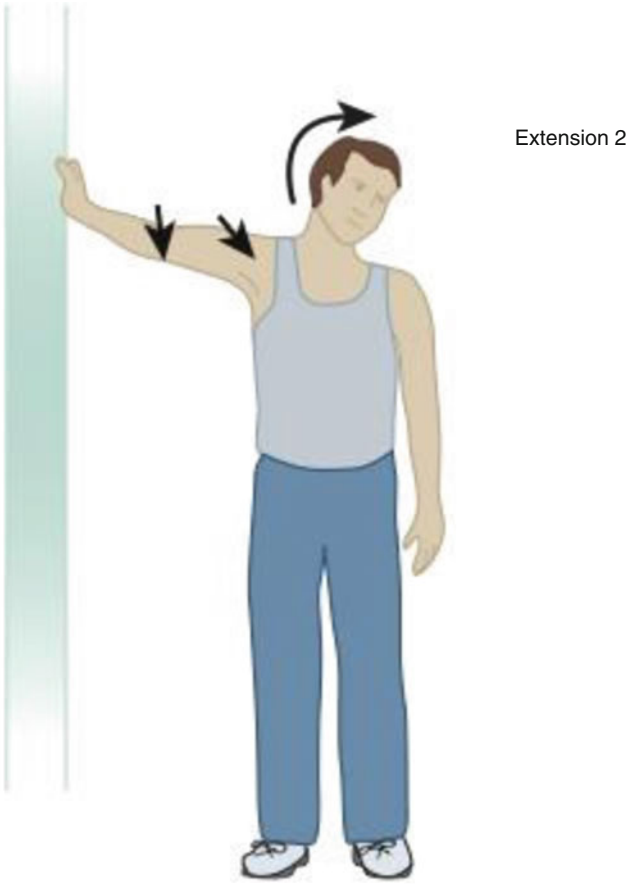


Fig. 8.37 Next, slowly tilt head in opposite direction from outstretched arm to achieve gentle tension

localization [38]. The TunL Kath and the TunL-XL catheter can be used as stimulating catheters to identify the nerve root (s) and treat during the same procedure.

After entering the epidural space, advance the catheter into the ventrolateral epidural space superior to the suspected target level. Ensure that the tip of the catheter is pointing laterally toward the foramina, just below the pedicle. Withdraw the catheter stylet back approximately 1 cm. Using alligator clips, connect the cathode to the stylet and ground the anode on the needle (insulated by the catheter coating), or ground pad, or a 22-gauge needle inserted into the skin. Apply electrical stimulation with a stimulator box with a rate of 50 Hz and a pulse width of 450 ms, dialing up the amplitude until a paresthesia is perceived in small increments, usually less than 2 or 3 V. Inquire of the patient as to whether or not the paresthesia correlates with the area of the patient's recognized greatest pain. This process is repeated at each successive level until the most painful nerve root is identified

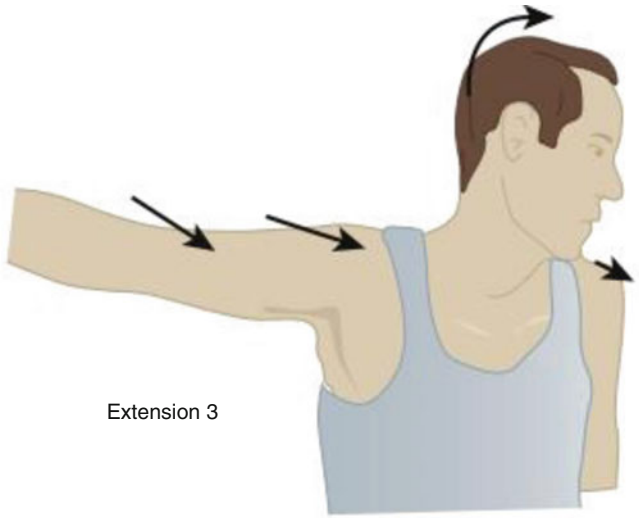


Fig. 8.38 Finally, rotate chin toward opposite shoulder as is comfortable. Hold this final position for approximately 20–30 s

Fig. 8.39 Lay down supine on an exercise mat without a pillow. Slowly bring both knees close to the chest with bent legs and hold this position for 20 s. Release and assume a neutral position

Fig. 8.40 Again in supine position, raise both legs to 90°, with knees straight while laying flat on a firm surface. Hold for 20 s. Assume a neutral position and rest briefly

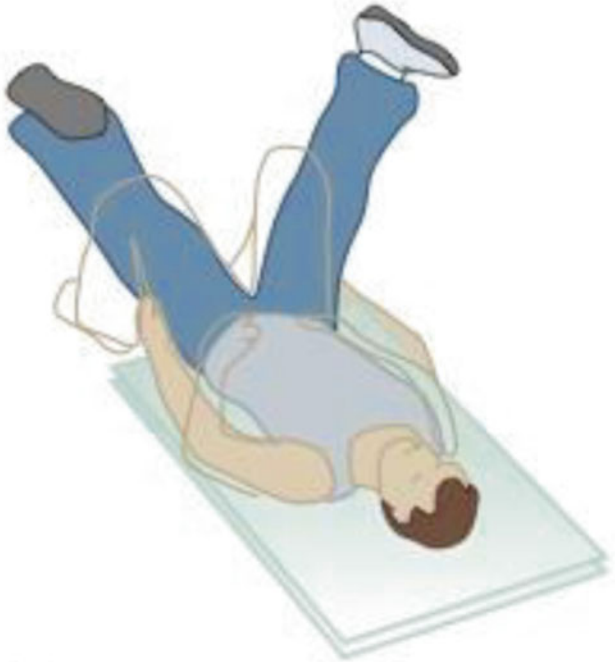


Fig. 8.41 Bring both legs to a 90° angle while lying supine. Slowly spread legs in a V shape, as much as is comfortable, and hold for 20 s

or the best correlation is identified. Once identified, the adhesiolysis is performed at that level. The mapping procedure is also useful to identify the optimal site of surgery either before the first surgery or when surgery has failed one or more times, as an alternative or supplement to electrodiagnostic or imaging studies.

Complications

As with any invasive procedure, complications are possible despite proper technique. These complications include bleeding, infection, headache, damage to nerves or blood vessels, catheter shearing, bowel/bladder dysfunction, paralysis, spinal cord compression from loculation of the injected fluids or hematoma, subdural or subarachnoid injection of local anesthetic or hypertonic saline, and reactions to the medications used. We also discuss and include on the consent form that the patient may experience an increase in pain or no pain relief at all.

Although the potential list of complications is long, the frequency of serious complications is very rare. However, there is clearly a learning curve, and recent studies reflect this. For example, the Florida Workmen's compensation director noted that outcomes are better in experienced and trained practitioner hands.

Subdural spread is a complication that should always be monitored when injecting local anesthetic. During caudal

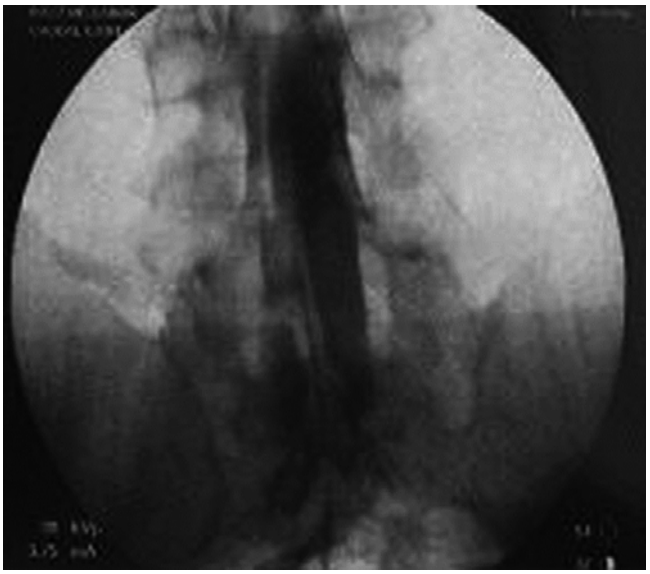


Fig. 8.42 Midline catheter placement enters subdural space. There is also some epidural dye spread. But the patient starts to complain of bilateral leg pain

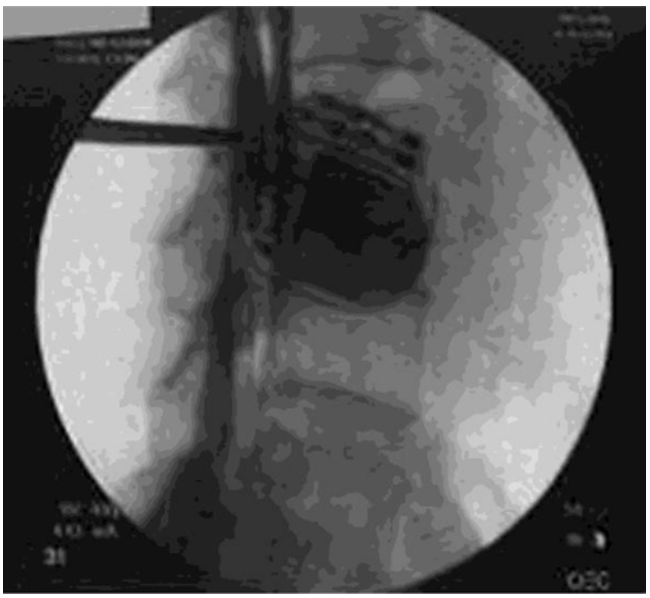


Fig. 8.43 A 22-gauge spinal needle and extension set with syringe placed in the subdural space and 12-mL fluid aspirated. The patient reported immediate reversal of bilateral leg pain. Note the dye in the extension tubing and syringe at the 7-o'clock position

adhesiolysis, particularly if the catheter is advanced along the midline, subdural catheter placement is a risk (Figs. 8.42 and 8.43). Identification of a subdural motor block should occur within 16–18 min. Catheters used for adhesiolysis should never be directed midline in the epidural space.

Most epidural hematomas and other major complications are associated with the use of sharp needles. The use of blunt needles or catheters should be used to reduce the risk of major complications with the lysis procedure or transforaminal procedures [39].

Venous run off is most likely on the first epidural procedure due to high-pressure veins being engorged and large. Following lysis of adhesions and fluid foraminotomy, high-pressure veins are converted to low-pressure veins and venous run off is less likely. In fact, no cases of epidural hematoma have been reported after lysis of adhesions and fluid foraminotomy in the ventrolateral epidural space [40].

A case of a hematoma has been reported after the MILD procedure without a lysis procedure performed first. Lysis should be considered prior to the MILD procedure to achieve fluid foraminotomies and allow fluid to pass out of the spinal canal and avoid venous run off and hematomas [41].

Outcomes

Initially in the early 1980s, the protocol was designed to direct site-specific medication onto the dorsal root ganglion; however, after performing a number of the procedures, it was observed that the dorsal root ganglion was exceptionally hard to reach secondary to developing scar tissue or adhesions. In those early days, our understanding was coming from the use of local anesthetics for surgery giving a 2-to 4-h block for the surgeon to operate. It was gratifying to see chronic pain patients achieve months and years of pain relief following the placement of the new steerable x-ray visible catheter, suddenly reaching the target site which from the very beginning was the dorsal root ganglion (DRG).

However, frequent finding was scar tissue (assumption at the time—even without surgery) blocking the accurate catheter tip placement.

Initially, we were pleased to see some patients experiencing 3–4 months of relief and recovery of foot drop. Similar observations were also reported in 2008 by Sakai et al. [42], and they found that adhesiolysis with catheter-directed steroid and local anesthetic injection during epiduroscopy alleviated pain and reduced sensory nerve dysfunction in patients with chronic sciatica. These findings have led to the changes in the procedure into what it is today [43].

The early report in 1985 by Racz et al. [44] described the use of phenol at the dorsal root ganglion followed by an observational listing of outcomes. These results were clearly not as good as the latest studies on failed back surgery and spinal stenosis showing 75–80 % improvement at 12 months' follow-up by Manchikanti [37].

Racz and Holubec first described epidural adhesiolysis in 1989 [45]. Larger doses of local anesthetic were used initially and hyaluronidase was not used. Catheter placement was lesion specific (i.e., the tip of the catheter was placed in the target foramen corresponding to the vertebral level and

side of the suspected adhesions). The initial retrospective analysis conducted 6–12 months after the procedure found pain relief in 72.2 % of patients ($N=72$) at time of discharge. Pain relief was sustained in 37.5 % and 30.5 % of patients at 1 and 3 months, respectively. Forty-three percent of patients decreased their frequency and dosage of medication use and 16.7 % discontinued their medications altogether. 30.6 % of patients returned to work or returned to daily functions.

In April 1990, at a presentation of the seventh IASP World Congress on Pain in Adelaide, Australia, Arthur et al. [46] reported results with epidural adhesiolysis in 100 patients. Half of the patients received hyaluronidase as part of the procedure. 81.6 % of the participants had initial pain relief in the hyaluronidase group, compared to 68 % in the group with no hyaluronidase. Concerns about hyaluronidase allergy have limited its acceptance, but an informal survey of ophthalmologic anesthesiologists found no cases of anaphylaxis to hyaluronidase used for retrobulbar blocks. In this survey, skin testing for allergy to hyaluronidase was not performed. This implies that severe allergic reactions are rare; however, it is recommended that these procedures be performed in an environment with medications to treat allergies and resuscitative equipment [47].

In 1994, Stolker et al. [48] added hyaluronidase to the procedure, but did not use hypertonic saline. In a study of 28 patients, they reported 50 % pain reduction or more in 64 % of patients at 1 year. The authors stressed the importance of the patient selection and believed that the effectiveness of adhesiolysis was based on the effect of the hyaluronidase on the adhesions and the action of the local anesthetic and steroids on the sinuvertebral nerve.

Devulder et al. published a study of 34 patients with failed back surgery syndrome with suspected or diagnosed epidural fibrosis with MRI [24]. An epidural catheter was inserted via the sacral hiatus to a distance of 10 cm into the caudal canal. Injections of contrast dye, local anesthetic, corticosteroid, and hypertonic saline (10 %) were performed daily for 3 days. Hyaluronidase was not used. Epidurogram filling defects were noted in 30 of 34 patients, but significant pain relief was noted in only 7 patients at 1 month, 2 patients at 3 months, and no patient at 12 months. They concluded that epidurography may confirm epidural filling defects for contrast dye in patients with filling defects, but a better contrast dye spread, assuming scar lysis occurs, does not guarantee sustained pain relief. This technique has been criticized for lack of lesion-specific catheter placement resulting in nonspecific drug delivery [49]. The catheter was not directed to the ventral lateral epidural space where the dorsal root ganglion is located and the lateral recess scarring occurs. This study model was subsequently used by Manchicanti as the placebo arm of the prospective randomized epidural lysis of adhesions study that confirmed the convincing outcome data of 1-day lysis of adhesions, resulting in the second CPT code of 62264.

Heavner et al. [50] performed a prospective, randomized, blinded trial of lesion-specific epidural adhesiolysis on 59 patients with chronic intractable low back pain. The patients were assigned to one of four epidural adhesiolysis treatment groups: (1) hypertonic (10 %) saline plus hyaluronidase, (2) hypertonic (10 %) saline, (3) isotonic (0.9 %) saline, or (4) isotonic (0.9 %) saline plus hyaluronidase. All treatment groups received the same corticosteroid and local anesthetic. Overall, 83 % of patients had significant pain relief at 1 month compared to 49 % at 3 months, 43 % at 6 months, and 49 % at 12 months. The hyaluronidase and the hypertonic saline study group had a much lower incidence of additional need for subsequent pain procedures than the placebo groups, indicating that site-specific catheter placement is important. With the help of Neurosurgery in the American Medical Association Code Committee approval for the three reinjection lysis of adhesions, the code CPT62263 was assigned.

Manchikanti et al. [51] reported a retrospective evaluation of a modified Racz adhesiolysis protocol in 232 patients with low back pain. The study involved lesion-specific catheter placement, but the usual 3-day procedure was modified to a 2-day (group 1) or a 1-day (group 2) procedure. Group 1 (2 day) had 103 patients and group 2 (1 day) had 129 patients. Other modifications included changing the local anesthetic from bupivacaine to lidocaine, substituting methylprednisolone acetate or betamethasone acetate and phosphate for triamcinolone diacetate, and reduction of the volume of injectate. Of the patients in groups 1 and 2, 62 % and 58 % had 50 % or greater pain relief at 1 month, respectively, with these percentages decreasing to 22 % and 11 % at 3 months, 8 % and 7 % at 6 months, and 2 % and 3 % at 1 year. Of significant interest is that the percentage of patients reporting 50 % or greater pain relief after four procedures increased to 79 % and 90 % at 1 month, 50 % and 36 % at 3 months, 29 % and 19 % at 6 months, and 7 % and 8 % at 1 year for groups 1 and 2, respectively. Short-term relief of pain was demonstrated, but long-term relief was not.

Manchikanti, in 1999, evaluated two groups of patients retrospectively. One group consisted of 150 patients for a 2-day reinjection procedure, and a second 150 patients for a 1-day procedure out of a pool of 536 patients. It was concluded that repeat use of the 1-day procedure is cost-effective when evaluated on a 12-month follow-up. The cost-effectiveness suggests that the lysis procedure to be superior to surgery or the rehabilitation activity program [51].

In a randomized, prospective study, Manchikanti et al. [52] evaluated a 1-day epidural adhesiolysis procedure versus a control group of patients who received conservative therapy. Results showed that cumulative relief, defined as relief greater than 50 % with one to three injections, in the treatment group was 97 % at 3 months, 93 % at 6 months, and 47 % at 1 year. The study also showed that overall health

status improved in the adhesiolysis group. Conservative therapy included physical therapy and analgesic medications.

In 2004, Manchikanti et al. [53] published results of a randomized, double-blind, controlled study on the effectiveness of 1-day lumbar adhesiolysis and hypertonic saline neurolysis in treatment of chronic low back pain. Seventy-five patients whose pain was unresponsive to conservative modalities were randomized into one of three treatment groups. Group 1 (control group) underwent epidural catheterization where the catheter was in the sacral canal without adhesiolysis, followed by injection of local anesthetic, normal saline, and steroid. Group 2 consisted of epidural catheterization with site-specific catheter placement being ventrolateral for adhesiolysis, followed by injection of local anesthetic, normal saline, and steroid. Group 3 consisted of site-specific epidural catheter placement for adhesiolysis, followed by injection of local anesthetic, hypertonic saline, and steroid. Patients were eligible to have additional injections based on the response, either after unblinding or without unblinding after 3 months. Blinded patients were offered either the assigned treatment or another treatment based on their response. If any patients in group 1 or 2 received adhesiolysis and injection and injection of hypertonic saline, they were considered withdrawn, and no subsequent data were collected. Outcomes were assessed at 3, 6, and 12 months following the procedure using visual analog scale pain scores, Oswestry Disability Index, opioid intake, range-of-motion measurement, and P-3. Significant pain relief was defined as average relief of 50 % or greater. Seventy-two percent of patients in group 3, 60 % of patients in group 2, and 0 % of patients in group 1 showed significant pain relief at 12 months. The average number of treatments for 1 year was 2.76 in group 2 and 2.16 in group 3. Duration of significant relief with the first procedure was 2.8 + 1.49 months and 3.8 + 3.37 months in groups 2 and 3, respectively. Significant pain relief (>50 %) was also associated with improvement in Oswestry Disability Index, range of motion, and psychologic status.

Manchikanti et al. [54, 55] furthered this research using comparisons of percutaneous adhesiolysis versus fluoroscopically guided caudal epidural steroid injections. The first study involved a population of patients with chronic low back pain and known spinal stenosis. The results showed a 76 % reduction in pain relief at 1 year with epidural adhesiolysis compared to 4 % in the control group. The second study, performed in a population of patients with postlumbar surgery syndrome, showed a reduction in pain and improvement in functional status in 73 % of the epidural adhesiolysis group compared to 12 % in the control group.

In 2006, a study by Veihelmann et al. [56] evaluated patients with a history of chronic low back pain and sciatica. Inclusion criteria were radicular pain with a corresponding nerve root compression on MRI or CT. All patients were randomized to receive physiotherapy, analgesics, or lysis of adhesions. The lysis group had statistically significantly better outcome than the physical therapy treatment group.

Two other prospective evaluations by Chopra et al. and Gerdesmeyer et al. [57, 58] evaluated patients with monosegmental radiculopathy of the lumbar spine. All the patients suffered from chronic disk herniations or failed back syndrome. All these randomized trials showed positive short-term and long-term relief. Two prospective evaluations also showed positive short- and long-term relief [58, 59].

Gerdesmeyer has published a randomized, prospective, double-blind, sham-controlled multicenter trial, which has been the most significant evaluation of the technique. The target site remained at the ventral lateral epidural space at the most likely level of the pain generator. The study continued for over 12 months and the significant finding was that the study arm of the procedure showed better outcomes, compared to the sham procedure group, at all points of measurements. The sham-placebo group was treated with a subcutaneously placed catheter so that the patient could not tell the difference during the three daily reinjections or subsequently. The study has succeeded in differentiating the placebo group from the treatment group in each study site location of the multicenter trial. The results have led to the conclusion that percutaneous lysis of adhesions for patients with chronic lumbosacral radicular pain should be offered this procedure as first choice of interventional treatment [60].

A systematic review of percutaneous adhesiolysis for chronic low back pain in postlumbar surgery syndrome and spinal stenosis by S Helm II et al. found effectiveness of the procedure for both spinal stenosis and in postlumbar surgery syndrome [57]. Additionally, it was noted that there have not been any hematomas reported. The results of the review support the use of the procedure for the conditions listed. The systematic review supported the use of percutaneous lysis of adhesions in spinal stenosis and the first-time observation that there were no hematoma reported points to the importance of the ventral lateral targeting of catheter tip placement, and the opening of lateral runoff through the neural foramina is a fluid foraminotomy that results in decompression of high-pressure veins and significant gain of available space in the spinal canal.

The randomized, double-blind, active control trial by Koh et al., in patients with lateral spinal canal stenosis, demonstrated that the hypertonic saline showed significant short-term pain relief [61]. Postprocedure pain after the use of steroids was a significant problem in the early days of percutaneous lysis of adhesions. Those patients reported significant postprocedural pain prior to the introduction of hyaluronidase and hypertonic saline to the sequence of injections.

The parallel observation from the use of increased volume of injection was that the hypertonic saline addition has not only reduced the radiculopathy pain but also reduced the patient's back pain. Small-volume injections more likely help radiculopathy, but larger volume ventral transforaminal catheter placement also is beneficial with back pain as well.

The injected volume increase was from the 2 mL per injection range to the 5 mL range of each fluid component. The sequence of injections is first contrast, followed, in order, by hyaluronidase, local anesthetic, and steroid, and 20–30 min later, if there was no motor block, the injection of hypertonic saline.

Manchikanti's et al. 2-year follow-up of randomized controlled trial compared 1-day lysis of adhesion procedure to caudal epidural injection where the reinjection was triggered by the patient's pain relief dropping to below 50 % pain relief from the previous injection. During the 2-year study, the study group received 6.4 ± 2.35 procedures, and 82 % of the patients received at least 50 % pain relief, whereas the caudal epidural injection had only 5 % of patients with at least 50 % pain relief. This strongly supports the effectiveness of the percutaneous epidural lysis of adhesions [62].

Park's et al. evaluation of patients with cervical spinal stenosis with transforaminal adhesiolysis and lumbar neuroforaminal stenosis showed effectiveness regardless of the severity of lumbar stenosis [63].

Park et al. evaluated epidural neuroplasty for patients with cervical disk herniation and demonstrated effectiveness when conservative measures had failed. There was no control group in the study, but the clinical results indicate reduction in cervical radiculopathy.

The overall clinical experience has showed us that there is a need for evaluation for cervicogenic facet pain and appropriate treatment. It is not enough to ask the patient on follow up if they have any complaints of pain, but the examining physician must EXAMINE the patient including provocation neural flossing testing the appropriate extremities and compare patient's pain drawings with the preprocedure drawings and physician notes. For example, there may not be radiculopathy or back pain but persistent back spasm. The origin of pain may be from trochanteric bursitis, quadrates lumbar, or paraspinal muscle spasm, but no back pain on the dural tug examination. The treatment of these other explanations is considerably easier once the treating physician has a diagnosis than expecting pain relief without appropriate therapy.

Additionally, in patients suffering from cervicogenic radiculopathy—the anterior compartment between the anterior and middle scalene muscles may be additional pain generators in patients that have pain secondary to facet joint arthropathy [64]. Entrapment of the brachial plexus between the muscle groups can also give rise to radiating arm pain. This responds very well to an interscalene block for long periods.

Choi et al. compared two patient groups with herniation of intervertebral disks and postlumbar surgery syndrome and found better outcomes in nonoperated patients, showing the favorable outcome in presurgical patients.

While not absolute prognostic predictor, the recommendation is that percutaneous adhesiolysis is a reasonable nonoperative treatment option of herniation of intervertebral disks, spinal stenosis, and postlumbar surgery syndrome [65].

It is important to emphasize neural flossing exercises for patients to maintain long-term benefits. The concept of nerve flossing exercises has been demonstrated in cadaver studies of peripheral nerves [66]. Sliding exercises resulted in twice as much excursion as tensioning exercises. More recently, cervical nerve root mobility has been shown to increase significantly in cadavers by cutting foraminal ligaments [67]. These two studies are consistent with the rationale for neural flossing exercises, and continuing these exercises has been observed to improve long-term outcomes.

The cost-effectiveness of the Racz procedure compares favorably to other treatments for the same conditions. The cost utility for 1 year of quality-adjusted life year (QALY) of USD is $2,652 for postlumbar surgery syndrome and USD $2,649 for lumbar central spinal stenosis [66].

Epidural adhesiolysis has evolved over the years as an important treatment option for patients with intractable cervical, thoracic, and low back and leg pain. Studies show that patients are able to experience significant pain relief and restoration of function. Manchikanti's studies show that the amount and duration of relief can be achieved by repeat procedures. Recent prospective randomized double-blind studies on failed back surgery and spinal stenosis show 75 and 80 % improvement in visual analog scale scores and functional improvements at 12 months' follow-up. There have been no negative studies to date where the lysis target was the ventrolateral epidural space. The one negative study used a technique consisting of a 10-cm sacral mid-canal catheter placement which was nontarget specific [49]. This technique was subsequently used as the control group procedure in a study performed by Manchikanti. Manchikanti's study consisted of three treatment groups: placebo (sacral mid-canal catheter placement), target-specific ventrolateral epidural without hypertonic saline, and target-specific ventrolateral epidural with hypertonic saline. The latter two treatment groups had positive outcomes with the hypertonic saline group superior, whereas the control group with the nonspecific catheter placement did not [53]. The evolution in the recognition of the site-specific importance of the catheter and medication delivery together with the fact that physicians need to acquire the skills to be able to carry out the procedure led to the improved outcomes seen in recent prospective randomized studies.

The management of failed back surgery syndrome and postlaminectomy syndrome will likely continue to be controversial among the multitude of practitioners who treat these patients. However, in experienced hands, epidural lysis of adhesions is established as a reasonable option for many patients.

Percutaneous neuroplasty via a transforaminal approach evolved from the caudal approach. Lysis of adhesions via the caudal approach involves introducing a catheter through the sacral hiatus and advancing it to the affected nerve root in the ventrolateral epidural space. On the other hand, transforaminal percutaneous neuroplasty achieves a midline catheter placement in the epidural space that is able to target the two most heavily innervated structures in the spine—the posterior annulus fibrosus and the posterior longitudinal ligament [4]. Apart from a surgical approach, the ventral epidural structures have been otherwise inaccessible. Endoscopy offers direct visualization of the affected nerve roots in addition to mechanical adhesiolysis, and this technique may become more mainstream as the technique is refined.

Facet pain is common in patients with chronic back and leg pain. After provocative testing a month or so after lysis, in addition to epidural lysis of adhesions, the combined use of radiofrequency facet denervation gives us the best long-term outcome.

Epidural adhesiolysis has been accepted as a treatment for postlaminectomy syndrome, failed back syndrome, and cervical and thoracic radicular syndromes and spinal stenosis. Additional studies are underway to further refine the technique and indications. The combined use of patient education for long-term neural flossing exercises and the inclusion of facet denervation treatment in the algorithm further improves patient outcome. The identification of back pain provocation by saline injection and the successful use of percutaneous neuroplasty in the treatment represent hopeful promise for a cost-effective treatment of back pain.

The increasing overall evidence is positive for the use of percutaneous lysis of adhesions based on high-quality randomized trials and observational clinical studies. The procedure recommendation is for patients that failed conservative therapies. There are no negative studies reported regarding the use of percutaneous adhesiolysis from the sacral to the cervical areas, with recommended catheter placement.

Unusual, rare complications must be recognized and treatment coordinated in the postoperative observational period. This is within the scope of the physician's practice and should not be delayed. Secondary motor block in patients where only caudal catheter is used to treat spinal stenosis needs to be recognized as a consequence of fluid expansion from osmotic effect. Our preferred clinical practice is evolving in the direction of caudal and transforaminal catheter use at the level of stenosis based on the utilization of the above-mentioned transforaminal catheter reports (Van Zundert J, 2005, personal communication).

Clearly, additional studies will further improve safety and efficacy. Rare problems will come to light, such as allergies, unusual loculations, syrinx, or congenital malformations. Thus, the technique will become similar to other advanced medical interventions. The quality of outcome improves with improved training and experience. The most significant hazard is physicians that are not trained, performing a percutaneous lysis procedure without appropriate catheter placement. Therefore, the recommendation is to describe the procedure and/or save procedure fluoroscopic images that will document appropriate catheter placement on anteroposterior and lateral views. Midline catheter placement for lysis of adhesions should be avoided.

The treatment algorithm, for patients with leg and back pain, based on experience and accumulating evidence, should focus on radiculopathy and back pain. Next, at 1-month follow-up, the patient must be reexamined for the diagnosis and treatment of other causes of back pain, such as facet joint related, and pain from muscle spasms like gluteus medius, paraspinal, quadratus lumborum, psoas, and piriformis muscle-related radiculopathy in the lumbosacral area. Significant underdiagnosed problems include trochanteric bursa-related pain, cluneal nerve entrapments, and hip joint arthropathies. Similarly, the order of evaluation and treatment in the upper extremity addressed should begin with radiculopathy, followed by facet joints and interscalene entrapments. Involvement through neural flossing exercises and appropriate instructions as outlined in the above text has been remarkably well accepted by the patients.

References

1. Lawrence R, Helmick C, Arnett F, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum. 1998;41(5):778–99.
2. Straus B. Chronic pain of spinal origin: the costs of intervention. Spine. 2002;27(22):2614–9.
3. National Center for Health Statistics. National Hospital Discharge Survey. Washington, DC: US Department of Health and Human Services, Centers for Disease Control and Prevention; 1990. Report no. PB92-500818.
4. Kuslich S, Ulstrom C, Michael C. The tissue origin of low back pain and sciatica. Orthop Clin North Am. 1991;22:181–7.
5. Racz G, Noe C, Heavner J. Selective spinal injections for lower back pain. Curr Rev Pain. 1999;3:333–41.
6. Anderson S. A rationale for the treatment algorithm of failed back surgery syndrome. Curr Rev Pain. 2000;4:396–406.
7. Pawl R. Arachnoiditis and epidural fibrosis: the relationship to chronic pain. Curr Rev Pain. 1998;2:93–9.
8. Cervellini P, Curri D, Volpin L, et al. Computed tomography of epidural fibrosis after discectomy: a comparison between symptomatic and asymptomatic patients. Neurosurgery. 1988;23(6):710–3.

9. Manchikanti L, Staats P, Singh V. Evidence-based practice guidelines for interventional techniques in the management of chronic spinal pain. Pain Phys. 2003;6:3–81.
10. LaRocca H, Macnab I. The laminectomy membrane: studies in its evolution, characteristics, effects and prophylaxis in dogs. J Bone Joint Surg. 1974;5613:545–50.
11. Cooper R, Freemont A, Hoyland J, et al. Herniated intervertebral disc–associated periradicular fibrosis and vascular abnormalities occur without inflammatory cell in filtration. Spine. 1995;20:591–8.
12. McCarron R, Wimpee M, Hudkins P, et al. The inflammatory effects of nucleus pulposus; a possible element in the pathogenesis of low back pain. Spine. 1987;12:760–4.
13. Parke W, Watanabe R. Adhesions of the ventral lumbar dura: an adjunct source of discogenic pain? Spine. 1990;15:300–3.
14. Viesca C, Racz G, Day M. Special techniques in pain management: lysis of adhesions. Anesthesiol Clin North Am. 2003;21:745–66. Epidural lysis of adhesions and percutaneous neuroplasty. http://dx.doi.org/10.5772/58753. 329.
15. Songer M, Ghosh L, Spencer D. Effects of sodium hyaluronate on peridural fibrosis after lumbar laminectomy and discectomy. Spine. 1990;15:550–4.
16. Key J, Ford L. Experimental intervertebral disc lesions. J Bone Joint Surg Am. 1948;30:621–30.
17. Olmarker K, Rydevik B. Pathophysiology of sciatica. Orthop Clin North Am. 1991;22:223–33.
18. Ross J, Robertson J, Frederickson R, et al. Association between peridural scar and recurrent radicular pain after lumbar discectomy; magnetic resonance evaluation. Neurosurgery. 1996;38:855–63.
19. Gilbert K, Brismee J, Collins D, et al. Lumbosacral nerve roots displacements and strain: part 1. A novel measurement technique during straight leg raise in unembalmed cadavers. Spine. 2007;32(14):1513–20.
20. Heavner JE, Chokhavatia S, Kizelshteyn G. Percutaneous evaluation of the epidural and subarachnoid space with a flexible fiberscope. Reg Anesth. 1991;15:85.
21. Bosscher HA, Heavner JE. Incidence and severity of epidural fibrosis after back surgery: an endoscopic study. Pain Pract. 2010;10:18–24.
22. Hatten Jr H. Lumbar epidurography with metrizamide. Radiology. 1980;137:129–36.
23. Stewart H, Quinnell R, Dann N. Epidurography in the management of sciatica. Br J Rheumatol. 1987;26(6):424–9.
24. Devulder J, Bogaert L, Castille F, et al. Relevance of epidurography and epidural adhesiolysis in chronic failed back surgery patients. Clin J Pain. 1995;11:147–50.
25. Manchikanti L, Bakhit C, Pampati V. Role of epidurography in caudal neuroplasty. Pain Digest. 1998;8:277–81.
26. Day M, Racz G. Technique of caudal neuroplasty. Pain Digest. 1999;9(4):255–7.
27. Horlocker T, Wedel D, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain Med. 2003;28:172–97.
28. Omnipaque product insert. Princeton: Nycomed, Inc.
29. Isovue product insert. Princeton: Bracco Diagnostics, Inc.
30. Hypaque product insert. Princeton: Amersham Health, Inc.
31. Conray product insert. Phillipsburg: Mallinckrodt, Inc.
32. Racz G, Day M, Heavner J, et al. Hyaluronidase: a review of approved formulations, indications and off-label use in chronic pain management. Expert Opin Biol Ther. 2010;10(1):127–31. 330 Pain and Treatment.
33. Teske W, Zirke S, Nottenkamper J, Lichtinger T, Theodoridis T, Kramer J, Schmidt K. Anatomical and surgical study of volume determination of the anterolateral epidural space nerve root L5/S1 under the aspect of epidural perineural injection in minimal invasive treatment of lumbar nerve root compression. Eur Spine J. 2011;20(4):537–41.
34. Lauretti GR, Mattos AL, Trevellin W, Righeti CCF, Resende CS. 911 sacral neuroplasty for postlaminectomy chronic low back pain. Eur J Pain. 2009;13(S1):S258a–S258.
35. Matsumoto. Treatment of lower back and leg pain using the Racz Catheter-Matsumoto way via S1 foramen. Maastricht: WIP World Congress; 2014.
36. Paincast.com. Paincast | Paincast [Internet]. 2014.
37. Racz GB, Heavner JE. Cervical spinal canal loculation and secondary ischemic cord injury—PVCS—perivenous counter spread—danger sign!! Pain Pract. 2008;8:399–403.
38. Larkin T, Carragee E, Cohen S. A novel technique for delivery of epidural steroids and diagnosing the level of nerve root pathology. J Spinal Disord Tech. 2003;16(2):186–92.
39. Scanlon GC, Moeller-Bertram T, Romanowsky SM, Wallace MS. Cervical transforaminal epidural steroid injections: more dangerous than we think? Spine (Phila Pa 1976). 2007;32(11):1249–56.
40. Jamison AE, Hsu E, Cohen SP. Epidural adhesiolysis: an evidence based review. J Neurosurg Sci. 2014;58:65–76.
41. Racz GB, Heavner JE, Bosscher H, Helm II S. The MILD procedure. Pain Pract. 2013;13(7):594–6.
42. Sakai T, Aoki H, Hojo M, et al. Adhesiolysis and targeted steroid/local anesthetic injection during epiduroscopy alleviates pain and reduces sensory nerve dysfunction in patients with chronic sciatica. J Anesth. 2008;22(3):242–7.
43. Anderson S, Racz G, Heavener J. Evolution of epidural lysis of adhesions. Pain Physician. 2000;3(3):262–70.
44. Racz GB, Sabonghy M, Gintautas J, et al. Intractable pain therapy using a new type of epidural catheter. JAMA. 1985;248:579–80.
45. Racz G, Holubec J. Lysis of adhesions in the epidural space. In: Raj P, editor. Techniques of neurolysis. Boston: Kluwer; 1989. p. 57–72.
46. Arthur J, Racz G, Heinrich R, et al. Epidural space: identification of filling defects and lysis of adhesions in the treatment of chronic painful conditions. Abstracts of the 7th world congress on Pain. Paris: IASP Publications; 1993. Epidural lysis of adhesions and percutaneous neuroplasty. http://dx.doi.org/10.5772/58753 331.
47. Racz GB, Day MR, Heavener JE, Smith JP. "The Racz procedure: lysis of epidural adhesions (percutaneous neuroplasty)". In: Tim D, editor. Comprehensive treatment of chronic pain by medical, interventional, and integrative approaches. New York: Springer; 2013.
48. Stolker R, Vervest A, Gerbrand J. The management of chronic spinal pain by blockades: a review. Pain. 1994;58:1–19.
49. Racz G, Heavner J. In response to article by Drs. Devulder et al. Clin J Pain. 1995;11:151–4.
50. Heavner J, Racz G, Raj P. Percutaneous epidural neuroplasty: prospective evaluation of 0.9 % saline versus 10 % saline with or without hyaluronidase. Reg Anesth Pain Med. 1999;24:202–7.
51. Manchikanti L, Pakanati R, Bakhit C, et al. Role of adhesiolysis and hypertonic saline neurolysis in management of low back pain: evaluation of modification of the Racz protocol. Pain Digest. 1999;9:91–6.
52. Manchikanti L, Pampati V, Fellow B, et al. Role of one day epidural adhesiolysis in management of chronic low back pain: a randomized clinical trial. Pain Phys. 2001;4:153–66.
53. Manchikanti L, Rivera J, Pampati V, et al. One day lumbar adhesiolysis and hypertonic saline neurolysis in treatment of chronic low back pain: a randomized, double blinded trial. Pain Phys. 2004;7:177–86.
54. Manchikanti L, Cash K, McManus C, et al. The preliminary results of a comparative effectiveness of adhesiolysis and caudal epidural injections in managing chronic low back pain secondary to spinal stenosis. Pain Phys. 2009;12(6):E341–54.
55. Manchikanti L, Singh V, Cash K, et al. A comparative effectiveness evaluation of percutaneous adhesiolysis and epidural steroid injections in managing lumbar post surgery syndrome. Pain Phys. 2009;12(6):E355–68.

56. Veihelmann A, Devens C, Trouiller H, et al. Epidural neuroplasty versus physiotherapy to relieve pain in patients with sciatica: a prospective randomized blinded clinical trial. J Orthop Sci. 2006;11(4):365–9.
57. Helm II S, Benyamin R, Chopra P, Deer T, Justiz R. Percutaneous adhesiolysis in the management of chronic low back pain in post lumbar surgery syndrome and spinal stenosis: a systematic review. Pain Physician. 2012;15:E435–62.
58. Gerdesmeyer L, Lampe R, Veihelmann A, et al. Chronic radiculopathy: use of minimally invasive percutaneous epidural neurolysis according to Racz. Der Schmerz. 2005;19:285–95. 332 Pain and Treatment.
59. Gerdesmeyer L, Rechl H, Wagenpfeil S, et al. Minimally invasive epidural neurolysis in chronic radiculopathy: a prospective controlled study to prove effectiveness. Der Orhopade. 2003;32:869–76.
60. Gerdesmeyer L, Wagenpfeil S, Birkenmaier C, Veihelmann A, Hauschild M, Wag-ner K, Al Muderis M, Gollwitzer H, Diehl P, Toepfer A. Percutaneous epidural lysis of adhesions in chronic lumbar radicular pain: a randomized, double-blind, placebo-controlled trial. Pain Phys. 2013;16:185–96.
61. Koh WU, Choi SS, Park SY, Joo EY, Kim SH, Lee JD, Shin JY, Leem JG, Shin JW. Transforaminal hypertonic saline for the treatment of lumbar lateral canal stenosis: a double-blinded, randomized, active-control trial. Pain Physician. 2013;16:197–211.
62. Manchikanti L, Singh V, Cash K, Pampati V. Assessment of effectiveness of percutaneous adhesiolysis and caudal epidural injection in managing post lumbar surgery syndrome: 2-year follow-up of a randomized, controlled trial. J Pain Res. 2012;5:597–608.
63. Park CH, Lee SH. Effectiveness of percutaneous transforaminal adhesiolysis in patients with lumbar neuroforaminal spinal stenosis. Pain Physician. 2013;16:E37–43.
64. Park EJ, Park SY, Lee SJ, Kim NS, Koh DY. Clinical outcomes of epidural neuroplasty for cervical disc herniation. J Korean Med Sci. 2013;28:461–5.
65. Choi E, Nahm F, Lee PB. Evaluation of prognostic predictors of percutaneous adhesiolysis using a Racz catheter for post lumbar surgery syndrome or spinal steno- sis. Pain Physician. 2013;16:E531–6. Manchikanti L, Helm II S, Pampati V, Racz GB. Cost utility analysis of percutaneous adhesiolysis in managing pain of post-lumbar surgery syndrome and lumbar central spinal stenosis. Pain Pract. 2014. doi:10.1111/papr.12195.
66. Coppieters MW, Butler DS. Do '*sliders*' slide and '*tensioners*' tension? An analysis of neurodynamic techniques and considerations regarding their application. Man Ther. 2008;13(3):213–21. Epub 2007 Mar 30.
67. Lohman CM, Gilbert KK, Sobczeck S, et al. Cervical nerve root displacement and strain during upper limb neural tension testing: part 2. Role of foraminal ligaments in the cervical spine. Spine. 2015. doi:10.1097/BRS.0000000000000687.

Part II

Complementary Techniques

Theory and Mechanisms of Action of Neuroaugmentation

9

Octavio Calvillo, Gabor B. Racz, and Carl Noe

Introduction

Neuroaugmentation has evolved into a commonly performed procedure after 1967 when Shealy reported pain relief in a patient with malignant pain using spinal cord stimulation [SCS] [90]. Failed back surgery syndrome [FBSS] is probably the most common indication for SCS [3, 49, 61, 69, 72]. SCS has been used successfully for back pain plus peripheral field stimulation in some patients [66]. Complex regional pain syndrome type I and II is the second most common type of pain in which SCS has been used. SCS is a reasonable option when all alternative treatments have been exhausted. Calvillo [9, 10, 12] reported a series of patients with upper extremity CRPS treated with SCS. Some patients were implanted with SCS and also with peripheral nerve stimulators. Other reports have been published in patients with complex regional pain syndrome [47–49, 110]. Phantom limb pain and postamputation stump pain have been treated with SCS, but the reported results have been variable; some reported with high success but not others [26, 112]. SCS, in patients with angina pectoris, has been reported to reduce pain, improve exercise capacity, prevent hospital admissions, and improve the quality of life [57]. SCS can improve blood flow through creation of collateral circulation due to increased physical activity after implantation. The antianginal effects are due to a decrease in myocardial oxygen consumption [34, 57]. SCS can be an option for high-risk patients who could not be considered because of comorbidities and increased surgical risk of surgical complications. SCS is indicated in the treatment of peripheral vascular disease. Critical limb ischemia is usually treated with surgery, but it can be contraindicated in some patients due to comorbidities and high surgical risk. Patients with small vessel disease where revascularization is not possible can be candidates for SCS. The main indication is severe ischemic pain at rest without tissue involvement. Other indications include lumbar spinal stenosis in patients who are not surgical candidates and may be treated successfully with SCS [58].

Cervical SCS has been hypothesized to be useful cerebral spasm after subarachnoid hemorrhage. SCS may work by as preventing vasoconstriction of the cerebral arteries inducing functional sympathectomy acting at the cervical spine level [31, 95]. Cervical SCS has been used for several pain conditions of the head and neck [58, 107]. Wolter reported long-term alleviation of Raynaud's syndrome with spinal cord stimulation [118]. Occipital neuralgia, one patient with neurofibromatosis and cervicogenic headache responded dramatically to stimulation of the occipital nerve [94]. Weiner and Reed reported positive results with peripheral stimulation of peripheral nerves for occipital neuralgia [58, 107, 117]. Other applications of SCS include stimulation of selective sacral nerves [9, 10, 12], chronic visceral abdominal pain [41, 42], and chronic pancreatitis [43].

Pain management has evolved from a model in which nerve destruction was considered a simplistic approach to control pain. During the second half of the twentieth century, it became apparent that nerve destruction was far from the ideal treatment of pain, and the procedure led to anesthesia dolorosa that was exquisitely painful sometimes more than before the procedure. In 1965, based on gating mechanisms in the dorsal horn, Melzack and Wall proposed the gate control theory that led to the developing of techniques to modulate pain by activating A fibers. The gating theory proposed a mechanism based on the activation of large-diameter afferent fibers serving somatosensory sensations like touch and pressure that was capable of inhibiting synaptic input conveyed along C fibers concerned with nociception.

O. Calvillo, MD, PhD, FIPP, ABIPP
Department of Anesthesiology, Methodist Hospital, Houston, TX 77030, USA

G.B. Racz, MD, ABA, FIPP, ABIPP (✉)
Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX, USA
e-mail: gbracz@yahoo.com

C. Noe, MD
Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_9

It incorporated mechanisms of presynaptic control of synaptic transmission from large and small sensory fibers. This concept led to the formulation of gating in the dorsal horn. Other features included the convergence of small and large sensory inputs on spinal neurons that transmit information to the forebrain as well as the ability of descending control pathways to affect and control the gate. The theory enjoyed great popularity because it encompassed concepts of perception of synaptic input denying credence to the concept of pain as specific somatosensory modality. The theory of gating mechanisms promoted an unparalleled impetus in pain research and treatment.

The first human experiment on neuromodulation was reported by Wall and Sweet in 1967. Other reports followed demonstrating the value of neuroaugmentation in chronic pain management. Based on the assumption that the gating idea was in fact operational, Gybels and Sheally implanted electrodes to stimulate the dorsal columns that contain predominantly large-diameter fibers [33, 90]. The procedure caused pain relief thus marked the beginning of neuroaugmentation.

The gating theory stimulated research and controversy in many laboratories worldwide [6, 29, 122]. It was proposed by Mendell and Wall that positive dorsal root reflexes could be produced by stimulating nerves under anodal block [59]. This observation provoked a significant number of laboratories; in particular the publication by Burke showing that stimulating with radiant heat in the noxious range produced negative dorsal root potentials, thus negating primary afferent hyperpolarization of unmyelinated fibers in the dorsal horn [6].

Calvillo provided evidence that primary afferent terminals are susceptible to modulation by large-diameter afferents as suggested by Melzack and Wall in 1965 [11].

Convincing evidence was provided in the study of Calvillo by demonstrating collision between antidromically and orthodromically evoked C fiber potential. These observations suggest that there is a presynaptic gating mechanism operating in the dorsal horn; however, the possibility of the gate operating postsynaptically remains as reasonable option to explain the gating mechanism to modulate pain. The gating theory was formulated and linked exclusively to presynaptic mechanisms, in as much as there is evidence to support that contention it is necessary to propose postsynaptic mechanisms to explain the theory.

Mechanism of Action of Spinal Cord Stimulation [SCS]

Neurochemical and Neurophysiological Evidence

The experimental model of chronic neuropathic pain is based on the model of Bennett and Xie [4]. In rats with sciatic nerve ligation, the animals developed allodynia, hyperesthesia, hyperalgesia, and possibly pain. It may not be ideal, but the ideal model has served as a useful model in experimental pain research. The concept of using exclusively electrical neuromodulation for pain suppression is perhaps an oversimplification. The central nervous system [CNS] operates based on neurochemical and electrical events. The neurochemicals participating in pain mechanisms include serotonin [involved in descending inhibition], epinephrine, GABA, and acetylcholine. In addition to these neuromediators, there is also an adenosine-dependent mechanism [7], and all these mechanisms present an opportunity for potentiation of SCS effects [32, 55].

The available evidence does not support the contention that the effects of SCS-induced analgesia are mediated by endogenous opioid release. No increase in these peptides has been demonstrated in cerebrospinal fluid as a result of SCS [35]. The effects on SCS cannot be reversed by naloxone; therefore, the role of endogenous opioids is unlikely to explain the mechanism of action of SCS [56]. Gamma-aminobutyric acid [GABA] is an inhibitory neurotransmitter capable to induce dynamic changes segmentally. The GABAergic inhibitory interneurons in superficial laminae of the dorsal horn can become activated by GABAb input and release GABA [22, 85]. In neuropathic pain models, SCS increased spinal GABA release in animals that became analgesic, and the release of glutamate and aspartate decreased [15, 55, 104]. The inhibition of animal pain behavior and neuronal excitability was closely associated with the time course of increased levels of GABA in the dorsal horn induced by SCS. The observations of Stiller et al. suggest that GABAb receptor plays a more important role than GABAa receptor in mediating the analgesic effect of SCS [104]. Intrathecal administration of baclofen enhanced SCS analgesia in both animal models and patients. The duration of time that extracellular levels of GABA remained elevated significantly exceeds the duration of SCS [15]. This observation might explain the observation in patients that continue to report pain relief after SCS.

There is evidence that the levels of glycine are elevated after SCS without any evident changes in taurine glutamate or aspartate. Thus, they hypothesized that glycine may be responsible for the analgesic response to SCS [101, 102]. In the experiments of Simpson et al., using rats with nerve ligation and neuropathic pain reported an increase in the pain threshold in the affected extremity. The pain threshold was decreased by the administration of strychnine [a glycine antagonist]; thus, it was suggested that glycine may mediate at least partly the analgesic effects of SCS. Glycine containing interneurons are predominantly present in the motor nucleus of the spinal cord [5]; however, glycine is also present in the dorsal horn [2].

Adrenergic and Cholinergic Mechanisms

The findings of Levin and Hubschmannn provide support for the role of noradrenaline in the SCS analgesia [62]. Two other mechanisms of SCS analgesia are cholinergic and adrenergic neurotransmission. In vivo studies suggested that SCS induces release of both acetylcholine and noradrenaline in the spinal cord [62, 84, 100]. Dorsal horn acetylcholine levels were significantly elevated only in rats with neuropathy, whereas the release was not affected in nonresponsive animals. It is important to note that SCS-induced analgesia was reversed or prevented by intrathecal atropine, thus suggesting muscarinic mediation.

Muscarinic receptors and alpha-1 adrenoceptors are located on GABAergic interneurons in the dorsal horn [14]. Acetylcholine and noradrenaline may excite spinal GABAergic receptors by binding to the respective receptors to induce analgesia after SCS. The studies of Linderoth et al. have added to our understanding of the neurochemistry of SCS [64]. They provided evidence that activation of muscarinic and alpha-1 adrenoceptors may initiate a feedforward of various spinal inhibitory mechanisms [53, 63, 83]. Some studies have been published, and they demonstrate that serotonin is probably involved in the analgesic effects of SCS [64]. They also demonstrate that the increase in serotonin after SCS might relate to local GABAergic mechanisms [98]. Song studied the roles of different spinal 5-HT receptors in SCS-induced analgesia under neuropathic pain conditions [99]. They proposed that activation 5-HT2A, 5-HT3, and 5-HT4 receptors in the dorsal horn may contribute to the SCS-induced decrease in neuronal excitability and diminished pain processing. Activating 5-HT receptor increased release of serotonin also may increase the synthesis and expression of dynorphin, enkephalin, and GABA in the spinal cord [116]. This may provide an explanation for the delayed and prolonged analgesic action of SCS involved in descending inhibition.

Neurophysiology

The clinical beneficial of SCS is substantial, but a clear understanding of its mechanism of action is lacking. The practice of stimulating the dorsal columns sprang from concepts proposed by Melzack and Wall in 1965. They suggested a gating mechanism in the dorsal horn activated by A fiber input acting on C fiber synaptic transmission. In 1967, Sheally implanted electrodes surgically in the dorsal columns demonstrating analgesia in a patient with malignant pain [90]. Subsequently, anesthesiologist implanted electrodes percutaneously attaining analgesia in patients with lower extremity pain.

Segmental Mechanisms

Nociceptive afferent neurons of the dorsal ganglia [DRG] and trigeminal ganglia transmit noxious to the spinal cord principally to laminae I-II and V [13].

Nociceptive information is amenable to modulation presynaptically at the terminals of primary afferent fibers before transmitting nociceptive information to spinal dorsa neurons or postsynaptically and supraspinal structures. Thus, the dorsal horn functions as relay station for ascending nociceptive information as well as a place for integration and modulation of pain. Evidence from SCS in patients demonstrates that stimuli delivered to the dorsal columns mediate the analgesic response to SCS. Thus, a segmental mechanism operates to produce analgesia without ruling out a supraspinal component.

SCS is most effective in neuropathic pain, whereas in acute nociceptive pain, SCS is not effective which is surprising since the gate hypothesis may suggest otherwise. Most studies on the mechanism of action of SCS have been on chronic neuropathic pain in animals with tight ligatures of peripheral nerves [15, 56]. Impulses delivered to the dorsal columns produce paresthesia by causing orthodromic stimulation of dorsal horn cells, this could be an epiphenomenon; however, there is evidence that the stimuli cause antidromic activation of dorsal horn neurons. The exact target in the spinal cord has not been identified; however, there are several theoretical areas such as the dorsal columns [28], dorsolateral funiculi [49], spinobulbar fibers, spinocerebellar tract [68], and dorsal root fibers [73]. Several studies have attempted to prove the mechanism of action of SCS. Most experimental data in this regard are derived on models of neuropathic in which pain must be validated indirectly from animal models. Hypersensitivity after a nerve injury is the most common behavioral sign of pain in animal models [4, 23]. This is interpreted as equivalent to allodynia in animal models and humans, but not pain.

SCS arose as a consequence of the postulates of the gating theory of Melzack and Wall. The gating theory postulates that activating large-diameter afferent fibers inhibits transmission in unmyelinated fibers. The gating theory does not explain the mechanism of action accurately since it principally modulates neuropathic pain without having any effect on nociceptive pain. Stimulation of large-diameter fibers in the dorsal columns elicits paresthesia in the corresponding dermatomes which is needed to attain pain relief.

This seems to be an epiphenomenon and questionably needed to produce pain relief [28, 40, 48, 68]. The mechanism of action of SCS most likely causes activation of dorsal column fibers which activates interneurons in or near the substantial gelatinous or marginal layer of the dorsal horn [24, 60, 68]. Peripheral nerve injury and therefore pain seem to induce a state of hyperexcitability of dorsal horn neurons, and it has been suggested that SCS might reduce that state toward closer to normality [28, 48].

Supraspinal Mechanisms

The dorsolateral funiculi contain descending fibers that modulate the activity of nociceptive dorsal horn in rats. This may be another target for SCS-induced analgesia [44, 70]. Saade et al. demonstrated in their study that the dorsolateral funiculi participate in the analgesia produced by SCS [79]. Furthermore, they investigated the role of various transmitters both excitatory and inhibitory in the spinal cord. Prior to applying SCS, antagonists to GABA a or b, 5-HT1 or 1–2 or alpha-/beta-adrenoceptor were injected intraperitoneally, and they concluded activation of the dorsal columns is relayed to supraspinal structures involved in pain attenuation probably the descending fibers in the dorsolateral funiculus. They reported 80–90 % decrease in the behavioral manifestations of pain in rats with intact spinal cords. Dorsolateral fasciculus lesions attenuated the effects of SCS by 50 %.

In other experiments [83, 98, 99], the precise structure that mediates the analgesic effects of SCS remains to be determined; however, the available evidence supports both spinal segmental and supraspinal mechanisms. Lesions at the dorsal column nuclei and segmental spinal cord reduced pain behavior; however, lesions of the dorsal columns reduced the analgesic effects of SCS by about 50 % demonstrating that there are supraspinal mechanisms to explain the analgesic effects of SCS. The role of locus coeruleus was investigated; it was concluded that the locus coeruleus does not participate in the analgesia of SCS [97].

Rees and Roberts suggested that the long-lasting inhibition of dorsal horn neurons involved activation of the pretectal nucleus and its output activates the descending pain pathway [74]. Studies conducted by Saade et al. and El-Khoury et al. have demonstrated activation of a spinal-brainstem loop by SCS [27, 78, 80]. They propose that SCS induces ascending inhibition relayed by thalamocortical systems, triggering the descending pain inhibition mediated by the brainstem. Ren et al. have demonstrated that an important component of SCS analgesia may be descending of both serotonergic and adrenergic pathways [75].

Dorsal Root Ganglion

The dorsal root ganglion [DRG] has become a target in pain medicine and reports on selective stimulation of this structure have become available [8, 81, 87]. The DRG contains the primary sensory neurons responsible for transducing the responses from peripheral sensory organs and passing the signal on to the central nervous system [CNS] following nerve injury or inflammation. These neurons may become an important source of increased nociceptive signaling due to increased neuronal excitability and generation of ectopic discharges [82]. DRG cells do not have dendrites or afferent synapses. They have microvilli perikaryal projections but do not have synaptic contacts [19]. DRG neurons are pseudounipolar. They emit a single stem axon from the axon hillock-initial segment. From the soma, the stem axon ends into a T or a Y. One branch from the T-junction proceeds into the spinal nerve and from there to a sensory ending in the skin, muscle, or viscera. The other end enters the dorsal root and spinal cord or brain stem. As opposed to the blood-brain barrier in the central nervous system [CNS], the DRG and peripheral axons lack a neurovascular barrier that allows diffusion of large molecular weight compounds in the interstitium surrounding the DRG neurons [1]. Devor has reported on some physiological peculiarities of DRG cells [19].

Afferent impulses from sensory organs pass the T-junction and continue into the dorsal root and spinal cord. Sensory communication between peripheral sense organs and CNS does not require the action potential to invade the cell soma, but in most DRG neurons, the afferent signal propagates along the axon and invades the soma [20]. Devor proposed a hypothesis concerning spike invasion of the soma: as the axon diameter expands into the soma, much of the longitudinal current needed to keep the spike migrating would be dissipated in charging the capacitance of the membrane or be dissipated through the soma conductance [20]. The hypothesis that Devor proposes is that soma excitability is not the result of slopping targeting but a specific design feature of DRG neurons [19].

The DRG has assumed importance as a target for neurostimulation (see review by [46]) in treating chronic pain of neuropathic origin. In the past, the DRG was portrayed as passive structure without significant involvement in neuropathic pain. Its role was considered mostly supportive in communication between the peripheral nervous system and the central nervous system. Scientific evidence regarding the anatomy and physiology of the DRG shows that it is an important structure in the development of neuropathic pain [19].

Injury in a peripheral afferent fiber leads to hyperexcitability in axotomized DRG neurons. Injured DRG neurons become more excitable and the cells in satellite glial cells increase in number, and they exhibit ectopic firing [18, 119]. The development of neuropathic pain involves the participation of multiple factors besides the nervous pathways [114]. Sukhotinsky et al. have suggested that ectopic firing in DRG neurons induces central sensitization and allodynia [105]. Activation of glial cells by injury causes release of inflammatory mediators. This lowers the threshold for neuronal firing leading to peripheral and central sensitization and neuropathic pain.

Xiao et al. found upregulation of neuropeptides, ionic channels, and other factors in the development of neuropathic pain [120]. Hardedge et al. researched changes in gene expression after transection of the sciatic nerve in adult rats and found increases in c-Jun and Jun-D within the DRG [38].

These changes in gene transcription cause alterations in the cell bodies at the level of the perikaria, possibly a key element to neuromodulation of DRG neurons. After peripheral afferent injury, there are changes in ionic currents. Honmou et al. have demonstrated various Na sodium channels, and it is hypothesized that various subtypes of these channels are associated with neuropathic pain [39]. Klein et al. reported a change in electrical stimulation can alter the expression of sodium channel genes in subtype-specific manner; thus, we can envision electrical stimulation inducing changes in sodium channel expression and function to the extent that pathology can be reversed toward a normal level [45]. Electrical stimulation of the DRG may be equivalent to promoting production of growth factors [65, 93]. Activity of growth factors and of the growth-associated protein 43 [GAP-43] within the DRG neurons does play a role in neuropathic pain and since electrical stimulation of the DRG stimulates the synthesis of growth factors. It is possible that perturbations of these growth factors could be modified stimulation of the DRG resulting in reducing chronic pain [46]. The DRG is an intraspinal structure, but it can be reached transspinally for therapeutic stimulation. The DRG is technically a component of the peripheral nervous system; however, due to its proximity to the spinal cord together, it is grouped with SCS.

DRG stimulation was the subject of a multicenter study [52]. Of 51 patients studied, 39 reported more than 50 % pain relief in the back and 32 proceeded to implantation [8]. Schu et al. reported a series of patients with groin pain that were treated with DRG stimulation. Of the 29 patients in the study, the authors reported significant pain relief in 25 patients for 27 weeks [87]. Evidently, traditional SCS does not cover all painful areas, and selective stimulation of the DRG opens the possibility of covering areas previously missed by SCS.

Stimulation Paradigms

SCS paradigms have remained largely unchanged since the modality was introduced. Electrical stimulation has been associated with paresthesias in the distribution in the painful dermatomes. The electrical stimulation is delivered on a continuous basis in a regular fashion within a relatively narrow frequency range. All these parameters, i.e., paresthesia production, continuous stimulation, regular pattern, and low frequency, have been challenged as a requisite for pain relief. Delivering stimulation in a stochastic pattern as opposed to synchronous stimulation, it is hoped that stochastic pattern will prevent tolerance to stimulation; however, there are no clinical studies to validate this concept [88].

In the absence of paresthesia, within 1–200 Hz, pain relief has not been observed. Mapping and patient response with paresthesia production during electrode implantation remain as a prerequisite in the painful dermatomes. However, once the stimulation frequency is increased, paresthesias disappear, whereas pain relief is reported or even improves [106]. This was observed when the frequency was increased to 10,000 Hz with 30 microsecond stimulation pulses and the current ranging from 0.5 to 5.0 mA. It appears that 10,000 kHz stimulation results in significant pain relief in the back and lower extremities [109]. High-frequency stimulation is discussed in more detail in the next chapter. Another type of stimulation paradigm is burst stimulation pattern. This type of stimulation delivers short trains of stimuli to the spinal cord. Each train of stimuli includes five 1 ms-wide spikes with a 1-ms spike interval at a rate of 500 Hz. The trains are delivered 40 times per second in 40-Hz burst mode.

Thalamic cells display dual-firing properties. They can fire in tonic and burst modes and the burst-firing mode being a more powerful activator of brain cortex [16]. De Ridder et al. further investigated the effects of burst stimulation in a double-blind, placebo-controlled paradigm and confirmed the ability of burst SCS to relieve pain in a statistical way significant for back pain and extremity pain [17]. The concept of double-blind, placebo-controlled studies in SCS was not possible before the burst stimulation. The paresthesia allowed the subjects immediately to differentiate placebo versus stimulation.

Adaptive stimulation employs a built-in accelerometer able of detecting the body position [89]. This device introduced several functional improvements with adaptive stimulation, such as improved comfort during position changes, improved activity, and improved sleep. The presence and details from compound action potentials may be revealed by recording from the implanted electrode [121]. It suggested a correlation between depression in the evoked action potential and threshold for stimulation. Remarkably, the in vivo recordings in patients undergoing stimulation revealed a correlation between depression in the evoked action potential and the degree of coverage of the painful area [77]. See Slavin [96] for a review of spinal stimulation [96].

Catastrophic Cases Requiring Neuroaugmentation with Additional Interventions

Catastrophic cases are confusing, but long-standing complex pain syndromes frequently do not respond adequately to monotherapies, leaving patients, physicians, and society as a whole disappointed. An approach of identifying and treating components of pain, such as allodynia and peripheral neuromas, separately has been effective. Peripheral neuropathic pain is always associated with a peripheral nerve injury or disease, by definition. CRPS is no exception and spontaneous firing from neuromas or other peripheral nerve pathology may occur. Movement may increase this peripheral input, and

patients may display fear-avoidance behavior and develop stiffness and contractures with conditions such as CRPS.

The dorsal root ganglion (DRG) can develop ectopic firing as well and may be the dominant source of spontaneous firing [21]. However, neuromas may be more important for activity-related pain, and tactile allodynia may result from either the DRG or peripheral neuroma [21]. Local anesthetic infusion to block the DRG has been temporarily effective in patients with phantom pain [111]. Peripheral nerve resection, cautery, relocation of nerve stumps into muscle, and more proximal nerve-crushing procedures have been reported to successfully treat a catastrophic patient with CRPS II [115]. In this catastrophic case, the superficial peroneal and sural nerves were resected near the ankle, cauterized, and the proximal ends placed into calf musculature. The nerves were also crushed near the fibular head. The patient had good long-term results after a long affliction with CRPS II. This case illustrates the possibility of substantial pain relief with treatment that is not amenable to study with randomized trials, in the hands of experienced clinicians who are able to accurately identify peripheral pain and target successful treatment.

Peripheral nerve neuroaugmentation has been used to successfully treat a patient with a metal spike through the median nerve. During the stimulator trial, spontaneous firing was recorded from the implanted electrode [36, 37]. Peripheral stimulation reduced allodynia, lancinating pain, and vasoconstriction. Allodynia does not respond as well to spinal cord stimulation, but spinal cord stimulation does inhibit sympathetically maintained pain. The combination of SCS and peripheral stimulation may be required for some patients with refractory CRPS [9, 10, 12]. The return to work rate at 5-year follow-up in patients with combined stimulation is 55 % in males and 35 % in women [91].

Clinical Observation: Reversal of Painful Spinal Cord Stimulation

A patient with painful spinal cord stimulation has been successfully treated with a stepwise approach. The patient had undergone reconstruction of the arch of the left foot and developed pain and allodynia in the left leg, trunk, and face. An epidural infusion of 0.1 % ropivacaine and fentanyl at 6 ml/h was used with the catheter tip placed at the area of the left L4 DRG.

Reversal of centralization of pain is by time-dependent infusion (5 days) epidurally.

After 5 days of infusion, the allodynia retracted. Next, several small area of local pain and tenderness were located. These were injected with local anesthetic and the patient was able to bear some weight for the first time since the condition developed. Pain from these local neuromas does not respond well to spinal cord stimulation. The patient also had postoperative scarring around tendons on the dorsum of the foot producing an extended great toe. These scars were also injected and the range of motion improved.

Multiple areas of injection were later treated with cryoneurolysis, and the patient was able to ambulate at the end of a 5-day hospitalization. Two months later, another physician implanted a paddle electrode at T11-12 and placed the impulse generator device (IPG) in the left posterior buttock area. Her pain recurred and stimulation worsened her pain and she turned the generator off. She deteriorated almost back to her previous condition. An epidural infusion was repeated, and her allodynia again improved until the following morning when her pain returned and she was unable to empty her urinary bladder. An x-ray showed that her catheter had migrated from the L4 DRG area to the first sacral level. The catheter was replaced at the L4 DRG area and the pain diminished and was localized around the impulse generator device. The IPG was turned on and stimulation was no longer painful. The IPG was relocated to the right side without problems.

At the time this occurred, neuromodulator devices were limited, but small volume of local anesthetic injections followed by cryoneurolysis was effective in salvaging the stimulator. Small volumes of local anesthetic injected at painful points were also associated with a vasodilatory response suggestive of sympathetic hyperactivity. Peripheral stimulation was not possible due to the absence of a single identifiable nerve corresponding to the multiple pain points. In the presence of allodynia, it is not possible to localize these pain points. Local anesthetic on the DRG will suppress allodynia and allow for the identification of discrete pain points that can be injected with local anesthetic as a therapeutic and prognostic step. If a pattern of residual pain that is consistent with a peripheral nerve distribution after allodynia is suppressed, then peripheral nerve neuroaugmentation can be considered.

This patient was able to return to school and work. She required two additional infusions and cryoneurolysis treatments and sympathetic blocks. One of her catheters migrated from the L4 level and was once again associated with the return of allodynia. The painful stimulation has resolved and she has used her spinal cord simulator routinely for the past 3 years. Her last intervention was 18 months ago.

It is unreasonable to expect SCS to suppress all pain mechanisms in a catastrophic pain patient since multiple mechanisms are in play. DRG stimulation may be a significant step forward, but multiple levels will need to be stimulated simultaneously.

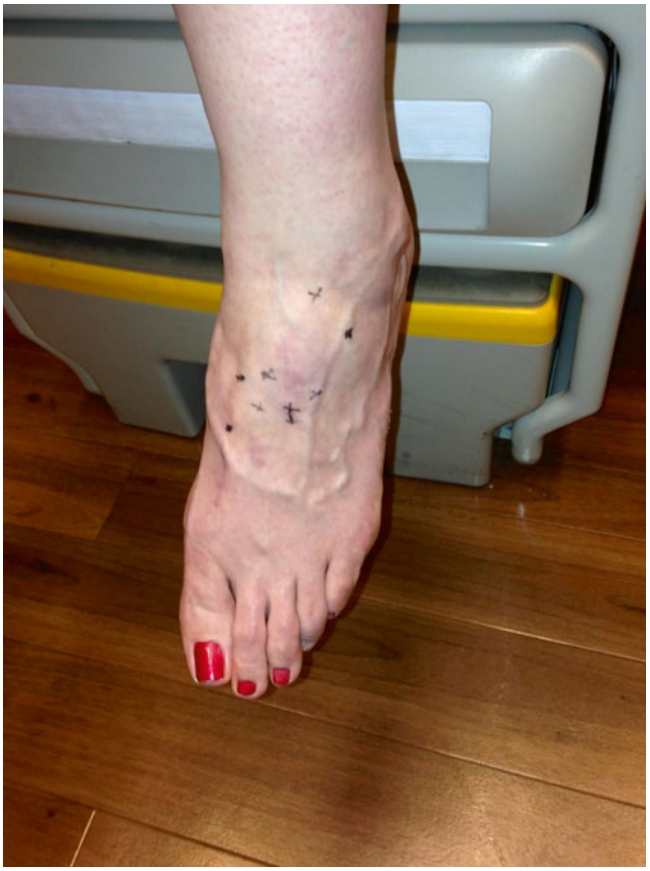


Fig. 9.1 Painful points are injected with less than 1 ml each of lidocaine 1 %. Short-term pain relief follows postinjection vasodilation

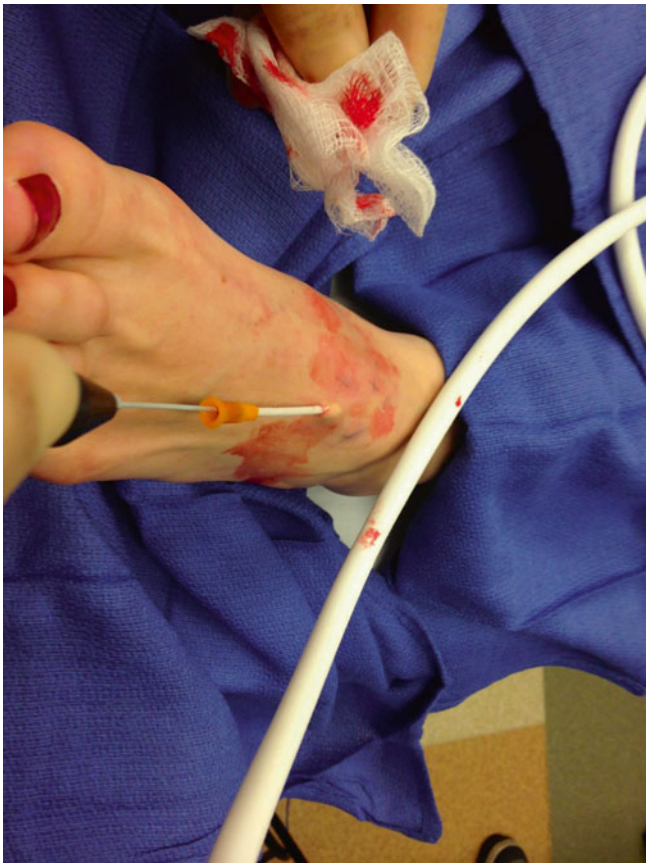


Fig. 9.2 Prior to injection, there were no distended veins. 10 minutes after small volumes of local anesthetic injection at the painful points, all extremities show venous dilatation

This approach has been used routinely and has been an effective use of multimodal interventional modalities including local anesthetic block of the DRG, peripheral local anesthetic injection of potential sites of ectopic firing, cryoneurolysis of these sites, sympathetic blocks, and neuroaugmentation, both centrally and peripherally (Figs. 9.1, 9.2, and 9.3).

Clinical Studies

Spinal cord stimulation has been studied in numerous randomized clinical trials. Failed back syndrome was an initial focus of spinal cord stimulation. In 2005, North reported superiority of spinal cord stimulation compared to reoperation in patients with failed back syndrome [67]. Kumar reported superiority of spinal cord stimulation compared to conventional medical management [50, 51]. Neuropathic pains, other than chronic radiculitis, have also been studied. Geurts reported positive results from a trial of spinal cord stimulation in patients with complex regional pain syndrome and has published positive long-term results [30]. Slangen reported significant analgesia in a trial of spinal cord stimulation in patients with painful diabetic neuropathy [103].

Headache syndromes have been studied with positive results. Silberstein has reported positive results from a multicenter randomized trial of occipital neuroaugmentation for chronic migraine [92]. Cardiovascular disease is another area of significant research. Torre-Amione found spinal cord stimulation to be effective in the management of symptoms of heart failure [108]. Zipes reported a positive trend in patients with angina who were not candidates for revascularization [123].

Lind has reported positive results from a randomized trial of spinal cord stimulation in patients with irritable bowel syndrome [54].

Several studies have focused on stimulation pattern. Schu reported better results with burst stimulation in patients with failed back syndrome [86]. De Ridder found burst stimulation to be superior to tonic stimulation [17]. However, Perruchoud found no difference between high-frequency

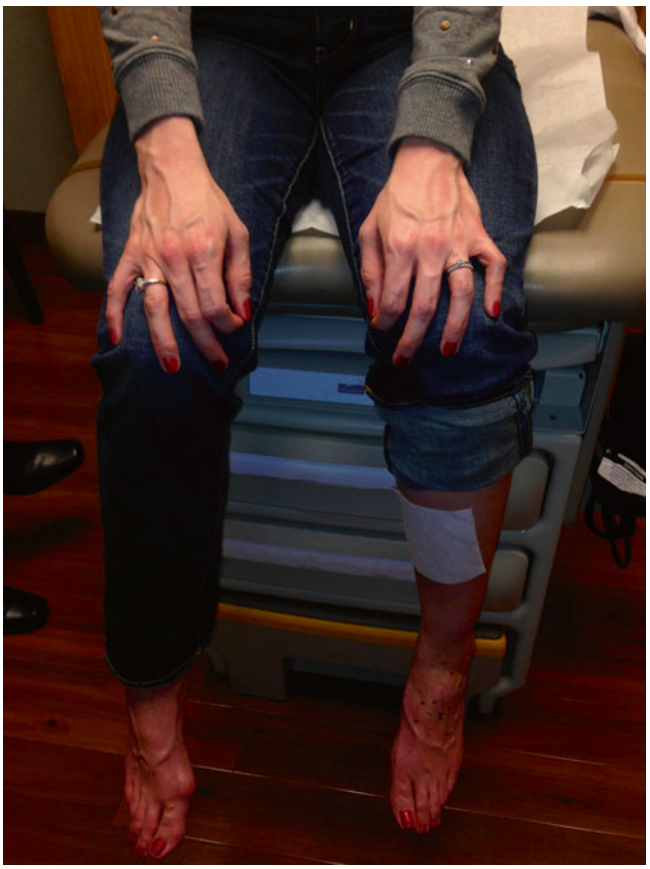


Fig. 9.3 Prior to injection, there were no distended veins. Within 10 min, all extremities are vasodilated

stimulation and controls in patients with neuropathic and vascular pain [71]. Washburn compared constant current stimulation to constant voltage stimulation and found that constant current stimulation was superior [113].

Summary

Neuromodulation for pain relief is widely used by anesthesiologist, neurosurgeons, physical medicine and rehabilitation physicians, and other physicians. There are multiple indications and more will be discovered. Techniques have become more refined over the past decades and will continue to evolve into a more cost-effective modality as an alternative to treatments such as opioids and ineffective therapies. Stimwave is an example of new technology with FDA approval that delivers energy to implanted electrodes without an implanted generator or connecting wires, presumably capitalizing on Lenz's law.

Several large randomized controlled trials are underway to study patients with chronic pain. Rigoard et al. are currently conducting a large trial of spinal cord stimulation in patients with failed back syndrome [76]. Patients will be randomized to spinal cord stimulation alone, optimal medical management, or both. Eldabe et al. are conducting a trial of spinal cord stimulation for patients with refractory angina [25].

References

1. Abram SE, Yi J, Fuchs A, Hogan QH. Permeability of injured and intact peripheral nerves and dorsal root ganglia. Anesthesiology. 2006;105(1):146–53.
2. Aprison MH, Shank RP, Davidoff RA. A comparison of the concentration of glycine a transmitter suspect in different areas of the brain and spinal cord in seven different vertebrates. Comp Biochem Physiol. 1969;28:1345–55.
3. Atkinson L, Sundaraj SR, Brooker C, et al. Recommendations for patient selection in spinal cord stimulation. J Clin Neurosci. 2011;18:1295–302.
4. Bennett GY, Xie Y-Q. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain. 1988;33:87–107.
5. Berger SI, Carter JC, Lowry OH. The distribution of glycine in the spinal neurons in the cat. J Neurophysiol. 1968;31:81–95.
6. Burke RE, Rudomin P, Vyklický L, Zajac III FE. Primary afferent depolarization and flexion reflexes produced by radiant heat stimulation of the skin. J Physiol. 1971;213(1):185–214.
7. Burnstock G, Sawynok J. Chapter 14 Adenosine Triphosphate and Adenosine Receptors and Pain. In: Beaulieu P, Lussier D, Porreca F, Dickenson AH, editors. Pharmacology of Pain. Seattle: IASP Press; 2010. p. 303–26.
8. Buyten JP, Smet I, Liem L, et al. Stimulation of dorsal root ganglia for the management of complex regional pain syndrome: a prospective case series. Pain Pract. 2014;15:208–16.
9. Calvillo O, Esses S, Ponder C, et al. Neuroaugmentation in the management of sacroiliac pain: report of two cases. Spine. 1998;23:1069–72.
10. Calvillo O, Racz G, Didie J, et al. Neuroaugmentation in the treatment of complex regional pain syndrome of the upper extremity. Acta Othop Belg. 1998;14:57–63.
11. Calvillo O, Madrid J, Rudomin P. Presynaptic depolarization of unmyelinated primary afferent fibers in the spinal cord of the cat. Neuroscience. 1982;7:1389–400.
12. Calvillo O, Racz G, Didie J, Smith K. Neuroaugmentation in the treatment of complex regional pain syndrome of the upper extremity. Acta Orthop Belg. 1998;64(1):57–63.
13. Cavanaugh DJ, Lee H, Lo L, et al. Distinct subsets of unmyelinated primary sensory fibers mediate behavioral responses to noxious thermal and mechanical stimuli. Proc Natl Acad Sci U S A. 2009;106:9075–80.
14. Chen R, Pan HR. Spinal GABAB receptors mediate antinociceptive actions of cholinergic agents in normal and diabetic rats. Brain Res. 2003;965:67–74.
15. Cui JG, O'Connor WT, Ungerstedt U, Linderoth B, Meyerson BA. Spinal cord stimulation attenuates augmented dorsal horn release of excitatory amino acids in mononeuropathy via a GABAergic mechanism. Pain. 1997;73:87–95.
16. De Ridder D, Vanneste S, Plazier M, et al. Burst spinal cord stimulation: toward a paresthesia-free pain suppression. Neurosurg. 2010;66:986–90.
17. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. World Neurosurg. 2013;80(5):642–9 e1.

18. Devor M. Ectopic discharges in Ab afferents as a source of neuropathic pain. Exp Brain Res. 2009;196:115–28.
19. Devor M. Unexplained peculiarities of the dorsal root ganglion. Pain. 1999;82:27–35.
20. Devor M, Obermeyer ML. Membrane differentiation in dorsal root ganglia and possible consequences for back pain. Neurosci Lett. 1984;51:341–6.
21. Devor M, Tal M. Nerve resection for the treatment of chronic neuropathic pain. Pain. 2014;155(6):1053–4.
22. Daniel CA, MacDermott AB. Low-threshold primary afferent drive onto GABAergic interneurons in the superficial dorsal horn of the mouse. J Neurosci. 2009;29:686–95.
23. Decosterd I, Woolf CJ. Spared nerve injury: animal model of persistent peripheral neuropathic pain. Pain. 2000;87:149–58.
24. Dubuison D. Effect of dorsal-column stimulation on gelatinous and marginal neurons of cat spinal cord. J Neurosurg. 1989;70:257–65.
25. Eldabe S, Raphael J, Thomson S, Manca A, de Belder M, Aggarwal R, Banks M, Brookes M, Merotra S, Adeniba R, Davies E, Taylor RS. The effectiveness and cost-effectiveness of spinal cord stimulation for refractory angina (RASCAL study): study protocol for a pilot randomized controlled trial. Trials. 2013;14:57.
26. Ephraim PL, Wegener ST, Mackenzie EJ, et al. Phantom pain, residual limb pain in amputees: results of a national survey. Arch Phys Med Rehabil. 2005;86:1910–9.
27. El-Khoury C, Hawwa N, Baliki M, et al. Attenuation of neuropathic pain by segmental and supraspinal activation of the dorsal column nuclei in awake rats. Neuroscience. 2002;112:541–53.
28. Feirabend HK, Choufoer S, Ploeger S, et al. Morphometry of human superficial dorsal root and dorsolateral column fibers: significance to cord stimulation. Brain. 2012;23(125):1137–49.
29. Franz DN, Iggo A. Dorsal root potentials and ventral root reflexes evoked by nonmyelinated fibers. Science. 1968;162:1140–2.
30. Geurts JW, Smits H, Kemler MA, Brunner F, Kessels AG, van Kleef M. Spinal cord stimulation for complex regional pain syndrome type I: a prospective cohort study with long-term follow-up. Neuromodulation. 2013;16(6):523–9.
31. Goeller E, Slavin KV. Cervical spinal cord stimulation may prevent cerebral vasospasm by modulating sympathetic activity of the superior cervical ganglion at the lower cervical spinal level. Med Hypotheses. 2009;73:410–3.
32. Guan Y. Spinal cord stimulation: neurophysiological and neurochemical mechanisms of action. Curr Pain Headache Rep. 2012;16:217–25.
33. Gybels J, Kupers R. Central and peripheral electrical stimulation of the nervous system in the treatment of chronic pain. Acta Neurochir Suppl (Wien). 1987;38:64–75.
34. Hauvast RW, DeJonste MJL, Staal MJ. Spinal cord stimulation in chronic intractable angina pectoris: a randomized, controlled efficacy study. Am Heart J. 1998;136:1114–20.
35. Hawkes CH, Fawcet D, Cooke ED. Dorsal column stimulation in multiple sclerosis: effects on bladder, leg blood flow and peptides. Appl Neurophysiol. 1981;41:62–70.
36. Heavner JE, Racz G, Diede JM. Peripheral nerve stimulation: current concepts. In: Waldman SD, Winnie AP, editors. Interventional pain management. Philadelphia: WB Saunders; 1996. p. 423–4.
37. Heavner JE, Racz G, Raj PP. Peripheral nerve stimulation: current concepts. In: Waldman SD, editor. Interventional pain management. 2nd ed. Philadelphia: W.B. Saunders Company; 2001. p. 588–92.
38. Herdege T, Fiallos-Estrade CE, Schmid W, et al. The transcription factors c-Jun, Jun-D and CREB, but not c-Fos and KROX-24 are differentially regulated in axotomized neurons following transection of the sciatic nerve. Brain Res Mol Brain Res. 1992;14:155–65.
39. Honmou O, Utzchneider DA, Rizzo MA, et al. Delayed depolarization and slow sodium currents in cutaneous afferents. J Neurophysiol. 1994;71:1627–41.
40. Holsheimer J, Wesselink WA. Computer modeling of spinal cord stimulation and its contribution to therapeutic efficacy. Spinal Cord. 1998;36:531–40.
41. Kapural L, Deer T, Yakovlev A, Bensitel T, et al. Technical aspects of spinal cord stimulation for managing chronic visceral abdominal pain: the results from a national survey. Pain Med. 2010;11:685–91.
42. Kapural L, Narouze SN, Janicki T, et al. Spinal cord stimulation is an effective treatment for chronic intractable visceral pain. Pain Med. 2006;7:440–3.
43. Kapural L, Rakic M. Spinal cord stimulation for chronic visceral pain secondary to chronic non-alcoholic pancreatitis. J Clin Gastroenterol. 2008;42:750–1.
44. Khasabov SG, Ghilardin JR, Mantyh PW, et al. Spinal neurons that express NK-1 receptors modulate descending controls that project through the dorsolateral funiculus. J Neurophysiol. 2005;93:998–1006.
45. Klein JP, Tendi EA, Dib-Hajj SD, et al. Patterned electrical activity modulates sodium channel expression in sensory neurons. J Neurosci Res. 2003;74:192–8.
46. Krames E. The dorsal root in chronic pain and as target for neuromodulation. Neuromodulation. 2015;18:24–32.
47. Kumar K, Rizvi S, Bnurs SB. Spinal cord stimulation is effective in management of complex regional pain syndrome I: fact or fiction. Neurosurgery. 2011;69(3):566–78; discussion 5578–80. doi. 10.1227/NEU.0b013e3182181e60.
48. Jeon Y, Hub BK. Spinal cord stimulation for chronic pain. Ann Acad Med Singapore. 2009;38:998–1003.
49. Jeon Huh 2009; Yakhnista V, Linderoth B, et al. Spinal cord stimulation attenuates dorsal horn hyperexcitability in a rat model of mononeuropathy. Pain. 1999;79:223–33
50. Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain. 2007;132:179–88.
51. Kumar K, Taylor RS, Jacques L, et al. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery. 2008;63:762–70.
52. Liem L, Russo M, Huygen FJ. A multicenter, prospective trial to assess the safety and performance of spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. Neuromodulation. 2013;16:471–82.
53. Lind G, Schechtmann G, Winter J, Meyerson BA, Linderoth B. Baclofen-enhanced spinal cord stimulation and intrathecal baclofen alone for neuropathic pain: Long-term outcome of a pilot study. Eur J Pain. 2008;12(1):132–6. Epub 2007 May 1.
54. Lind G, Winter J, Lindroth B, Hellstrom PM. Therapeutic value of spinal cord stimulation in irritable bowel syndrome: a randomized crossover pilot study. Am J Physiol Regul Integr Comp Physiol. 2015;308:R887–94.
55. Ling G, Linderoth B. Pharmacological enhanced spinal cord stimulation for pain: an evolving strategy. Pain Manag. 2011;1(5):441–9.
56. Meyerson B, Brodin E, Linderoth B. Possible neurohumeral mechanisms in CNS stimulation for pain suppression. Appl Neurophysiol. 1985;48:175–80.
57. Mannheimmer C, Eliasson T, Andersson B, et al. Effects of spinal cord stimulation in angina pectoris induced by pacing and possible mechanism of action. BMJ. 1993;307:477–80.
58. Mekhail NA, Mathews M, Nageeb F, et al. Clinical applications of neurostimulation: forty years later. Pain Pract. 2010;10:103–12.

59. Mendell LM, Wall PD. Presynaptic hyperpolarization: a role for fine afferent fibres. The Journal of Physiology. 1964;172(2):274–94.
60. Meyerson BA, Linderoth B. Mode of action of spinal cord stimulation in neuropathic pain. J Pain Symptom Manage. 2006;31(4 Suppl):S6–12.
61. Leveque JC, Villavicencio AT, Bulsara KR, et al. Spinal cord stimulation for failed back surgery syndrome. Neuromodulation. 2001;4:1–9.
62. Levin BE, Hubschmann OR. Dorsal column stimulation: effect on human cerebrospinal fluid and plasma catecholamine. Neurology. 1980;30:65–70.
63. Lind G, Schechtmann G, Winter J, et al. Drug-enhanced spinal stimulation for pain: a new strategy. Acta Neurochir Suppl. 2007;97:57–63.
64. Linderoth B, Gazelius B, Frank J, et al. Dorsal column stimulation induces release of serotonin and substance P in the cat dorsal horn. Neurosurgery. 1992;31:1289–96.
65. Ming GL, Henley J, Tessier-Lavigne M, et al. Electrical modulates growth cone guidance by diffusible factors. Neuron. 2001;29:441–52.
66. Mironer YE, Hutcheson JK, Satterwaite JR, et al. Prospective, two part study of the interaction between spinal cord stimulation and peripheral field stimulation in patients with low back pain: development of anew spinal-peripheral neurostimulation method. Neuromodulation. 2011;14:151–4.
67. North RB, Kidd DH, Farrokhi F, et al. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. Neurosurgery. 2005;56:98–106.
68. Oakley JC, Prager JP. Spinal cord stimulation: mechanism of action. Spine. 1976;2002:2574–83.
69. Oakley JC, Prager JP. Spinal cord stimulation: mechanism of action. Spine. 2002;1976:2574–83.
70. Prasad A, Sahin M. Characterization of neural activity recorded from the descending tracts of the rat spinal cord. Frontiers in Neuroscience. 2010;4:21. doi:10.3389/fnins.2010.00021.
71. Perruchoud C, Eldabe S, Batterham AM, Madzinga G, Brookes M, Durrer A, Rosato M, Bovet N, West S, Bovy M, Rutschmann B, Gulve A, Garner F, Buchser E. Analgesic efficacy of high-frequency spinal cord stimulation: a randomized double-blind placebo-controlled study. Neuromodulation. 2013;16(4):363–9.
72. Racz GB, McCarron RF, Tallboys P. Percutaneous dorsal column stimulator for chronic back pain. Spine. 1989;14:1–4.
73. Raslan AM, McCartney S, Burchiel KJ. Management of chronic severe pain: spinal neuromodulatory and neuroablative approaches. Acta Neurochir Suppl. 2007;97(Pt 1):33–41.
74. Rees H, Roberts MH. Activation of cells in the anterior pretectal nucleus by dorsal column stimulation in the rat. J Physiol. 1989;417:361–73.
75. Ren B, Linderoth B, Meyerson BA. Effects of spinal cord stimulation on the flexor reflex and involvement of supraspinal mechanisms: an experimental study in mononeuropathic rats. J Neurosurg. 1996;84:244–9.
76. Rigoard P, Desai MJ, North RB, Taylor RS, Annemans L, Greening C, Tan Y, Van den Abeele C, Shipley J, Kumar K. Spinal cord stimulation for predominant low back pain in failed back surgery syndrome: study protocol for an international multicenter randomized controlled trial (PROMISE study). Trials. 2013;14:376.
77. Parker JL, Karantonis DM, Single PS, et al. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. Pain. 2012;153:593–601.
78. Saade NE, Tabet MS, Soueidan SA, Bitar M, et al. Supraspinal modulation of nociception in awake rats by stimulation of the dorsal column nuclei. Brain Res. 1986;369:307–10.
79. Sadee N, Barchini J, Tchahahian S, et al. The role of the dorsolateral funiculi in the pain relieving effect of spinal cord stimulation: a study in a rat model of neuropathic pain. Exp Brain Res. 2015;233:1041–52.
80. Saade N, Atweh AF, Tabet MS, et al. Inhibition of nociceptive withdrawal flexion reflexes through a dorsal column-brainstem spinal loop. Brain Res. 1985;335:306–8.
81. Sapunar D, Kostic S, Banozic A, et al. Dorsal root ganglion-a potential new therapeutic target for neuropathic pain. J Pain Res. 2012;5:31–8.
82. Sapunar D, Ljubkovic M, Lirk P, et al. Distinct membrane effects of spinal nerve ligation on injured and adjacent dorsal root ganglion neurons in rats. Anesthesiology. 2005;103(2):360–76.
83. Schechtmann G, Lind G, Winter J, et al. Intrathecal clonidine and baclofen enhance the pain-relieving effect of spinal cord stimulation: a comparative placebo-controlled randomized trial. Neurosurgery. 2010;67:173–81.
84. Schechtmann G, Lind G, Winter J, et al. Cholinergic mechanisms involved in the pain relieving effect of spinal cord stimulation in a model of neuropathy. Pain. 2008;139:136–45.
85. Schoffingger D, Heinke B, Sommer C, et al. Physiological properties of spinal lamina II GABAergic neurons in mice following peripheral nerve injury. J Physiol. 2006;577:869–78.
86. Schu S, Slotty PJ, Bara G, von Knop M, Edgar D, Vesper J. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. Neuromodulation. 2014;17(5):443–50.
87. Schu S, Gulve A, Dave EL, et al. Spinal cord stimulation for groin pain-a retrospective review. Pain Pract. 2015;15:293–9.
88. Schecter R, Yang F, Xu Q, Young-Kuan C, et al. Conventional and kilohertz-frequency spinal cord stimulation produces intensity and frequency-dependent inhibition of mechanical hypersensitivity in a rat model of neuropathic pain. Anesthesiology. 2013;119:422–32.
89. Schultz DM, Webster L, Kosec P, et al. Sensor-driven position-adaptive spinal cord stimulation for chronic pain. Pain Physician. 2012;15:1–12.
90. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Anal. 1967;46:489–91.
91. Shetter AG, Racz GB, Lewis R, Heavner JE. Peripheral nerve stimulation. In: North R, Levy R, editors. Neurosurgical management of pain. New York: Springer; 1997. p. 261–70.
92. Silberstein SD, Dodick DW, Saper J, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia. 2012;32:1165–79.
93. Sisken BF, Walker J, Orgel M. Prospects on clinical applications of electrical stimulation for nerve regeneration. J Cell Biochem. 1993;51:404–9.
94. Skaribas I, Calvillo O, Delikanis-Skaribas E. Occipital peripheral nerve stimulation in the management of chronic intractable occipital neuralgia with neurofibromatosis type 1: a case report. J Med Case Reports. 2011;5:174–6.
95. Slavin KV, Vannemreddy PS, Goellner E, et al. Use of cervical spinal cord stimulation in treatment and prevention of arterial vasospasm after aneurysmal hemorrhage. Neuroradiol J. 2011;1:139–43.
96. Slavin K. Spinal stimulation for pain: future applications. Neurotherapeutics. 2014;11:535–42.
97. Song Z, Ansah OB, Meyerson BA, et al. Exploration of supraspinal mechanisms in effects of spinal cord stimulation: role of the locus coeruleus. Neuroscience. 2013;253:426–34.
98. Song Z, Ultenius C, Meyerson BA, et al. Pain relief by spinal cord stimulation involves serotonergic mechanisms: an experimental study in a rat model of mononeuropathy. Pain. 2009;147:241–8.

99. Song Z, Meyerson BA, Linderoth B. Spinal 5-HT receptors that contribute to the pain-relieving effects of spinal cord stimulation in a rat model of neuropathy. Pain. 2011;152:1666–73.
100. Song Z, Meyerson BA, Linderoth B. Muscarinic receptor activation potentiates the effect of spinal cord stimulation on pain-related behavior in rats with mononeuropathy. Neurosci Lett. 2008;436:7–12.
101. Simpson RK, Robertson CS, Goodman C. Glycine: a potential mediator of electrically induced pain modification. Biomed Lett. 1993;48:193–207.
102. Simpson RK, Gondo M, Robertson CS, et al. Reduction in the mechanoreceptor response by intrathecal administration of glycine and related compounds. Neurochem Res. 1996;21: 1221–6.
103. Slangen R, Schaper NC, Faber CG, Joosten EA, Dirksen CD, van Dongen RT, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care. 2014;37(11):3016–24.
104. Stiller CO, Cui JG, O'Connor WT, et al. Release of gamma-aminobutyric acid in the dorsal horn and suppression of tactile allodynia by spinal cord stimulation in mononeuropathic rats. Neurosurgery. 1996;39:367–74.
105. Sukhotinsky I, Ben-Dor E, Raver P, et al. Key role of the dorsal root ganglion in neuropathic tactile hypersensibility. Eur J Pain. 2004;8:135–43.
106. Tiede J, Brown L, Gekht G, et al. Novel spinal cord stimulation parameters in patients with predominantly back pain. Neuromodulation. 2013;16:370–5.
107. Tomycz ND, Deibert CP, Moossy JJ. Cervicomedullary junction spinal cord stimulation for head and facial pain. Headache. 2011;51:418–25.
108. Torre-Amione G, Alo K, Estep JD, Valderrabano M, Khalil N, Farazi TG, et al. Spinal cord stimulation is safe and feasible in patients with advanced heart failure: early clinical experience. Eur J Heart Fail. 2014;16(7):788–95.
109. Van Buyten JP, Al-Kaiisy A, Palmisani S, et al. High frequency spinal cord stimulation for the treatment of chronic back pain: results of a prospective multicenter European clinical study. Neuromodulation. 2013;16:59–66.
110. Van Ejis F, Stanton-Hicks M, Van Zundert J, et al. Evidence-based interventional pain medicine according to clinical diagnosis. 16 complex regional pain syndrome. Pain Pract. 2011;11:70–87.
111. Vaso A, Haim-Moshe A, Gjika A, Zahaj S, Zhurda T, Vyshka G, et al. Peripheral nervous system origin of phantom limb pain. Pain. 2014;155(7):1384–91.
112. Viswanathan A, Phan PC, Burton AW. Use of spinal cord stimulation in the treatment in the treatment of phantom limb pain: case series and review of the literature. Pain Pract. 2010;10(5): 479–84.
113. Washburn S, Catlin R, Bethel K, Canlas B. Patient-perceived differences between constant current and constant voltage spinal cord stimulation systems. Neuromodulation. 2014;17(1):28–35.
114. Watkins LR, Milligan ED, Maier SF. Glial activation: a driving force for pathological pain. Trends Neurosci. 2001;24:450–5.
115. Watson CP, Peter CN, Mackinnon SE, Dostrovsky JO, Jonathan O, Bennett GJ, et al. Nerve resection, crush and re-location relieve complex regional pain syndrome type II: a case report. Pain. 2014;155(6):1168–73.
116. Wang YY, Wu SX, Wang W, et al. Effects of c-fos antisense oligodeoxynucleotide on 5HT-induced upregulation of preprodynorphin, proenkephalin and glutamic acid decarboxylase mRNA expression in cultured rat spinal dorsal horn neurons. Biochem Biophys Res Commun. 2003;309:631–6.
117. Weiner RL, Reed KL. Peripheral neurostimulation for control of intractable occipital neuralgia. Neuromodulation. 1999;3:217–21.
118. Wolter T, Kieselbach K. Spinal cord stimulation for Raynaud's syndrome: long-term alleviation of bilateral pain with a single cervical lead. Neuromodulation. 2011;14:229–33.
119. Wu G, Ringkamp M, Murrison BB. Degeneration of myelinated afferent fibers induces spontaneous activity in uninjured C-fiber afferents. J Neurosci. 2002;22:7746–53.
120. Xiao HS, Huang QH, Zhang FX. Identification gene expression profile of dorsal root in the rat peripheral axotomy model of neuropathic pain. Proc Natl Acad Sci U S A. 2002;99:8360–5.
121. Zuo C, Yang X, Wang Y, et al. A digital wireless system for closed-loop inhibition of nociceptive signals. J Neural Eng. 2012; 9:056010.
122. Zimmermann M. Dorsal root potentials after C fiber stimulation. Science. 1968;160:896–8.
123. Zipes DP, Svorkdal N, Berman D, Boortz-Marx R, Henry T, Lerman A, Irwin C. Spinal cord stimulation therapy for patients with refractory angina who are not candidates for revascularization. Neuromodulation. 2012;15(6):550–8.

High-Frequency Stimulation: A Novel Strategy in Waveform Applications

10

Jason E. Pope and Timothy R. Deer

Introduction

Spinal cord stimulation (SCS) has undergone a renaissance recently, shifting from hardware improvements to software enhancement, including efforts to improve the deficiencies of traditional tonic spinal cord stimulation [1, 2, 3]. Namely, these conventional strategies center on the need for perceived therapeutic stimulation and include positionality of the therapy and inability to cover discrete anatomical areas.

Currently, in the United States, tonic spinal cord stimulation (SCS or tSCS) is the most popularly offered neuromodulation therapy and is FDA approved. Recently, high-frequency stimulation utilizing 10,000 Hz (HF10) was formally introduced at a national meeting, echoing the results of the European experience and suggesting a potential upcoming change in the pain care algorithm [4–7]. Clinically, this new innovation may offer the ability for paresthesia-free stimulation.

History

Spinal cord stimulation is dependent on Ohm's law, and the delivery of electrical energy to affect a change on the spinal cord by cathodal stimulation. This is typically performed by applying either a constant current or constant voltage system. These systems create a perceived paresthesia, often described as a buzzing and/or tingling sensation. Importantly, for traditional spinal cord stimulation to be therapeutic, it needs to be placed overlying the typical painful area describing coverage, it needs to provide pain reduction, and it needs to be tolerated (or enjoyed) by the patient. This inherently creates challenges. First, coverage can be perceived as poor, either by too much or not discrete enough. Second, as perception is dependent on amplitude and distance of the cathode from the neural target, creating positionality that may be burdensome. Currently, off-label strategies are employed to capture the back, by creating hybrid systems using peripheral nerve field stimulation (PNfS) leads in conjunction with epidural SCS leads [8].

Regardless of power for the circuit, both constant current and constant voltage systems describe tonic spinal cord stimulation (tSCS), functioning near 40 Hz. Alternatively, high-frequency stimulation, as the name suggests, functions at a much higher frequency than typical tSCS. Although currently ill defined, high-frequency stimulation is generally accepted to be >500 Hz (Fig. 10.1).

Technical Aspects and Equipment

It is important to note that the mechanism of action of HF-10 and tSCS is distinctly different. The gate control theory proposed by Melzak and Wall describes that stimulation of low-threshold A-beta fibers within the dorsal horn inhibits the propagation of the information from nociceptive c, a-delta, and wide dynamic range neurons (WDR) [8–12]. It has been theorized that high frequency at 10 kHz may also impact both antidromic and orthodromic pathways, but the mechanism of action is currently not well defined. HF10 may suppress hypersensitized wide dynamic range (WDR) neurons [13].

The only HF10 is currently under investigation in the United States and is not FDA approved. The HF10 system or SENZA® is made by NEVRO (Menlo Park, CA) and includes an implantable pulse generator (IPG) and eight-contact cylindrical leads (Fig. 10.2). No paddles are currently available.

Unlike tSCS that requires paresthesia mapping, as defined by Borolat [15], HF10 lead placement does not.

J.E. Pope, MD, DABPM, FIPP
Summit Pain Alliance, 392 Tesconi Court, Santa Rosa, CA 95401, USA
e-mail: popeje@me.com

T.R. Deer, MD (✉)
The Center for Pain Relief, Inc.,
400 Court Street, Suite 100, Charleston, WV 25301, USA
e-mail: mmiller@centerforpainrelief.com

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_10

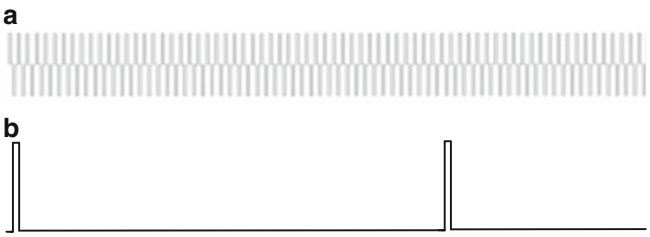


Fig. 10.1 Stimulation strategies: high frequency 10,000 Hz (**a**), tonic stimulation 40 Hz (**b**)

Fig. 10.2 The SENZA system by NEVRO [14]

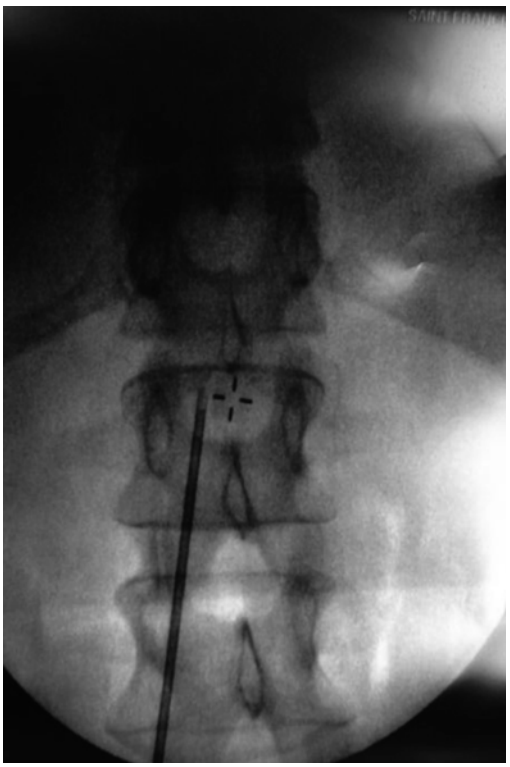


Fig. 10.3 Needle placement within the epidural space, T12-L1, left paramedian, after squaring off inferior endplate of L1 and with slight ipsilateral tilt

Techniques

Placement of the HF10 trialing system and the permanent HF10 therapy is very similar to percutaneous lead placement with tSCS. Adequate training and procedure optimization, as defined by the recent NACC guidelines, is paramount [16].

After informed consent and appropriate preoperative preparation and counseling, the patient is positioned prone on the fluoroscopy table. Standard sterile prep and drape is performed. It is preferred that little to no anesthesia be given intravenously. Adequate preoperative antibiotics are given within 30 min of incision. After squaring off the inferior endplate of the L1 vertebral body, and with a very slight ipsilateral tilt, the target interlaminar space is marked, as is a distance approximately near the caudal border of the L2 vertebral body, just outside of the pedicular line. A skin wheal is created with local anesthetic and then a stab incision is created. The 14-gauge introducer needle is then advanced under fluoroscopic guidance until contact is made of the L1 lamina, ipsilateral to the needle entry. It is then walked cephalad and into the L1–L2 interlaminar space. Entry into the epidural space is performed using the traditional loss of resistance (LOR) (see Fig. 10.3). A second needle is placed just cephalad of the existing needle, same interlaminar space.

The leads are then introduced while the patient is conversant within the posterior epidural space. A lateral view should be performed to ensure appropriate lead placement. Once posterior placement within the epidural space is confirmed, the lead(s) is (are) then advanced to the target location most cephalad of T7–T9, placed in the midline. No paresthesia testing needs to be performed (Fig. 10.4).

The needles are removed and then secured using nonabsorbable suture. A sterile dressing is placed, and the patient is followed as an outpatient for up to a week, with strict precautions to keep the area dry, to take postoperative antibiotics, and to perform typically pain-provoking activities.

For the permanent therapy, the procedure is exactly the same, with the difference of marking the incision line, typically in the sagittal place, from the entry site to approximately the superior border of the L2 vertebral body. The dissection is then performed to the lumbodorsal fascia, with an appropriate lateral dissection to accommodate the hardware and stress relief loops of the leads. The IPG location is then marked, typically on the ipsilateral side, equidistant from the 12th rib and the iliac crest. Once the dissections are completed and hemostasis is achieved, the leads are then placed as aforementioned during the trial procedure. Once the leads are in place and secured, a tunneling device is employed to tunnel

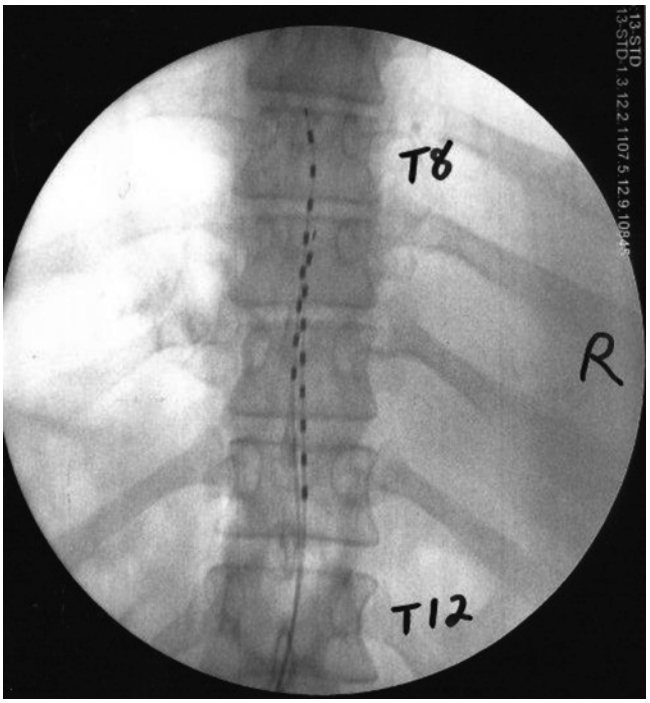


Fig. 10.4 Lead placement spanning T8-11, midline position [17]

from the flank incision to the paraspinal incision. The leads are then pulled though, connected to the IPG, and tightened. Circuitry testing is performed, both incisions are then copiously irrigated with NS, and then the IPG is internalized and the incisions are closed using a two-layered closing technique, followed by steri-strips (Fig. 10.5). Sterile dressings are applied, along with an abdominal binder.

Outcome Data

For purposes of dissection of the evidence, HF10 will be used to describe high-frequency stimulation at 10,000 Hz. HF5 will be used to describe high-frequency stimulation at 5,000 Hz. As the data [3–6] and recent reviews suggest [1, 2], there appears to be a therapeutic difference between HF10 and HF5. They will be discussed separately.

HF10

HF10 stimulation has undergone impressive study. It has been evaluated in the most rigorous, prospective, randomized, comparative trial in spinal cord stimulation history. Although at the time of this writing it has been formally published, it was presented at the North American Neuromodulation Society Annual meeting in December 2014. Dr. Leo Kapural presented the data from the US pivotal trial that demonstrated statistical superiority for HF10 as compared to traditional SCS to treat both back and leg pain

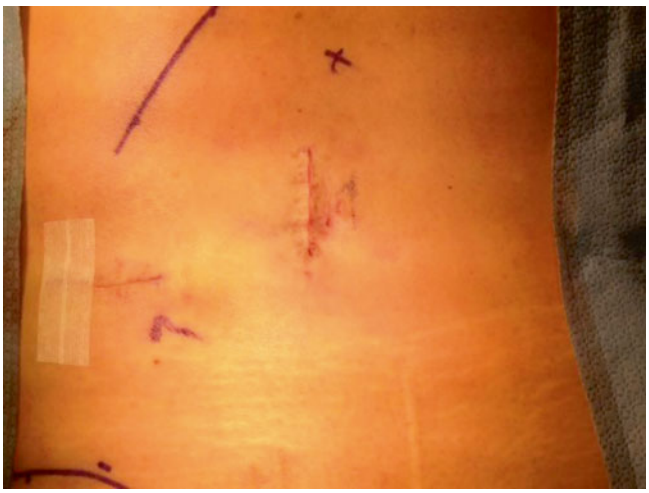


Fig. 10.5 Incisions following closure, while placing steri-strips

[6]. Furthermore, it mirrors the data from Europe [3, 4] and the investigation in the United States [5] (Table 10.1).

The European experience suggests HF10 is better than tSCS in the treatment of back and leg pain, both at 6 months and at 24 months [3, 4]. At 6 months, the average back pain VAS was 2.7 from 8.4, while leg VAS was 1.4 from 5.4. At 24 months, mean back VAS was 3.3 from 8.4, and leg VAS was 2.3 from 5.4 [4]. Further, improvements were seen in disability scores, sleep improvements, and opioid reduction [3]. In the US study, the responder rate, as defined by a greater than 50 % reduction in the visual analog scale (VAS), was greater for HF10 as compared to tSCS (83 % vs 58 %). Eighty eight percent of the patients trialed preferred HF10 over tSCS [5]. This is in stark contrast to the experience with HF5 (Table 10.2).

HF5

Perruchound et al. investigated HF5 in patients with successful tSCS and randomized them to either HF5 or sham [18], with a tSCS washout, then a cross over, with all phases lasting 2 weeks. The primary outcome was a minimal improvement in the patient's global impression of change (PGIC). Secondary measures were pain relief, as measured by the VAS and quality of life, as measured by the EuroQol questionnaire EQ-5D. No measures were statistically different for the HF5 as compared to placebo.

Complications

Not surprisingly, complications associated with HF10 are similar to that of tSCS. In the aforementioned studies, the most common challenge was lead migration. Similar management and troubleshooting should be performed, as it would be for tSCS, as innately, hardware is placed within the

Table 10.1 HF10 Stimulation studies identified

Study	Methodology	Participants	Intervention	Conclusion(s)	Complications
Van Buyten et al. [3]	PO	83 patients with axial back and leg pain	HF10 delivered via two eight-contact leads, 6 mo f/u	HF10 improved back and leg pain in 70 % of patients	Complications similar to tSCS
Al-Kaisy et al. [4]	PO	82 patients with axial low back pain underwent with HF10	HF10	HF10 improved low back pain, sleep, reduced opioid use, and achieved a high degree of patient satisfaction	Complications similar to tSCS
Tiede et al. [5]	PO	24 patients with axial back > leg pain; 5 UC centers	Percutaneous trial for 4 days with tonic SCS and HF10	HF10 improved back pain more so than tSCS	None reported

RCT randomized controlled trial, *PO* prospective, observational, *HF10*: 10,000 Hertz Spinal Cord Stimulation, *SCS* spinal cord stimulation, *tSCS* traditional (tonic) SCS

Table 10.2 HF5 Studies identified

Study	Methodology	Participants	Intervention	Conclusion(s)	Complications
Perruchound et al. [18]	RCT	40 with tSCS with success achieved; randomized to sham vs HF5	Sham vs HF5	HF5 was equal to sham for the primary outcomes of global impression of change, pain, and quality of life	None reported

RCT randomized controlled trial, *PO* prospective, observational, *HF5 5,000* Hertz Spinal Cord Stimulation; *SCS*: spinal cord stimulation, *tSCS* traditional (tonic) SCS

epidural space. Of note, the animal studies suggest no histologic challenges with HF10 on the spinal cord and no study reported neurologic deficits from HF10 [3, 4, 6, 19].

Conclusion and Discussion

HF10 is an exciting new facet of neuromodulation to explore. This may offer advantages over tonic stimulation, as it appears to be superior for axial back and leg coverage in a soon-to-be-published pivotal, landmark RCT [kapural], may mitigate the need for discrete therapeutic paresthesia coverage, and eliminates positionality challenges. Notwithstanding, although HF10 demonstrated superiority to tSCS, an important takeaway is that tSCS was successful in treating both back and leg pain. The placement of HF10 within the pain care algorithm will continue to evolve as more studies are performed.

References

1. Pope JE, Deer TR, Amirdelfan K, Kapural L, Verrills P. New concepts for waveform and current delivery for spinal cord stimulation: burst and high frequency. Minimally invasive surgery for pain. 2015 Vol 3. http://southernacademicpress.com/misp-vol-3/.
2. Pope JE, Falowski S, Deer TR. Advanced waveforms and frequency with spinal cord stimulation: burst and high frequency energy delivery. Expert review of medical devices. 2015;12(4):431–7.
3. Mironer E et al. Prospective, two-part study of the interaction between spinal cord stimulation and peripheral nerve field stimulation in patients with low back pain: development of a new spinal-peripheral neurostimulation method. Neuromodulation: Technol Neural Interface. 2011;14(2):151–5.
4. Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High frequency spinal cord stimulation fo the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. Neuromodulation. 2013;16(1):59–65.
5. Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz High Frequency Spinal Cord Stimulation for Patients with Chronic, Low Back Pain: 24-Month Results of a Prospective Multicenter Study. Pain Med. 2014;15:347–54.
6. Tiede J, Brown L, Gekht G, Vallejo R, Yearwood T, Morgan D. Novel spinal cord stimulation parameters in patients with predominant back pain. Neuromodulation. 2013;16(4):370–5.
7. Kapural L et al. SENZA-RCT pivotal study, a prospective randomized controlled pivotal study. Las Vegas: NANS Presentation; 2014.
8. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971–9.
9. Roberts MHT, Rees H. Physiological basis of spinal cord stimulation. Pain Rev. 1994;1:184–98.
10. Linderoth B, Foreman RD. Physiology of spinal cord stimulation: review and update. Neuromodulation. 1999;2:150–64.
11. Oakley J, Prager J. Spinal cord stimulation: mechanism of action. Spine. 2002;27(22):2574–83.
12. Barchini J, Tchachaghian S, Shamaa F, Jabbur SJ, Meyerson BA, Song Z, et al. Spinal segmental and supraspinal mechanisms underlying the pain-relieving effects of spinal cord stimulation: an experimental study in a rat model of neuropathy. Neuroscience. 2012;215:196–208.
13. Cuellar JM, Alataris K, Walker A, Yeomans DC, Antognini JF. Effect of High-Frequency Alternating Current on Spinal Afferent Nociceptive Transmission. Neuromodulation. 2013;16:318–27. doi:10.1111/ner.12015.

14. http://www.nevro.com.
15. Borolat G, Massoro F, He J, Zeme S, Ketcik B. Mapping o sensory responses to epidural stimulation of the intraspinal neural structures in man. J Neurosurg. 1993;78:233–9.
16. Deer TR, Mekhail N, Provenzano D, Pope J, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. Neuromodulation. 2014;17(6):515–50; discussion 550.
17. Image courtesy of NEVRO.
18. Perruchound C, Eldabe S, Batterham AM, Madzinga G, et al. Analgesia efficacy of high frequency spinal cord stimulation: a randomized, double blind placebo controlled study. Neuromodulation. 2013;16(4):363–9.
19. Saade NE, Jabbur SJ. Nociceptive behavior in animal models for peripheral neuropathy: spinal and supraspinal mechanisms. Prog Neurobiol. 2008;86:22–47.

Interventional Peripheral Nerve Therapies for Chronic Head Pain

11

Ken Reed

Introduction

Chronic head pain, a common malady presenting to interventional specialists, remains a burden to the patients and society. Migraine alone afflicts at least 4 % of the population and dramatically impacts function in terms of lost school and workdays [1]. The past two decades have witnessed a marked shift in clinical attention to considerations of various interventional modes of therapy for severe, intractable cases, including most notably specific techniques for neural decompression and implantable neuromodulation.

Neural Decompression

Neural decompression for chronic head pain historically has centered most prominently on the occipital nerve, where the techniques may be generally divided into injection methods and open surgical techniques of release. With respect to injection therapies, the validity of simple blockade of the greater occipital nerve (GON), a well-accepted and commonly practiced procedure in interventional practices, has been extensively documented. Notably, in 1992 Anthony reported positive results in a series of 500 headache patients treated with GON blockade [2]. However, evolving from simple perineural injection of the GON came specific injection decompression techniques, which were developed and reported by Racz et al. [3]. His team, observing C1 compression in the suboccipital compartment (SOC) in some patients with occipital headaches, demonstrated significant efficacy by injection decompression per a fluoroscopically guided stealth needle directed toward the C1 arch. Previously, Heavner and Racz had demonstrated improved safety of blunt over sharp needles for these techniques in elegant animal studies [4]. In 2013 Lauretti further validated Racz's SOC technique by demonstrating an average of 24 weeks of analgesia when patients with cervicogenic headaches were treated with SOC injections, as opposed to only 2 weeks by classical GON injections. Taken together, these reports provide persuasive therapeutic and safety evidence for clinicians revising the traditional GON injection method to the Racz SOC stealth needle technique.

Open surgical decompression of the peripheral nerves of the head has historically most commonly been applied to the GON [5, 6]. The success and safety profiles have varied widely in the limited reports available, but overall the clinical outcomes for surgical decompressions limited to single nerves have proven disappointing, such that it should only be considered in severe, debilitating neuropathic pain that has proven refractory to all other modes of therapy. More recently, interest has shifted to surgical decompression of multiple trigger points as described by Guyuron and supported by others [7]. While there is a progressively increasing evidence base here supporting improved efficacy and safety over the previous techniques, the procedure has yet to receive adequate independent validation, and given its open surgical nature, should still be considered only after failure of more conservative measures.

In conclusion, all interventionalists, when faced with patients suffering from intractable occipital pain, should consider the Racz technique of percutaneous stealth needle SOC decompression. For those patients that continue to prove refractory, then occipital nerve stimulation (ONS) or other implanted peripheral nerve stimulation (PNS) should be considered, before other more invasive, risky techniques such as open surgical decompression or deep brain stimulation (DBS).

Implantable Neuromodulation

History

Following our initial report in 1999 on ONS treatment for refractory occipital neuralgia (ON) [8], the development of PNS for head pain proceeded along two general diagnostic

K. Reed, MD
Interventional Pain Management, Reed Migraine Center, Dallas, TX, USA
e-mail: klreed1@swbell.net

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_11

avenues: certain cephalic neuralgias (occipital neuralgia and certain trigeminal neuralgias) and the distinct, more general primary headache syndromes. Regarding the cephalic neuralgias, numerous subsequent investigators supported our initial findings for occipital neuralgia [9–13], while others successfully extended this treatment methodology to the frontal region and various trigeminal neuralgias [14–16].

As the evidence base for PNS in the treatment of cephalic neuralgias increased, attention shifted to its potential in treating primary headaches. In 2003, Popeney and Alo observed strongly positive responses in a series of patients with transformed migraine headaches [17], and Dodick observed a similar response in a patient with cluster headaches [18]. Subsequent investigations reported that various headache syndromes responded variably to ONS with the majority of studies involving three general diagnostic categories: occipitocervical headaches [10, 14, 19, 20], cluster headaches [21–27], and chronic migraines [13, 28–30]. While summaries of these studies reveal a consistently high (average 88 %) response rate for occipital neuralgia and cervicogenic headaches, they indicate only roughly a 40–50 % rate for primary migraines and cluster headaches (Tables 11.1 and 11.2), which suggests that a substantial subset of patients with these types of primary headaches may indeed not respond to ONS.

The reason for this disparity in results of ONS for occipital vs. frontal pain likely relates to paresthesia concordancy, where a concordant paresthesia is one that generally covers the area of perceived pain and is taken to indicate that the appropriate portion of the nervous system is being stimulated. For example, during an SCS implant in a patient with low back and left leg pain, the implanting physician will seek as best as possible to have the induced paresthesia cover the low back and left leg. Similarly, for intractable occipital neuralgia, ONS will provide for a concordant occipital paresthesia. However, when ONS is applied to frontotemporal pain due to migraine and cluster headaches, the result is a non-concordant paresthesia.

From this standpoint, Dodick's 2003 report on cluster headache responding to a non-concordant occipital paresthesia represented a paradigm shift from the traditional approach to neurostimulation and pain. Over the decades the vast bulk of investigational work on neurostimulation and pain involved spinal cord stimulation for back and extremity pain, and throughout this period the clinical approach has always been to produce a paresthesia over the part of the body that hurt, which indicated that the correct portion of the nervous system was being stimulated. Even the reports of salutary effects from spinal cord stimulation for such pain problems as intractable angina and abdominal visceral pain still have the paresthesia covering the related anatomic areas of pain (e.g., a precordial paresthesia was found to be best for angina) [31, 32]. Indeed, prior to 2003, there is no reasonable evidence, regardless of anatomic location, that neurostimulation reliably eased pain that was significantly outside of the area of paresthesia. The departure thus came with head pain where in 2003 investigators began evaluating the response of the frontotemporal pain of migraine and cluster headaches to an occipital paresthesia [17, 18]. The shift in the paradigm was that we went from treating pain with neurostimulation based on producing an anatomically concordant paresthesia, irrespective of diagnosis, to treating pain with neurostimulation based on diagnostic categories (e.g., migraines, cluster headaches), irrespective of paresthesia coverage. Therefore, the application of ONS to occipitally focused headaches was fully consistent with the traditional method, as ONS produced a paresthesia localized to the painful area (occiput), with resultant high reported response rates (Table 11.1). On the other hand, the application of ONS to migraine and cluster headaches departed from this standard, as the pain over the frontotemporal regions was being treated with a distant paresthesia localized solely to the occiput (no frontotemporal paresthesia is produced by ONS), and the response rates were correspondingly lower (Table 11.2).

Method

Patient Selection and Planning

In general a patient is considered a candidate for evaluation for a PNS if they have severe, chronic headaches that have failed to respond to an extended course of more conservative measures. While there are no strict criteria for candidacy, reasonable guidelines include:

- Chronic, debilitating headaches
- Failed extended course (>3–6 months) of more conservative management under an experienced headache specialist
- Passed psychological prescreening
- Either on no, or minimal and stable doses of, narcotics

Issues that generally do not affect candidacy include:

- Headache diagnosis. PNS has been studied and found effective in various types of headaches including migraine, cluster, hemicranias continua, chronic daily headache, transformed migraine, tension-type headaches, occipital neuralgia, post-traumatic headaches, and cervicogenic headaches, among others.
- Gender
- Age. Our implanted group's ages range from 14 to 72 and include over 30 adolescents.

Planning for the upcoming stimulator involves the determination of how many leads to implant and where to implant them. Following the guideline of always seeking paresthesia

Table 11.1 Summary of patients treated with concordant neurostimulation

Report	Dx	No perm	Resp rate	Notes
Occipital neuropathic pain treated with ONS alone				
Weiner and Reed [8]	ON	13	80 %	80 % had good to excellent relief
Rodrigo-Royo et al. [20]	ON	4	100 %	97 % avg decrease in VAS
Kapural et al. [11]	CEH	6	100 %	70 % avg decrease in VAS
Slavin et al. [36]	ON	10	70 %	All had excellent pain relief at 6 months
Johnstone and Sundaraj [12]	ON	7	71 %	73 % avg decrease in VAS
Melvin et al. [19]	ON	11	100 %	73 % rated relief as good to excellent
Shaldi et al. [37]	ON	8	88 %	71 % avg decrease VAS
Magown et al. [38]	ON	7	100 %	6 had 75–100 % improvement
Vadivelu et al. [39]	AC	15	87 %	All had over 50 % improvement
Pameliere et al. [40]	NC	8	100 %	80 % avg relief
Oh et al. [10]	ON	10	100 %	All had 90–100 % relief
			89 % avg	
Trigeminal neuropathic pain treated with trigeminal stim alone				
Dunteman [41]	PHN	1	100 %	SON
Johnson and Burchiel [15]	TNP	10	70 %	I SON; 2 ION
Slavin et al. [14]	TNP	7	82 %	4 SON; 3 ION
Amin et al. [16]	SON	10	100 %	SON
Yakovlev and Resch [42]	AFP	2	100 %	Subcu octrodes over mandible
Stidd et al. [43]	TNP	3	100 %	1 SON; 2 SON-ION
			88 % avg	
Occipitally-focused migraine headaches treated with ONS alone				
Popeney and Alo [17]	TM	25	100 %	100 % responded
Oh et al. [10]	TM	10	90 %	90 % had >75 % imp at 3–6 months
Matharu et al. [13]	CM	8	100 %	100 % had good to excellent relief
			98 % avg	
Frontal (cluster) headaches treated with trigeminal stim alone				
Narouze and Kapural [44]	Cl	1	100 %	SON stim
Vaisman et al. [45]	Cl	5	100 %	SON stim
Simopoulos et al. [46]	CM	1	100 %	ATN stim
			100 % avg	
Hemicephalic/global (chronic migraine headaches) treated with combined stim				
Reed et al. [47]	CM	7	100 %	ON-SON stim
Deshpande and Wininger [48]	CM	1	100 %	ON-ATN stim
Mammis et al. [49]	Cl	1	100 %	ON-SON-ION stim
Reed et al. [50]	CM	44	87 %	ON-SON stim
			89 % avg	
Summary: *93 % average response rate for all studies*				

Notes

1. *ON* occipital neuralgia, *TM* transformed migraine, *CEH* cervicogenic headaches, *Dx* diagnosis, *IC2H* intractable C-2 headaches, *AC* Arnold-Chiari, *CM* chronic migraine, *ATN* auriculotemporal nerve, *ION* infraorbital nerve, *SON* supraorbital nerve
2. Unless otherwise specified all success rates indicate >50 % improvement in VAS or HA freq

Table 11.2 Summary of patients treated with non-concordant neurostimulation

Report	Dx	No perm	Resp rate	Notes
Cluster treated with ONS alone				
Dodick [18]	Cl	1	100 %	HA free after 12 months
Burns et al. [24]	Cl, HC	20	45 %	9 of 20 had >50 % imp
Magis and Schoenen [51]	Cl	14	85 %	80 % had >90 % imp
Trentman et al. [52]	Cl	5	60 %	3 had fair to exc resp
Schwedt et al. [22]	Cl	8	60 %	60 % had >50 % imp
de Quintana et al. [53]	Cl	4	100 %	All had >50 % imp
Fontaine et al. [54]	Cl	13	77 %	77 % had >50 % imp
Mueller et al. [55]	Cl	10	40 %	All had >50 % imp in freq/sev
			62 % avg	
Chronic migraine treated with ONS alone				
Saper (Medtronic) et al. [30]	CM	51	39 %	Used 30 % VAS imp as test (2)
Silberstein (St. Jude) et al. [35]	CM	157	38 %	Not stat sig (3)
Lipton (Boston Sc) et al. [56]	CM	132	?	Results not stat significant
Pameliere et al. [40]	MWA	8	63 %	47 % average relief
Serra [57]	CM	29	100 %	MIDAS, SF36 all stat sig
			48 % avg	
Summary: *48 % average response rate for all studies*				
39 % average response rate for the "benchmark" St. Jude and Medtronic studies				

Notes
1. *Cl* cluster, *CM* chronic migraine, *HC* hemicranias continua, *MWA* migraine without aura
2. The Medtronic study used a VAS improvement of 30 % as the test, rather than the historical standard of 50 %
3. The St. Jude study did find that 38 % of patients responded with a VAS > 50 %; however, this number was not statistically significant ($p > .05$)

concordancy, the trial leads should be placed over the painful regions. For patients suffering occipital pain due to occipital neuralgia, then only ONS is required. Or, if a patient has severe cluster headaches perceived almost exclusively over the frontal regions, then only supraorbital leads are planned for the trial. However, as most patients with chronic migraines will have holocephalic pain, most will require combined ON-SON stimulation.

Trial Stimulation: Procedure Technique

Trial stimulation is carried out in the operative suite under IV sedation and medically standard sterile technique. The method for implanting the trial stimulator is depicted in Figs. 11.1, 11.2, 11.3, 11.4, 11.5, and 11.6, and a video of the full procedure can be found here http://www.reedmigraine.com/technique.php.

At the lateral aspect of the forehead, a Tuohy-type needle is introduced and advanced in the subcutaneous layer medially such that it passes approximately 2 cm over the eyebrow to a point where the tip is just past the eyebrow. A neurostimulating lead (preferably octapolar) is then advanced per the introducer, which is withdrawn leaving the active array across the supraorbital nerve. For bilateral placements the procedure is repeated on the contralateral side. The leads are secured into position with a suture anchor and sterile dressing. The patient is then repositioned prone, whereby the occiput is sterilely prepped and draped. The hair is shaved up approximately 4 cm to allow

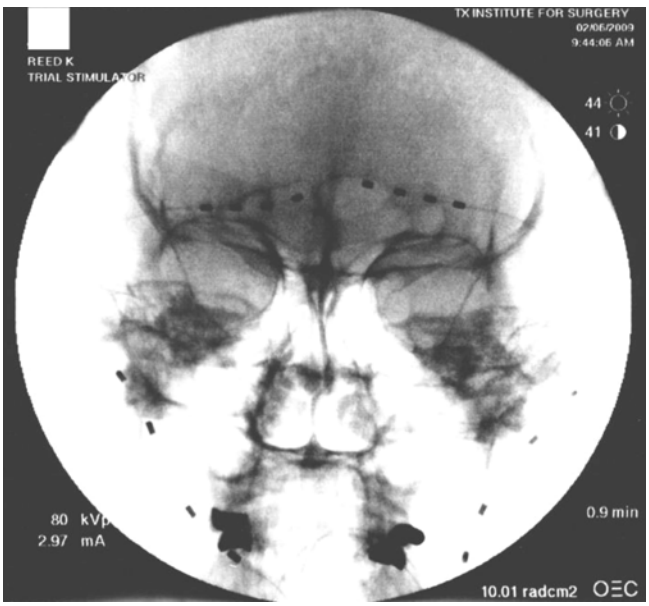


Fig. 11.1 Radiograph of quadripolar supraorbital and occipital leads in proper position

room for taping. The course of the greater occipital nerves as they cross the occipital ridge is noted by standard techniques and marked. Approximately 4 cm caudal and medial to this mark, Tuohy-type needles are introduced and passed subcutaneously in a lateral and cephalad fashion (directed toward the top of the pinna) until the tip is approximately

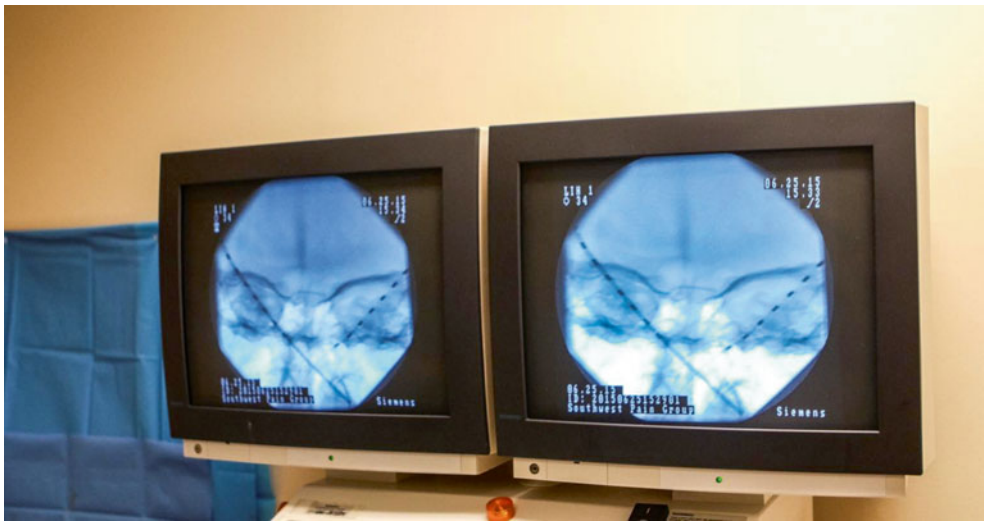


Fig. 11.2 Radiographs of octopolar occipital leads in proper position

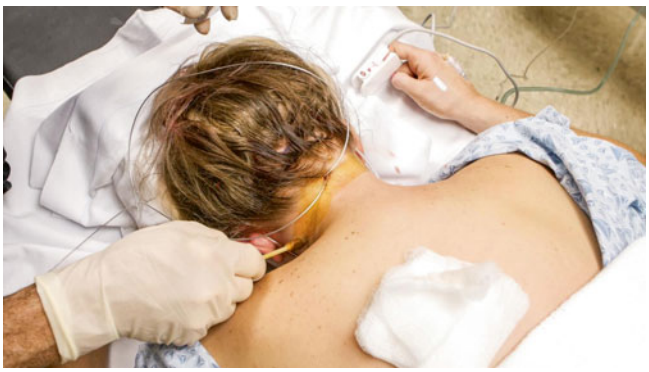


Fig. 11.3 Trial occipital leads prior to suture and taping

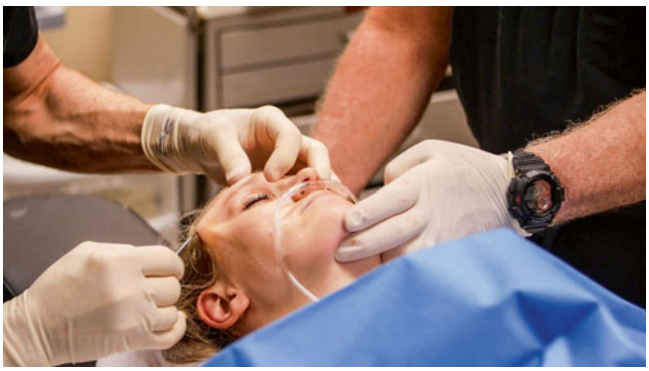


Fig. 11.5 Placement of supraorbital leads

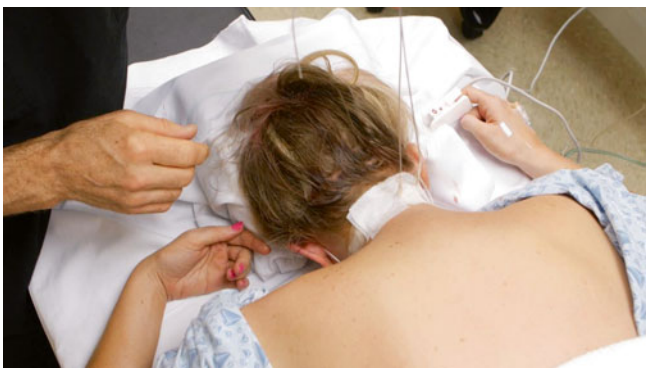


Fig. 11.4 Taping method for occipital leads

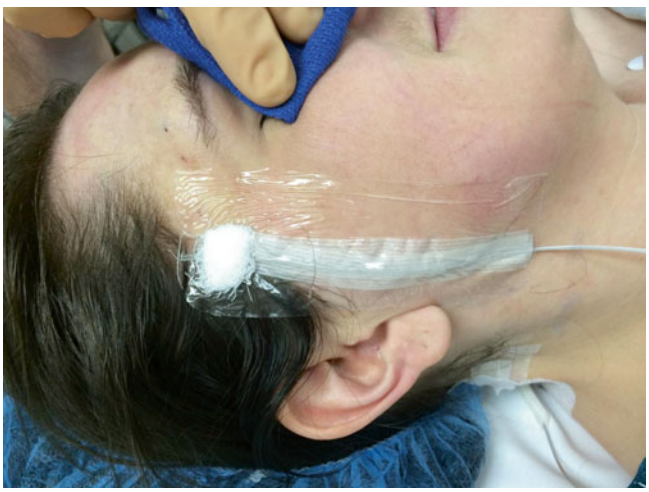


Fig. 11.6 Taping method for supraorbital trial leads

2.5 cm beyond the path of the nerves. Then, standard neurostimulating leads are advanced per the introducers, which are then withdrawn leaving the active arrays across each nerve. These are then secured into position with suture anchors and sterile dressings. All leads are then connected to the external programmable pulse generator. Once the patient is fully alert, the units are programmed (pulse width, frequency, amplitude, etc.) such as to provide a comfortable paresthesia over all areas. The patient is then discharged home for a 5–7 day period of trial stimulation. A minimum criteria for a positive trial was at least 50 % overall improvement in the pain intensity (VAS) and/or headache frequency.

Permanent Implant: Operative Technique

The procedure is carried out under general anesthesia. As opposed to spinal cord stimulation, the leads are reliably placed without the need to awaken the patient mid-procedure to confirm proper paresthesia. As part of the prep, the hair is shaved up approximately 6 cm at the occiput and 3 cm over both ears. Small 1 cm incisions are made over the lateral aspects of the patient's forehead and over each ear, and a 4–6 cm midline incision is made over the upper cervical region. Per these incisions, introducer needles are advanced subcutaneously across the bases of the supraorbital and greater occipital nerves in a fashion similar to the trial. Standard neurostimulating leads are then placed per the frontal introducers and passed to an incision over the ears, where they are anchored and further advanced to the occipital incision. In a similar fashion, leads are placed across the occipital nerves and anchored, whereby strain relief loops are fashioned in all leads. An incision is made over the upper outer gluteal region, where a pocket is fashioned to accept an IPG. The leads are tunneled to the pocket and connected to the IPG. Following closure, a sterile dressing is applied. Following recovery from anesthesia, a representative of the manufacturer programs the neurostimulator. The patient is received and is fully instructed in the use of a portable handheld programmer, which provides the patient the continuous option of adjusting signal strength, frequency, and location. Disposition included prophylactic antibiotics and instructions on temporary activity restrictions.

Recovery

As all of the incisions are relatively superficial, recovery and resumption of activity is fairly rapid. Most patients are able to resume normal activities, including travel, within 2–3 days. Those who have sedentary work positions may return to work within a week. Patients should avoid extreme physical activity for the full recovery period of 6 weeks, at which point all restrictions are removed.

Life with a Neurostimulator

Following the 6-week recovery period, the most remarkable thing about managing a stimulator is how relatively simple it is. The only maintenance required involves the simple process of twice weekly recharging the unit, a procedure that is accomplished by simply sitting next to a portable recharging unit (radiofrequency couple) for an hour or so. Indeed, following the initial 6-week recovery period, we often have patients only return to the office on an as needed basis. Thus, from the patient's standpoint, most everything improves:

- Medication requirements decrease. Over 30 % of patients no longer require any routine meds, and most all of the rest see marked reductions.
- Psychological status, including issues with anxiety or depression, improves in proportion to the decrease in headache pain, noting a concomitant improvement in sense of well-being.
- Activity level. As they are no longer frequenting medical facilities, or having to stay in due a headache, most patients find that they are able to return to normal activities of daily living, including interacting with the family and enjoying social occasions. Further, we impose absolutely no activity restrictions. We have patients that have returned to, or became involved with, various strenuous physical activities, including all forms of exercise, gymnastics, horseback riding, martial arts, baseball, and skiing without problems.

Risks and Adverse Events

PNS for head pain is generally considered to be very safe over the long term. In practical terms most adverse events are relatively minor. In the last 20 years, we have not had (and are unaware of) any complications that have resulted in long-term morbidity. The most common adverse events typically involve the lead itself and include lead migration and/or lead fracture. Lead migration is the most common adverse event with some studies reporting over 20–40 % incidence [31–35]. While frustrating these incidents are corrected by relatively minor outpatient procedures.

The other adverse event of significance is a rather small risk of infection (3–6 %). However, given the subcutaneous location of the system, any infections are superficial and invariably respond to antibiotics and, if necessary, temporary explant of the device.

Results

The results of the extant studies on PNS and headaches are summarized in the tables, which divide the patient treatment groups into two – those implanted with systems that produce a concordant paresthesia, e.g., ONS for occipital neuralgia (Table 11.1), and those that produce a non-concordant paresthesia, e.g., ONS for migraine headaches (Table 11.2). Juxtaposing the results from the "concordant" group against those of the "non-concordant" group reveals a striking difference in the response rates and one that pivots on the single variable of paresthesia concordancy.

The average results of the five individual "concordant paresthesia" diagnostic groups (Table 11.1) are quite remarkable with respect to consistency, noting positive response rates of 88, 89, 89, 98, and 100 %, respectively (avg. 93 % rate). These results stand in sharp contrast to the non-concordant

paresthesia groups, e.g., ONS for the frontal pain of migraine (Table 11.2), which overall found less than a 40 % response rate. Indeed, close scrutiny of the benchmark Medtronic, Boston Scientific, and St. Jude "non-concordant" ONS studies for migraine indicates that they all actually found no practically significant response rates in these patients. Not only did both the St. Jude and Boston studies fail to show a significant therapeutic response with respect to the primary variables, Medtronic's report of 39 % rate also failed to meet the historical, clinical standard of only counting patients with 50 % or more improvement as responders.

It is this dramatic difference in the observed success rates between the "concordant" and "non-concordant" groups that provides such compelling support for the central importance of paresthesia concordancy.

Conclusions

Interventional techniques for chronic head pain have developed into standard and generally accepted means for treating some patients with debilitating, chronic head pain of various etiologies, when other more conservative modes of treatment have failed. Of the techniques reviewed here in terms of invasiveness and risk/benefit considerations, for the patient with chronic, intractable head pain, sequentially the sequence to consider would be the greater occipital nerve percutaneous decompression utilizing the stealth needle Racz decompression technique, followed by evaluation for implanted neurostimulation, and open surgical techniques should be reserved for cases when the patient proves refractory to all else.

References

1. Stang PE, Osterhaus JT. Impact of migraine in the United States: data from the national health interview survey. Headache. 1993;33:29–35.
2. Anthony M. Headache and the greater occipital nerve. Clin Neurol Neurosurg. 1992;94:297–301.
3. Racz G, Noe CE, Justiz R. Suboccipital compartment decompression. In: Raj PP, editor. Interventional pain management image-guided procedures. 2nd ed. Philadelphia: Saunders; 2008. p. 103–6.
4. Heavner JE, Racz GB, Jenigiri B, Lehman T, Day MR. Sharp versus blunt needle: a comparative study of penetration of internal structures and bleeding in dogs. Pain Pract. 2003;3:226–31.
5. Gille O, Lavignolle B, Vital J-M. Surgical treatment of greater occipital neuralgia by neurolysis of the greater occipital nerve and sectioning of the inferior oblique muscle. Spine. 2004;29:828–32.
6. Stechison MT, Mullin BB. Surgical treatment of greater occipital neuralgia: an appraisal of strategies. Acta Neurochir (Wien). 1994;131:236–40.
7. Janis JE, Barker JC, Javadi C, Ducic M, Hagan R, Guyuron B. A review of current evidence in the surgical treatment of migraine headaches. Plast Reconstr Surg. 2014;134:131S–41.
8. Weiner RL, Reed KL. Peripheral neurostimulation for control of intractable occipital neuralgia. Neuromodulation. 1999;2:217–21.
9. Weiner RL, Alo KM, Reed KL, Fuller ML. Subcutaneous neurostimulation for intractable C-2–mediated headaches. Annual AANS Meeting, Toronto: J Neurosurg: 938A. 2001.
10. Oh MY, Ortega J, Bellotte JB, Whiting DM, Aló K. Peripheral nerve stimulation for the treatment of occipital neuralgia and transformed migraine using a c1-2-3 subcutaneous paddle style electrode: a technical report. Neuromodulation. 2004;7:103–12.
11. Kapural L, Mekhail N, Hayek SM, Stanton-Hicks M, Malak O. Occipital nerve electrical stimulation via the midline approach and subcutaneous surgical leads for treatment of severe occipital neuralgia: a pilot study. Anesth Analg. 2005;101:171–4, table of contents.
12. Johnstone CS, Sundaraj R. Occipital nerve stimulation for the treatment of occipital neuralgia-eight case studies. Neuromodulation. 2006;9:41–7.
13. Matharu MS, Bartsch T, Ward N, Frackowial RS, Weiner RL, Goadsby PJ. Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain. 2004;127:220–30.
14. Slavin KV, Colpan ME, Munawar N, Wess C, Nersesyan H. Trigeminal and occipital peripheral nerve stimulation for craniofacial pain: a single-institution experience and review of the literature. Neurosurg Focus. 2006;21, E5.
15. Johnson MD, Burchiel KJ. Peripheral stimulation for treatment of trigeminal postherpetic neuralgia and trigeminal postherpetic pain: a pilot study. Neurosurgery. 2004;55:135–42.
16. Amin S, Buvanendran A, Park KS, Kroin JS, Moric M. Peripheral nerve stimulator for the treatment of supraorbital neuralgia: a retrospective case series. Cephalalgia. 2008;28:355–9.
17. Popeney CA, Aló KM. Peripheral neurostimulation for the treatment of chronic, disabling transformed migraine. Headache. 2003;43:369–75.
18. Dodick DW. Occipital nerve stimulation for chronic cluster headache. Adv Stud Med. 2003;3:S569–71.
19. Melvin EA, Jordan ER, Weiner RL, Primm D. Using peripheral nerve stimulation to reduce the pain of c2-mediated headaches: a preliminary report. Pain Physician. 2007;10:453–60.
20. Rodrigo-Royo D, Azcona J, Quero J, Lorente M, Acin P, Azcona J. Peripheral neurostimulation in the management of cervicogenic headache: four case reports. Neuromodulation. 2005;8:241–8.
21. Magis D, Allena M, Bolla M, De Pasqua V, Remacle JM, Schoenen J. Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. Lancet Neurol. 2007;6:314–21.
22. Schwedt TJ, Dodick DW, Trentman TL, Zimmerman RS. Occipital nerve stimulation for chronic cluster headache and hemicrania continua: pain relief and persistence of autonomic features. Cephalalgia. 2006;26:1025–7.
23. Burns B, Watkins L, Goadsby PJ. Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients. Lancet. 2007;369:1099–106.
24. Burns B, Watkins L, Goadsby PJ. Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients. Neurology. 2009;72:341–5.
25. Lainez MJ, Piera A, Salvador A, Roldan P, Gonzales-Darder J. Efficacy and safety of occipital nerve stimulation for treatment of chronic cluster headache (abs). Headache. 2008;48:S15.
26. Leone M, Franzini A, Cecchini AP, Broggi G, Bussone G. Stimulation of occipital nerve for drug-resistant chronic cluster headache. Lancet Neurol. 2007;6:289–91.
27. Vargas BB, Dodick D, Trentman TL, Radam TE, Zimmerman RS, Noble BN. Occipital nerve stimulation via the bion device for the treatment of medically refractory chronic cluster headache. Headache. 2008;48:S52.
28. Dodick DW, Schwedt TJ, Trentman TL, Zimmerman RS, Hentz J. Trigeminal autonomic cephalalgias: current and future treatments. Headache. 2007;47:981–6.
29. Schwedt TJ, Dodick DW, Hentz J, Trentman TL, Zimmerman RS. Occipital nerve stimulation for chronic headache--long-term safety and efficacy. Cephalalgia. 2007;27:153–7.
30. Saper JR, Dodick DW, Silberstein SD, et al. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia. 2011;31:271–85.

31. Linderoth B, Foreman R. Physiology of spinal cord stimulation: review and update. Neuromudulation. 1999;2:150–64.
32. Bartsch T, Paemeleire K, Goadsby PJ. Neurostimulation approaches to primary headache disorders. Curr Opin Neurol. 2009;22:262–8.
33. Reed KL. Peripheral neuromodulation and headaches: history, clinical approach, and considerations on underlying mechanisms. Curr Pain Headache Rep. 2013;17:305–18.
34. Reed KL, Will KR, Conidi F, Bulger R. Concordant occipital and supraorbital neurostimulation therapy for hemiplegic migraine; initial experience; a case series. Neuromodulation. 2015;18:297–304.
35. Silberstein SD, Dodick DW, Saper J, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia. 2012;32:1165–79.
36. Slavin KV, Nersesyan H, Wess C. Peripheral neurostimulation for treatment of intractable occipital neuralgia. Neurosurgery. 2006;58: 112–9; discussion 112–9.
37. Shaladi A, Crestani F, Saltari R, Piva B. Percutaneous electrical nerve stimulation of peripheral nerve for the intractable occipital neuralgia. Recenti Prog Med. 2008;99:295–301.
38. Magown P, Garcia R, Beauprie I, Mendez IM. Occipital nerve stimulation for intractable occipital neuralgia: an open surgical technique. Clin Neurosurg. 2009;56:119–24.
39. Vadivelu S, Bolognese P, Milhorat TH, Mogilner AY. Occipital nerve stimulation for refractory headache in the Chiari malformation population. Neurosurgery. 2012;70:1430–7.
40. Paemeliere K, Van Buyten JP, Van Buynder M, et al. Phenotype of patients responsive to occipital nerve stimulation for refractory head pain. Cephalalgia. 2010;30:662–73.
41. Dunteman E. Peripheral nerve stimulation for unremitting ophthalmic postherpetic neuralgia. Neuromodulation. 2002;5:279–90.
42. Yakovlev AE, Resch BE. Treatment of chronic intractable atypical facial pain using peripheral subcutaneous field stimulation. Neuromodulation. 2010;13:137–40.
43. Stidd DA, Wuollet A, Bowden K, et al. Peripheral nerve stimulation for trigeminal neuropathic pain. Pain Physician. 2012;15:27–33.
44. Narouze SN, Kapural L. Supraorbital nerve electric stimulation for the treatment of intractable chronic cluster headache: a case report. Headache. 2007;47:1100–2.
45. Vaisman J, Markley H, Ordia J, Deer T. The treatment of medically intractable trigeminal autonomic cephalalgia with supraorbital/supratrochlear stimulation: a retrospective case series. Neuromodulation. 2012;15:374–80.
46. Simopoulos T, Bajwa Z, Lantz G, Lee S, Burstein R. Implanted auriculotemporal nerve stimulator for the treatment of refractory chronic migraine. Headache. 2010;50:1064–9.
47. Reed KL, Black SB, Banta 2nd CJ, Will KR. Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: initial experience. Cephalalgia. 2010;30: 260–71.
48. Deshpande KK, Wininger KL. Feasibility of combined epicranial temporal and occipital neurostimulation: treatment of a challenging case of headache. Pain Physician. 2011;14:37–44.
49. Mammis A, Gudesblatt M, Mogilner AY. Peripheral neurostimulation for the treatment of refractory cluster headache, long-term follow-up: case report. Neuromodulation. 2011;14:432–5; discussion 435.
50. Reed KL, Will KR, Chapman J, Richter E. Combined occipital and supraorbital neurostimulation for chronic migraine headaches: an extended case series [abst]. 15th congress of the international headache society. Berlin: Cephalalgia, 2011: 98–99.
51. Magis D, Schoenen J. Occipital nerve stimulation for intractable chronic cluster headache: new hope for a dreadful disease? (abs). Acta Neurol Belg. 2011;111:18–21.
52. Trentman TL, Zimmerman RS, Seth N, Hentz JG, Dodick DW. Stimulation ranges, usage ranges, and paresthesia mapping during occipital nerve stimulation. Neuromodulation. 2008;11:56–61.
53. de Quintana-Schmidt C, Casajuana-Garreta E, Molet-Teixido J, et al. Stimulation of the occipital nerve in the treatment of drug-resistant cluster headache. Rev Neurol. 2010;51:19–26.
54. Fontaine D, Sol JC, Raoul S, et al. Treatment of refractory chronic cluster headache by chronic occipital nerve stimulation. Cephalalgia. 2011;31:1101–5.
55. Mueller OM, Gaul C, Katsarava Z, Diener HC, Sure U, Gasser T. Occipital nerve stimulation for the treatment of chronic cluster headache – lessons learned from 18 months experience. Cent Eur Neurosurg. 2011;72:84–9.
56. Lipton RB, Goadsby PJ, Cady RK, et al. PRISM study: occipital nerve stimulation for treatment-refractory migraine (p abs). Cephalalgia. 2009;29:30.
57. Serra G, Marchioretto F. Occipital nerve stimulation for chronic migraine: a randomized trial. Pain Physician. 2012;15:245–53.

Part III

Medicolegal

Medicolegal Aspects of Pain Medicine with Special Reference to Opioid Therapy

12

Gabor B. Racz, Carl Noe, Hans Hansen, and Rajesh Munglani

Introduction

Deviation from an acceptable standard of care is one of the central issues in a lawyer's mind in any malpractice lawsuit. However, the trigger for a lawsuit is the occurrence of a complication. That is, intense scrutiny of a doctor' practice usually only occurs once harm has occurred to a patient.

Thus avoiding complications is the maxim to follow. Understanding the situations in which complications leading to lawsuits may arise is most important.

Not all complications will lead to lawsuits depending on how they are handled and lawsuits, for example, nonnegligent complications and side effects, if appropriately consented for are unlikely to succeed.

The trend toward more accreditation may reduce rare but serious complications. Many boards (in the United States) and the Faculty of Pain Medicine (in the United Kingdom) among others and international organizations such as the World Institute of Pain (WIP) have introduced guidelines and standards of training to raise standards of medical care and so to reduce complications rates.

G.B. Racz, MD, ABA, FIPP, ABIPP (✉)
Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX, USA
e-mail: gbracz@yahoo.com

C. Noe, MD
Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

H. Hansen, MD
Department of Anesthesiology, The Pain Relief Centers, Statesville, NC, USA

R. Munglani, MBBS, DA, DCH, FRCA, FFPMRCA
Department of Anesthesiology, West Suffolk Hospital Cambridge University Trust, Bury St Edmunds, UK

Principles That May Help Avoid Lawsuits

There is evidence that dealing distressed or angry patients are associated with poorer outcomes and more complaints and higher rates of litigation [1]. Always be respectful and pleasant with patients and communicate with them; this leads to lower rates of litigation. Patients are treated in privacy. You are practicing in public, in front of a jury of your peers [2–5].

Steps to promote safety for interventional pain procedures include the "time-out" where activity stops and the team of the patient, nurses, and physicians verify the patient's identity, the diagnosis, the procedure, the side of the procedure (right or left), a valid consent form, allergies, and other critical information before proceeding with the procedure. Labeling syringes and marking the site of the procedure are also helpful. Numerous deaths have occurred from erroneous labeling and administering the wrong drug [6, 7].

Performing the correct procedure for a specific pain problem is more important than performing an alternative procedure first because it may be less expensive.

The practice of performing series of procedures and the use of algorithms of multiple procedures are nonspecific and need to be refined to be not only more cost-effective but to reduce risk.

The use of physician extenders is a risk factor for medicolegal disputes in pain management. Physician standards of care are the standard that patients expect and the evolving practice of pain management does not lend itself well for delegation of decision making for opioid prescribing and procedure selection [8].

Monitoring the patient, having venous access, and having equipment for anaphylactic reactions and other emergencies are advisable for procedures other than simple peripheral injections.

Anticoagulation has become very common in the United States, as has daily aspirin therapy. The management of these medications before and after pain management procedures is problematic since existing data does not answer all questions. Discontinuing aspirin has been associated with stroke and

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_12

myocardial infarction; however, new platelet function tests are markedly abnormal with one 325 mg tablet per day. Patients with mechanical valves or recent coronary stints or pulmonary emboli are not good candidates for discontinuing anticoagulation. Coordination with the anticoagulant managing physicians is important when these patients need procedures.

Discontinuing platelet inhibitors has more advocates than opponents but the risk of bleeding versus infarction is a subject that is well suited for a discussion with the patient's other physicians and with the patient.

If you are sued, remember no one is going to care more about the result than you do. Pick the best lawyer and experts to defend you.

Medical Malpractice

Medicolegal issues may arise in the form of a lawsuit, brought by a patient or their representative or from a hostile action from a licensing agency, a hospital privilege committee, a medical society, an insurance company or government health plan, a certifying board, or other government agencies or non-government party.

Four Conditions Constitute a Malpractice Claim

1. A duty must exist between a physician and the patient. In other words, a doctor–patient relationship must exist.
2. The duty must have been compromised by negligence.
3. The patient must have suffered damages.
4. The alleged negligence must be proven to have caused the damages.

Related to the above concepts is the burden of proof test.

In order to bring a successful claim against you, the patient, or other person bringing the claim, has to prove on the balance of probabilities:

Breach of duty – which the treatment was such that no reasonable practitioner would have delivered that care.

Causation – that the breach of duty or negligence caused or contributed to the injury, loss, or damage suffered and that the patient would not have suffered that injury without the breach.

Both these tests have to be established to prove negligence [9].

Negligence and Causation

Negligence, or a breach of duty, is a deviation from the standard of care. Standard care is the care provided by a reasonable and prudent physician of the same specialty and, under the same circumstances, otherwise known as the Bolam test [10]. Causation, or proof that damages resulted from negligence and were not coincidental, has a threshold of being more likely than not, otherwise known as the 50.1 % test.

Effects of Medical Malpractice of Healthcare Delivery

Physicians claim that medical malpractice liability increases healthcare costs and limit access to care for which there is now increasing evidence [11]. Practicing "defensive medicine" probably worsens outcomes for patients [12].

Advocates of the medical malpractice system argue that malpractice insurance premiums are a result of poor insurance company management. The Harvard Medical Practice Study in 1990 reposted that only a small fraction of patients with negligent injuries sued and that more suits were in order rather than less.

Tort and Its Reform

A tort is a civil wrong that causes injury, exclusive of a breach of contract. Medical malpractice is a tort resulting from negligence, which is defined as conduct that falls below the standard established by law for the protection of others against unreasonable risk of harm. An intentional tort may arise when informed consent is not obtained.

Tort reform initiatives have proposed several ways to reduce the costs of malpractice awards [13, 14].

Caps on noneconomic damages limit the amount of money that can be awarded for pain and suffering. Some jurisdictions have limits of $250,000. Economic damages cover medical expenses, lost wages, and costs of reeducation and/or rehabilitation.

Caps on punitive damages limit the amount of money awarded for conduct that is beyond negligence and includes fraud or evil. Advocates for caps have argued that evidence must be "clear and convincing" rather than "a preponderance" before punitive damages are awarded [15]. It has been argued that a portion of punitive damages go to a fund for a public purpose rather than to the plaintiff.

Abolishing joint and several liabilities would prevent each defendant from being liable for 100 % of the damages. The principle of joint a several liability serves to assign liability equally to all defendants rather than allow defendants to divide responsibility based on their portion of conduct.

The collateral source rule is it allows plaintiffs to be compensated twice for the same injury. Abolishing the collateral would result in an offset of damages based on other resources such as insurance payments and disability payments [16].

Contingency fee limits would require attorneys to be paid based on the amount of work they perform rather than a percentage of the awarded damages, but in other jurisdictions

such as the United Kingdom, there are imperatives which state the costs in a case must be proportionate [17]

Statues of limitations require malpractice lawsuits to be filed within a time period from the injury. In the United Kingdom, this is generally accepted to be 3 years in most circumstances [18]. If an injury is not discovered immediately or if the injured person is a child, the limitation is frequently expanded to allow a suit to be brought. A newborn baby is obviously unable to file a lawsuit but can when adulthood is reached. In the United Kingdom, the statute of limitation only starts when the child reaches 18 [19]. Medical records tend to degrade after years and memory is of limited help. These factors disadvantage the defense of a physician, though the advent of electronic records may prove helpful in this respect.

Periodic payment of damages would allow payments over time rather than a lump sum.

The American Society of Anesthesiologists Closed Claims Study

The ASA closed claim study has resulted in a number of reports regarding pain management and related liability. The number of claims against anesthesiologists for pain management doubled between 1985 and 1989. It doubled again between 1990 and 1994 [20]. Claims for postoperative pain management increased from 6 % during the 1980s to 8 % in 2000 [21] . Claims from chronic pain management increased from 7 % between 1985 and 1994 to 12 % between 1995 and 2004 [22].

In a large report, the number of claims increased since the 1980s before pain management began to grow as a specialty. Deaths from epidural injections were associated with epidural injection of local anesthetic and opioid. Nerve damage and pneumothorax were reported to be most common causes of claims. Intrathecal pump mishaps were also associated with deaths [23].

Forty-four percent of medication errors have been related to incorrect dosing, 30 % are related to wrong drug administration, 10 % are related to contraindicated drugs, and 8 % are related to incorrect timing of administration [24].

Most medication claims are associated with medication misuse and both patient and physician conduct contribute to a high proportion of deaths.

Medication management claims were associated with men with back pain who were prescribed long-acting opioids and also taking other psychoactive medications and had signs of medication misuse [25].

Blocks accounted for 84 % of claims during the 1990s [26].

Fifty percent of nerve injury claims involved spinal cord injury. Pneumothorax from trigger point injections has been a common claim [27].

Spinal cord injuries have been reported to be associated with cervical procedures in women under general anesthesia [28].

Twenty-two percent of chronic pain claims are related to cervical procedures and the injuries are commonly permanent and disabling.

Brain damage and death were associated with epidural steroid injection only when used with local anesthetic or opioid [23].

Ultrasound-guided nerve blocks have been associated with fewer claims. [29]

Other factors have been reported as a part of the closed claim study.

Agreement among experts in malpractice cases has been shown to correlate poorly (k 0.37) [30].

However, publishing and publicizing examples of questionable expert testimony has been discouraged for legal reasons [31].

Malpractice insurance rates vary widely from $15,000 to $64,000 per year depending on the states' legal system and award amounts over time [32].

The recommended amount of malpractice insurance coverage varies, but one to three million dollars per claim and three to six million dollars in aggregate have been proposed [33].

The closed claims study data is limited statistically because it reports the numerator but not a denominator, so trending is difficult to evaluate. However, it clearly serves a good purpose in identifying potential problems.

The closed claims study does not include information from non-anesthesiologists and pain management has become a multispecialty field with a variety of specialists performing procedures oftentimes with little training.

In the State of Georgia, one malpractice insurance carrier no longer offers coverage for psychiatrists who perform trigger point injections because of the high rate of pneumothorax. The use of a 25- or 30-gauge needle and fanning injections is associated with pneumothorax. Fanning injections with a small-gauge needle tends to produce multiple punctures along the same track rather than injecting in multiple directions as intended with the fanning motion. The reason is that the small-gauge needle lacks the stiffness necessary to overcome the "grip" of the muscle and has a "woodpecker effect" producing multiple punctures of the pleura. Using 22-gauge needles for trigger point injections or avoiding fanning, we have not seen this problem.

Complications and Mechanisms

Twenty-five plus years of serving as an expert in 350–400 cases (GBR) as well as taking into account the UK perspective (RM) has revealed some patterns of complications and

likely mechanisms. Many cases settle and no record of the complication is made and valuable information is lost. The following section represents some of that information.

With increasing emphasis on treatment of pain, there has been recognition of recurring patterns of complications. Therefore once understanding reaches a broad base, reduction of these serious but rare complications should be possible.

Pneumothorax

Pneumothorax is a complication for trigger point injections. Frequently the needle used was 25 G or smaller. These needles bend easily, and when "fanning" injections are made, the needle tract is uncontrollable. A "woodpecker" effect can result with multiple holes in the pleura and a pneumothorax requiring a chest tube is a common trigger for a lawsuit. Medicare will no longer pay for treatment of a pneumothorax from a central line placement and similar reimbursement patterns may be forthcoming for pain-related complications.

Injections Near the Cranium

This same mechanism can occur with other injections. For example, injecting a painful scalp scar after craniotomy for acoustic neuroma has resulted in local anesthetic being injected intracranially.

Cervical Sympathetic Injections

Cervical nerve root injection occurs after cervical sympathetic (stellate ganglion) block using the classic technique. Needles directed to Chassaignac's tubercle are directed to the vertebral artery and cervical nerve root. Local anesthetic injection may result in immediate seizures or paralysis but delayed complications may result from subdural blocks after patients have been discharged. Patients should be monitored for longer periods of time in an environment with full resuscitative personnel and equipment. A lesson learned from this is that the needle tip migrates into a nerve or artery where injection occurs. The new Bella D needle (Epimed, International) has a sealed tip and a side port for directional injection, and these features may reduce this occurrence.

Spinal Transforaminal Injections and the Erroneous Concept of a Safe Area

Deaths after transforaminal injections have occurred and the notion of a "safe" avascular area in the posterior foramen has been shown to be false. Huntoon has demonstrated arterial supply in each posterior cervical neuroforamina. Local anesthetic injection or arterial injury can result in catastrophic spinal cord injury and/or death [34]. The increasing number of cases of catastrophic neurological injury in the lumbar region following otherwise supposedly correct injection appropriate has also undermined the concept of this safe area and an alternative site Kambin's triangle has been alternatively proposed [35, 36]

Catastrophic has occurred following injection of saline, contrast, and steroid and is not prevented by digital subtraction angiography [37]. The onset of neurological may be delayed and was associated with the lack of any obvious untoward effects of a test dose of local anesthetic which was used to confirm epidural placement. The authors suggested that utilizing blunt needles or larger bevel needles in place of sharp, cutting needles may minimize the chances of this event occurring. Presumably, subdural injection causes vasospasm and infarction.

The Debate over Sharp Versus Blunt Needles

Sharp needles by their very design minimize the feedback produced as bodily structures are penetrated. This means there will be minimal awareness of vascular, neural, and spinal cord structure with needle advancement. Such injections are associated with lawsuits. The dura can be partially punctured and local anesthetic and corticosteroid preparations can be injected.

Despite the fact no randomized controlled data exist for sharp needle injection safety, serious concerns have been raised. Sharp needle movement after initial placement seems to be a factor as well. In response, the Bella D needle has been designed in an attempt to reduce punctures and migration associated with small movements. The tip is blunt and a side port is located proximal to the tip. Blunt needles have been shown to be less likely to puncture nerves and arteries in animal studies. Interscalene block complications have also been associated with sharp needles. Intercord injections, quadriplegia, Brown-Séquard syndrome, and brachial plexopathy have been reported. The true incidence of major complications is unknown. Sweet reported one death and several hematomas in a series of 7000 foramen ovale procedures. This may be a similar complication rate for pain procedures.

The RX-2 coude (Epimed International) epidural needle has a second stylet, which is blunt to convert the needle tip from sharp to blunt to reduce the incidence of a dural or venous laceration when rotating the needle in the epidural space. The second stylet is placed once the epidural space is reached but before any rotation. The blunt-tip stylet projects 1 mm beyond the tip of the needle and acts as a guard to the sharp edge of the needle.

The RX-2 coude needle is gaining wider acceptance for epidural needle and catheter placements as well as spinal cord stimulation electrode placements.

A lesson learned is that every case of spinal cord injury and death until has been associated with the use of sharp needles by direct trauma or the mechanism of arterial penetration and comprise of the arterial supply. Experimental studies suggest that blunt needles have not been associated with arterial wall penetration [38].

The available clinical information and animal data supporting the use of blunt needles only applies to blunt needles and cannot be extrapolated to pencil-point-tip needles. Pencil-point-tip needles are designed to penetrate the dura and have not been studied with regard to puncturing arteries and nerves.

The pencil-tip needles have not been studied regarding perforation into nerves or arteries. The blunt needles have been shown not to perforate from 18 gauge to 25 gauge.

The stellate ganglion disasters should be avoidable using the Bella D needle. Most of these complications seem to be related to the classic C 6 approach to Chassaignac's tubercle. The teaching to make bony contact and then pull back 1 mm is an inexact process and the needle tip and injection can be placed in an artery or nerve. Cases of immediate or delayed total spinal block and brain or spinal cord infarction have occurred. Using the Bella D needle placed at the lateral body of C7 may reduce the incidence of these complications.

While some of the evidence does suggest blunt needles may be safer, the first cases of spinal cord injury the use of blunt needles are now being reported to be associated with vascular spread [39].

The curved, blunt RF (Racz-Finch) needle is being used increasingly in an attempt to avoid intraneural, intracord, and intra-arterial placement especially with the use of particulate corticosteroids. Thus far, no cases involving these needles have surfaced.

The curved blunt needle must be used with an introducer, but once it is placed, it can be used as a percutaneous navigation device (PND) and directed around other structures to the target area.

This same concept is behind the RX-2 coude and the 14-gauge spinal cord stimulation electrode epidural needle, which can be used to steer the electrode safer and in less time.

Particulate Steroids

Patients with acute and chronic pain have received steroids in neuraxial blockade for many years. There has been recent controversy about their efficacy but also about the possibility of neurological complications associated with the use of particulate steroids such as methylprednisolone, triamcinolone, and betamethasone. In contrast dexamethasone is a non-particulate steroid with less platelet-aggregating properties [40] and it is noted that in the United States between 1998 and 2003, the number of cervical and thoracic TF ESI almost doubled. They noted at the time of writing 27 cases of brain and spinal cord infarction following TF ESI and their survey revealed a further additional 78 cases following a survey of 1400 or so physicians despite a response rate of approximately only 21 %. In no case was the use of non-particulate steroid dexamethasone associated with adverse neurological outcomes. Depomedrone, a particulate steroid, was seven times more likely to have been used in cases where there was evidence of brain and spinal cord infarction than either triamcinolone or betamethasone. No cases were reported with dexamethasone. It could be argued that this simply reflected a frequency of use rather than a propensity to cause problems.

In particular it was hypothesized that inadvertent intra-arterial injections of particulate steroids are thought possibly to lead to spinal cord ischemia by blocking of small arterioles and secondary catastrophic neurological and other complications and indeed. Studies showed that methylprednisolone and triamcinolone were more likely to aggregate than dexamethasone or betamethasone, sometimes up to 100um in diameter on microscopic slides which have the theoretical ability to block small arteries [41]. Use of contrast and aspiration are no guarantee that vascular uptake has not taken place who noted the overall incidence of intravascular uptake during lumbar spinal injection procedures as determined by contrast-enhanced fluoroscopic observation is 8.5 %. Preinjection aspiration failed to produce a flashback of blood in 74 % of cases that proved to be intravascular upon injection of contrast dye [42]. Despite this evidence, a survey in 2012 suggested a significant proportion of UK pain consultants continued to use particulate steroids for cervical injections and even greater proportion for lumbar root injections [43]. A clinical negligence barrister in the United Kingdom has commented that the current position of UK pain consultants who continue to use particulate steroids is uncertain in terms of breach of duty if they haven't offered patients the probably safer option of non-particulate steroids even if they continue not to accept the evidence as regards particulate steroids.

Unreliability of the Ligamentum Flavum as a Loss of Resistance Sign

Anatomical studies have shown the inconsistent presence of the ligamentum flavum. Ligamentum flavum resistance is an unreliable sign in the cervical spine and the first resistance appreciated may be the dura or cord [44]. This means that intracord injection may easily occur with interlaminar epidural steroid injections with Tuohy spinal needles using loss of resistance techniques.

Spinal Hematomas and Perivenous Counter Spread

Subdural, subarachnoid, or intracord needle placements followed by injections of contrast, local anesthetic, or corticosteroid can produce spinal cord injury, paralysis, and death.

The cervical venous plexus is predominantly lateral and ventral as opposed to the thoracic, which is predominantly posterior. Epidural hematomas are usually upper thoracic and lateral recess stenosis compounds the problem.

Lawsuits are rare when an epidural hematoma is diagnosed early and surgical decompression is carried out expeditiously [45]. A second opinion consult should be obtained if the first surgeon wishes to delay surgical treatment of an acute epidural hematoma though conservative management has been described [46].

Perivenous counter spread (PVCS) has been reported and occurs when epidural injection leads to pressure building on one side which forces flow to the opposite side [47]. If fluid is unable to escape the spinal canal, pressure can compress the cord and produce quadriplegia. When recognized, the patient should flex and rotate the neck. Then it causes the pars of the facet joints to slide over one another and enlarge the neural foramina. This provides an escape route for injected material and pressure release.

This procedure has become a standard of practice and is described in multiple publications. It should be used to spread cervical injectate and allow lateral runoff.

When pressure builds up, the patient will complain of ipsilateral pain possibly spreading bilaterally. Neck and arm pain precede chest pain and spinal cord ischemia. Numbness, weakness, and paralysis can be prevented by repetitive exercises.

PVCS has been described as a mechanism for acute compression, which may be relieved by repetitive chin to shoulder flexion exercises. These movements increase the size of the cervical canal, allowing spread of injectate and pressure reduction. Thoracic catheter placement and advancement to the cervical level in the lateral epidural space may reduce the risk of compartmental injection by opening lateral runoff. The practice of avoiding the lateral epidural space may predispose patients to loculation and syrinx formation.

Caution or avoidance of epidural injections in patients with a syrinx, Arnold–Chiari malformations, and arachnoiditis is advised. Paralysis and other severe neurological complications have been seen [48, 49].

The only effective treatment for injecting the wrong contrast is irrigation of cerebrospinal fluid with saline.

Injections in patients with arachnoiditis are hazardous because dissection can occur into the subdural space and loculation can occur leading to circulatory compromise to the spinal cord.

Spinal procedures in patients with syrinx should be avoided.

Suboccipital Injections

Suboccipital injections have been associated with the "locked in phenomenon," brain stem infarction, and death. Injectate can tract retrograde along the occipital nerve and dissect into the CNS.

Suboccipital decompression has not been associated with the "lock-in" phenomenon. Ten cases of complications with intraneural injection have occurred but not with the use of the Stealth (Epimed, International) 20-gauge 2″ needle aimed just below and slightly posterior to C1. The "lock-in" phenomenon, while rare, is an example of the importance of recognizing an emergency and being able to respond with resuscitative measures.

Arachnoiditis

It is still not clear what causes arachnoiditis though epidural injection of modern drugs is unlikely to be associated with such a complication. In contrast intrathecal injection of steroids has been associated with histological changes in animal studies and also probably humans. Studies of epidural steroids and contrast suggest greater changes with the injection of contrast media. Therefore contrast injection should be limited to agents, which are safe for intrathecal use. The cause of the recent report of urological problems and severe dense foot drop following a few days post blind caudal injections for contralateral radicular pain is uncertain but infection has been postulated for the arachnoiditis seen on imaging. Recently, a 30 million dollar lawsuit was brought after a patient developed arachnoiditis after multiple wet taps during attempted spinal cord stimulator electrode placement. The allegation was that an epidural blood patch caused the arachnoiditis. The medical records weighed 97 pounds and the trial lasted 2 weeks but the defense prevailed. Nevertheless, it is not uncommon for the Tuohy-type needle to enter the subdural space without the physician recognizing it. Cerebrospinal fluid may not appear during the procedure.

Radiofrequency of the Medial Branches

In principal radiofrequency of the medial branch seems to be an inherently safe procedure [50]. It is however important to warn patients about postoperative soreness and inconsequential long-term numbness due to a lesion of the lateral branch [51].

Radiofrequency procedure complications and medicolegal cases include instances where sharp needles enter nerves or arteries and where injection created pressure, which is transmitted to a distant structure. Additionally, thermocoagulation of unintended structures, such as the vagus nerve

during a C2–C3 facet denervation, can occur. Permanent losses of voice and hoarseness have been complications. The vagus nerve courses slightly anterior and lateral to the target [52]. For this reason, performing bilateral upper cervical facet denervations at the same sitting is not advisable. Patients should be brought back for the second side. In addition, weakness of cervical muscles can occur resulting in a permanent inability to raise the head.

Informed Consent

Written informed consent should be obtained before any procedure to document education of the patient regarding risks of the procedure and to fulfill the legal requirement and avoid a charge of battery.

In Texas, new laws require specific language for informed consent for three types of pain procedures [53]:

1. *Neuroaxial procedures* (*injections into or around spine*)
   Failure to reduce pain or worsening of pain
   Nerve damage including paralysis (inability to move)
   Epidural hematoma (bleeding in or around spinal canal)
   Infection
   Seizure
   Persistent leak of spinal fluid which may require surgery
   Breathing and/or heart problems including cardiac arrest (heart stops beating)
2. *Peripheral and visceral nerve blocks and/or ablation*
   Failure to reduce pain or worsen pain
   Bleeding
   Nerve damage including paralysis (inability to move)
   Infection
   Damage to nearby organ or structure
   Seizure
3. *Implantation of pain control devices*
   Failure to reduce pain or worsening of pain
   Nerve damage including paralysis (inability to move)
   Epidural hematoma (bleeding in or around spinal cord)
   Infection
   Persistent leak of spinal fluid which may require surgery

Rational for Particular Procedures and Drugs as Part of the Informed Consent

The scrutiny of the efficacy of particularly spinal injections compared to the possibility of adverse outcomes including catastrophic complications means that a more careful risk/benefit discussion now needs to form part of any consenting process. In contradictory studies, the presence of increasing number of guidelines means that a doctor should be able to demonstrate at some point in the notes, a thought-out treatment plan, and a proper discussion of the relative risks and benefits.

Particular issues currently exist as regards the therapeutic efficacy of spinal injections in general and epidural steroids in particular.

The Evolving Role of Opioid Treatment in Chronic Pain Management

Brief Overview

The prescription of strong opioids is a significant therapeutic event, which can be associated with poor outcomes including overdose and death. It is important that the rational for such a prescription is fully documented with informed consent [54].

Opioids for chronic pain management have recently become increasingly controversial, yet many patients continue to be treated with high doses for prolonged periods of time. The misconception between patients and providers alike is that these drugs can be taken without consequences.

This part of the chapter will review recent data on the subject of opioid prescribing, misuse, and abuse and present arguments both for and against opioid therapy for chronic pain. As part of good medical practice, prescribers must evaluate patients for risk factors of opioid abuse prior to initiating opioid therapy and during treatment.

Additionally, it is stressed to prescribers to limit opioid doses and duration of drug exposure to further decrease the potential for adverse outcome [55].

Factors Leading to the Over-Prescription of Opioids

The Burden of Pain

Healthcare spending accounts for 16 % of the gross domestic product and is continuing to climb, with expectations approaching 25 % of the GDP by 2025 [22]. Chronic illnesses are a major cost driver in this increase in spending with projected increases from 133 million in mid-2000 to 171 million in 2030 [56].

More than ¼ of Americans suffer from daily pain at a cost of almost $60 billion in lost productivity in the United States alone [24]. Those of lower educational and socioeconomic status spend nearly 20 % of their life in moderate to severe pain. The Institute of Medicine has published a report that reveals 116 million Americans suffer from pain that persists from weeks to years [57, 58]. The estimated financial impact is up to $635 billion per year in the United States [36–38]. Those with graduate education and higher socioeconomic status experienced less pain for 8 % of their lifetime.

Americans spend approximately $2.6 billion in over-the-counter pain medications alone and $14 billion on analgesics as a class [59].

The burden of pain is also felt psychologically. Over a quarter of patients believe they will always have pain and there is no solution. Up to 1/3 of chronic pain patients have reported they received little, if any, relief from treatments or therapies.

The prevalence of pain in the American population is substantial, with 4 out of 10 Americans saying they experience pain daily, which rises in the aging population approaching 60 % in those aged 65 and older. Nine out of 10 Americans say they experience pain some time each month, which would increase utilization of healthcare services to be directly related to these incidences of pain. In fact, despite the prevalence of pain, nearly two-thirds see a doctor only when they cannot stand the pain any longer [26].

Loss of work is a major problem related to pain. Almost 55 % of the workforce reports having pain the past 2 weeks. The incidence of low back pain peaks about the sixth decade of life, and 50 % of Americans report some episode of back pain. Neck pain occurs about half as often as low back pain, and effects 10 % of the general population [30].

In the United Kingdom, almost 50 % of the population experience pain at any one time with approximately 15 % report severe pain [60, 61]. European studies confirm the extraordinarily high level of musculoskeletal problems including spinal pain in the general population [62]

It is unsurprising therefore that pain remains one of the most frequent chief complaints in the primary care office, in which 40 % of primary care visits seeking relief and 15 % of patients require pain medication or treatment and 20 % of those are chronic pain visits.

It would seem logical that therefore treating pain with an opioid strategy would help mitigate this widespread experience of pain and resultant disability. Indeed up to 20 % of patients in a primary care setting are on chronic opioid therapy [61].

Assessing Pain

Chronic pain, which is often a cruel and disabling state, is not a life-threatening entity. The problem that pain is subjective means that pain must be addressed from the patients' point of view. Most physicians struggle with pain as a diagnosis because there are few tools available to verify its existence. The declaration of Montreal gave patients in pain or who were suffering further legitimacy in seeking pharmacotherapeutic options for relief [63, 64]. The Institute of Medicine has stated effective pain management is a moral imperative, a professional responsibility, and the duty of people in the healing professions and goes on to say the committee recognizes the serious problem of diversion and abuse of opioid drugs and questions about their long-term usefulness; it believes, however, that when opioids are used as prescribed and are appropriately monitored, they can be safe and effective, especially for acute, postoperative pain, procedural pain, and patients near the end of life who desire more pain relief [57]. We will examine the evidence base for such a statement further in chapter [58].

At first glance it would seem logical that treating pain with an opioid strategy would help mitigate this widespread experience of pain and resultant disability. In this rapidly evolving healthcare delivery system, the pain care provider will be challenged to render effective care, increase the quality of life of those in pain, and minimize risk and cost. Not surprisingly, it is expected that with rising healthcare costs, opioid use will be considered cheap and a first choice.

The Destigmatization of Opioids

Opioids have been destigmatized, and the origins can be traced to industry and a few thought leaders that have since retracted their belief that opioids may be prescribed without negative consequences.

The Controlled Substance Act of 1970 was a first step to address these concerns when "no relief or cure is possible, or none has been found after reasonable efforts to legitimize opioid/controlled substances prescriptive purposes" [65]. Steadily over the past few years, with advocacy and patients' bill of rights, medical societies support, and the generation of a perceived fifth pathway of pain control in the community, opioid use escalated. The National Vital Statistics Office has seen a steady rise in opioid prescriptions.

A report by Russell Portanoy and Kathleen Foley in 1986 opened the door to the subsequent belief that opioids are safe and have little consequences. The paper titled "Chronic Use of Opioid Analgesics and Nonmalignant Pain: Report of 38 Cases" opined that opioid maintenance therapy can be a "safe, salutary, and more humane alternative to options of surgery or no treatment for those patients with intractable nonmalignant pain and no history of drug abuse" [66].

During the 1990s, chronic and cancer pain was recognized as being undertreated worldwide. The result was to soften prescribing resistance, and as a result, many states in the United States passed intractable pain treatment acts to protect physicians from disciplinary action when prescribing opioids for non-cancer pain, as well as cancer pain.

Available opioids have realized a threefold rise from the late 1990s. The use of controlled substances for recreational purposes or diversion was not realized as a problem to its full extent until 1996. Prior to 1996, the DAWN and ARCOS data did not reveal any particular trend in abuse, misuse, or diversion.

Opioid prescribing has come to be seen as an easy and time-efficient method to treat pain in non-palliative care settings over the past two decades. The Federation of State Medical Boards endorsed opioids as a legitimate treatment option [67]. Opioids are now expected by patients, and as a society, expectations of relief are considered a "right"; resistance to change is met with varying degrees of resistance.

These layers of complexity in the clinical setting place the burden on the provider to secure a course of care that is compassionate, yet safe and effective.

The Institute of Medicine (IOM) does promote pain treatment with these agents though an updated report is now expected from them [68, 69]. The British Pain Society has previously strongly endorsed treatment with opioids [70, 71] but notes the data on outcome is only good for short and medium term but even its recommendation for use of opioids has been tempered in recent years including dose limitation and cautious patient selection [72]

There Has Been a Remarkable Rise in the Consumption of Opioids in the United States

According to the ARCOS data provided by the Drug Enforcement Administration, major classes of opioids have increased substantially in total grams of distribution despite the readily available data linking adverse outcome to availability [73]. In the early 1990s, opioid analgesics, led by morphine, fentanyl, oxycodone, and hydrocodone, had significant increases in use. From 2004 to 2011, hydrocodone use increased by 73 %, morphine 64 %, methadone 37 %, and fentanyl 35 %. Sales of opioids quadrupled between 1999 and 2010 [74]. Hydrocodone is the number one dispensed prescription in the United States, and the United States is the world leader in its consumption. The most remarkable increase in use and availability was buprenorphine. Buprenorphine is indicated for the treatment of addiction and dependency and, in some cases, pain.

There has been a rise from 96 mg of morphine equivalents per person in 1997 to 710 mg per person in 2010. The staggering opioid availability is equivalent to 7.1 kg of opioid for every 10,000 people [75]. There is tenfold rise in opioid consumption in the 20 years since 1992 and in particular of the drug OxyContin which was aggressively marketed as the extended version of oxycodone on release in 1995. Between 1997 and 2002, the amount of oxycodone use quadrupled [76]. Americans consume a remarkably large percentage of opioids prescribed worldwide. As a leading country in consumption, the United States only makes up 4.6 % of the world's population. The United States, however, consumes 80 % of the world's available opioids.

Has the Rising Use of Opioids Been Accompanied by Improvement in Pain Control or Quality of Life?

A 2009 Cochrane review of ten controlled trials compared opioids (oral codeine, oxycodone, oxymorphone, morphine, and transdermal fentanyl) for chronic non-cancer pain led to the conclusion that there were only small to moderate beneficial effects of non-tramadol opioids that are outweighed by large increases in the risk of adverse events, and so they should not be routinely used even for severe osteoarthritic pain [77].

A 2010 Cochrane review of long-term opioid management for chronic non-cancer pain (at least 6 months of treatment) reviewed 26 studies with 4893 participants. Quality of data was weak, with 25 case series or uncontrolled continuations of long-term trials and only one randomized controlled trial. All three modes of administration were associated with clinically significant pain reduction. However, many participants stopped treatment because of adverse effects or insufficient pain relief. The authors concluded that the evidence for pain relief with long-term opioid use was weak while that for quality of life or functional improvement was inconclusive [78].

Numerous recent studies have reported several problem areas react with chronic oral opioid [79] therapy. Opioids for arthritis pain has been associated with increased risk of fractures [80]. The reason for this association is unknown. The DAWN data teaches us that chronic opioid therapy is associated with increased emergency room visits. Increasing opioid dosing has also been associated with increased risk of trauma in automobile accidents [81]. A recent study in long-term opioid use in women concludes that long-term opioid use exposes women to unique risks, including endocrinopathy, reduced fertility, neonatal risks, as well as greater risk for polypharmacy, cardiac risks, poisoning, and unintentional overdose, among other risks. Risks for women appear to vary by age and psychosocial factors may be bidirectionally related to opioid use.

Among our military veterans, post-traumatic stress disorder and opioid therapy have been associated with poor outcomes in veterans with chronic pain [82].

Obesity, depression, multiple symptoms, and etiologies of chronic pain are predictors of poor long-term outcomes for patients with chronic pain who are continued on chronic opioid therapy [83].

Additional risk factors related to poor outcomes for chronic pain patients have been reported and include opioid use, older age, female gender, anti-social personality, government disability, and severe disability at initial evaluation and not working at discharge [84]. Furthermore, opioid prescription for longer than 7 days has been reported as a risk factor for long-term disability in workers with acute back pain. The threshold to prescribe opioids in the primary care setting is low, particularly with vague diagnosis states and external pressures. Those that are treated with opioids for chronic pain often request ever-increasing doses.

A 52-week study showed no major outcome difference between patient groups treated with a stable opioid dose regimen versus an escalating opioid dose regimen. This suggests that higher doses are not associated with additional benefit. Notably, 27 % of the subjects in this study were discharged due to misuse [85].

A recent study showed that the estimated total number of opioid analgesic prescriptions in the United States increased by 104 %, from 43.8 million in 2000 to 89.2 million in 2010. In 2000, 7.4 % of adult Americans were prescription opioid users compared with 11.8 % in 2010. In general population, there was a 6 % increase in the in opioid prescription from 2000 to 2010. However there were no demonstrable improvements in the age- or sex-adjusted disability and health status measures of opioid users. The authors go on to comment that on a public health level, these data suggest that there may be an opportunity to reduce the prescribing of opioid analgesics without worsening of population health metrics [86].

The largest studies of opioid treatment of chronic pain suggest that particularly in distressed group of patients, improvements in either pain scores or quality of life are *not* achieved [87, 88].

Sullivan has pointed out that the United States has, in effect, conducted an experiment of population-wide treatment of chronic pain with long-term opioid therapy. The population-wide benefits have been hard to demonstrate, but the harms are now well demonstrated [89]. This begs the question, has there been a proportionate growth in pain and suffering? Despite mounting evidence that chronic opioid therapy does not improve quality of life, their use continues to rise [90].

What is the meaning of this massive rise in opioid therapy? Have we undertreated pain as a legitimate affliction for decades, or have we been pressured to a more aggressive care model?

In contrast there is an abundance of evidence, however, that with this increased availability and use, increased morbidity and mortality escalate in an almost parallel fashion [91].

Evidence That the Escalating Opioid Use Has a Direct Relationship with Adverse Consequences

Increasing Death Rates Associated with Increasing Opioid Consumption

The National Centre for Health Statistics published a paper in 2009 reporting an increase in fatal opioid poisonings in the United States between 1999 and 2006 [92].

What was worrying was that the increasing death rate was particularly among younger people as can be seen on the graph above (Fig. 12.1). Overall the death rate tripled particularly among young white males and this particular study specifically highlighted methadone but also other opioids as a particular drug associated with these deaths (Fig. 12.2).

It was known that, for example, states like Florida had very high levels of death rate which were associated with the inappropriate prescribing – three times the rate of prescription of opioids compared to Illinois. As one commentator puts it, there was no evidence that the people in Florida suffered more chronic pain than the rest of the United States. Another comment was that enough prescription painkillers were prescribed in 2010 to medicate every American adult around-the-clock for a month. In fact in the same year two million people reported using prescription painkillers non-medically for the first time – nearly 5500 a day. Although most of these pills were prescribed for a medical purpose, many unfortunately ended up in the hands of people who misused or abused them. It was noted most prescription painkillers were prescribed by primary care and internal medicine doctors and dentists, not specialists. Roughly 20 % of prescribers prescribe 80 % of all prescription painkillers [93]

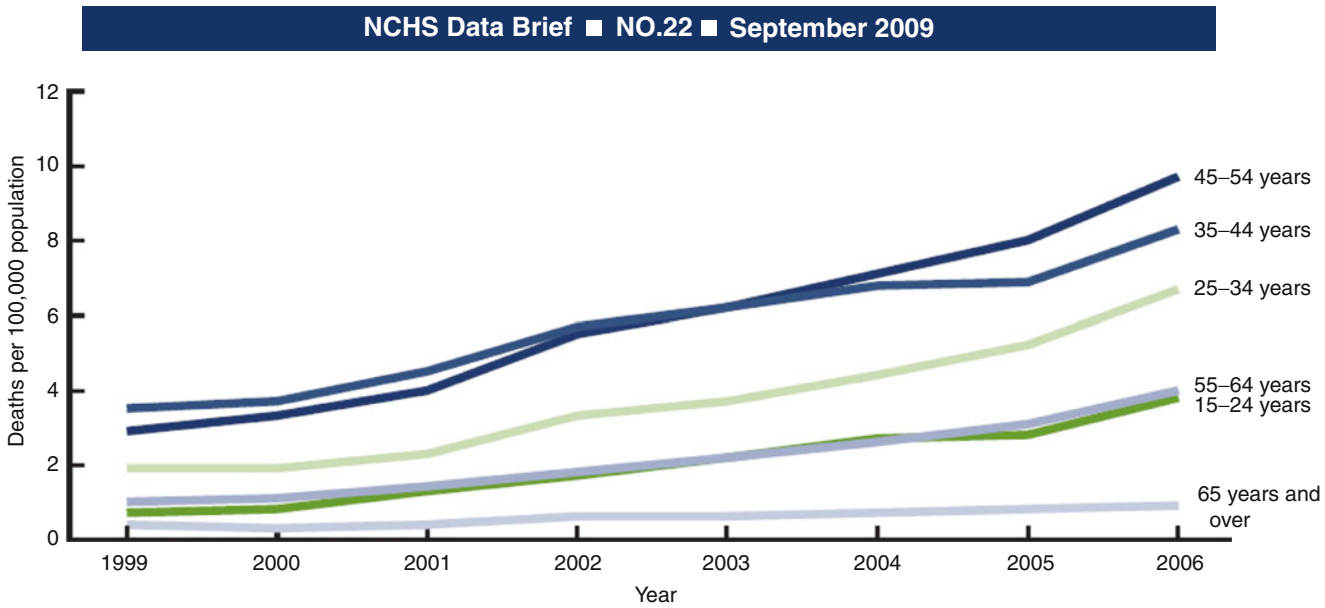


Fig. 12.1 Death rates for poisonings related to opioids (Source: CDC/NCHS, National Vital Statistics System)

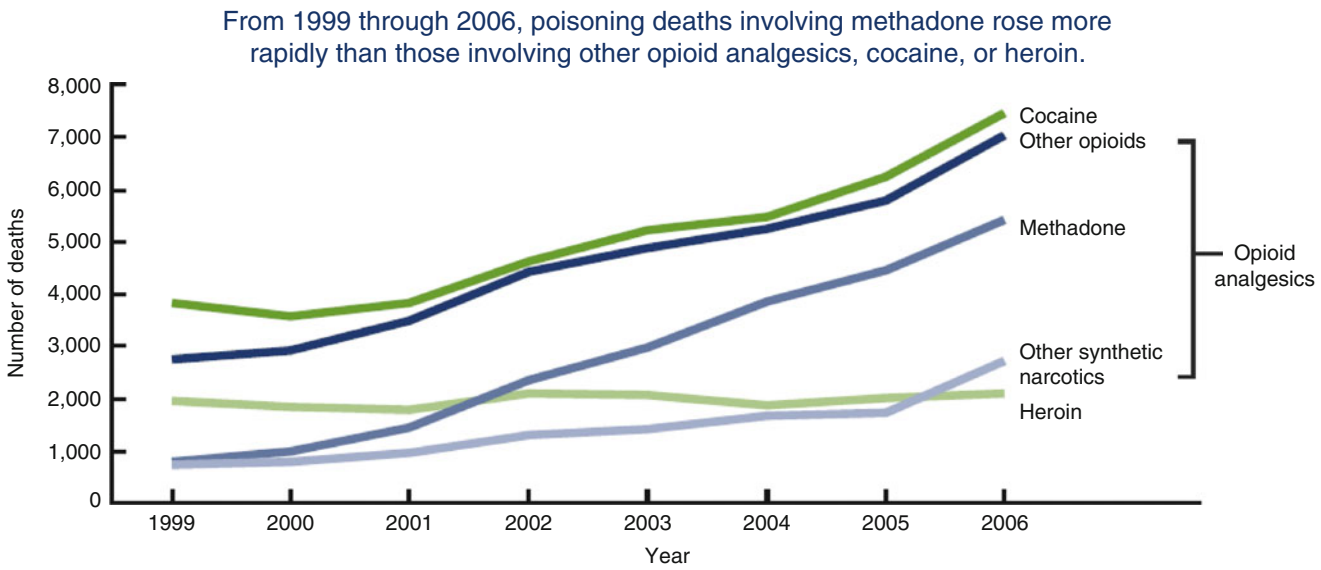


Fig. 12.2 Death rate for methadone compared to other drugs (Notes: Drug categories are not mutually exclusive. Deaths involving more than one drug category shown in this figure are counted multiple times. Access data table for Figure 2 at ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/Data_Briefs/db022/fig02.xls)

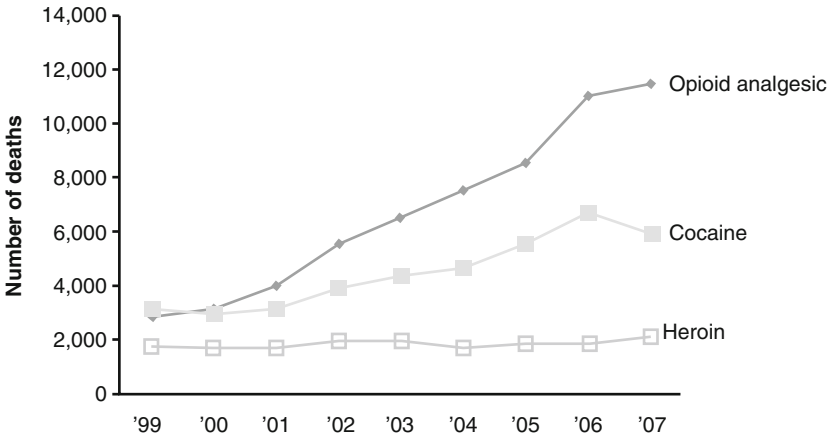


Fig. 12.3 Death rate for opioid analgesics compared to heroin and cocaine

The report also noted:

> Almost all prescription drugs involved in overdoses come from prescriptions originally. However, once they are prescribed and dispensed, prescription drugs were frequently diverted to people using them without prescriptions. More than three out of four people who misuse prescription painkillers used drugs prescribed to someone else.

The Centre for Disease Control and Prevention published a paper in July 2011 stating that during 2003–2009, death rates increased for all substances except cocaine and heroin [93] (Fig. 12.3). The death rate for prescription drugs increased 84.2 %, from 7.3 to 13.4 per 100,000 population. The greatest increase was observed in the death rate from oxycodone (264.6 %), followed by alprazolam (233.8 %) and methadone (79.2 %). By 2009, the number of deaths involving prescription drugs was four times the number involving illicit drugs. The death rate has grown in parallel with sales of opioid prescriptions (Fig. 12.4). Opioid analgesic deaths exceeded cocaine and heroin deaths at an ever-increasing rate since 1999. Cocaine deaths are actually decreasing. Recently, heroin deaths have increased, but still remains one-sixth that of opioid analgesics. Methadone is one of the cheapest and readily available opioids and is one of the leading drugs responsible for opioid fatalities. Methadone is just 3 % of opioid prescriptions in the United States but is associated with >30 % of deaths from opioids [94]. This staggering relationship could be attributed to methadone's unpredictable metabolism and half-life and the numerous drugs that interact with methadone metabolism and excretion.

Overdoses occur and are a feared complication of controlled substance management. Overdoses on opioids alone are rela-

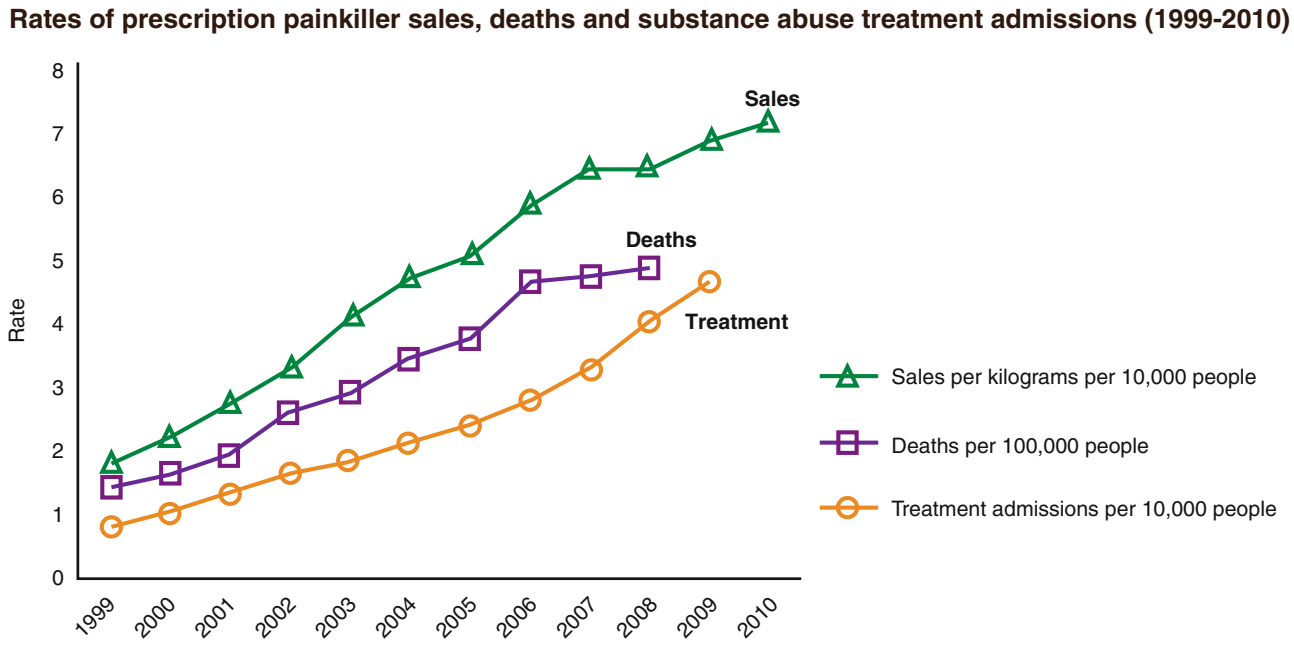


Fig. 12.4 Sales of prescription painkillers, deaths, and drug treatment admissions (Sources: National Vital Statistics System, 1999–2008; Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 1999–2010; Treatment Episode Data Set, 1999–2009)

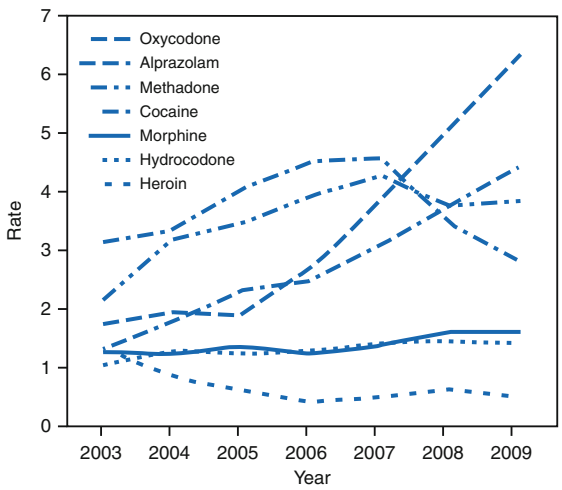


Fig. 12.5 Annual drug overdose rates in the state of Florida (*Per 100,000 population. Based on U.S. Census resident population estimates. Available at http://www.census.gov/popest/states/states.html)

tively uncommon. Usually overdoses occur with polypharmacy, other offending agents usually being benzodiazepines, or barbiturates. Barbiturates or alcohol, combined with opioids is extremely hazardous. Although opioids are the most common drug class associated with overdose, the combination of opioids with benzodiazepines and other psychotropic drugs are associated in up to 10 % of overdoses (Fig. 12.5).

A further example came from West Virginia when it was noted that there was a 550 % increase in unintentional overdoses opioid-related mortality between 1999 and 2004

While it seemed initially that the majority of the problem was due to diversion of opioid prescription to mainly young white males in 54 % of cases and this was often accompanied by doctor shopping until a prescription was obtained, therefore *that only about 44 % of the mortality was actually in those patients who were prescribed the opioid in the first place* [95].

Overdoses have increased significantly and are related to high doses and prolonged duration of treatment. In one study, those taking more than 100 mg equivalent morphine were seven to nine times more likely to overdose than if one was taking less than 20 mg [96, 97]. In a non-US study, that is, Canada, where opioids are prescribed on state funding without the financial incentives present in the United States, showed that between 1997 and 2006, patients who were prescribed more than 200 mg of morphine a day were three times more likely to die as a consequence of the prescription [81]. Bonerht found the overall death rate to be in the order of 0.04 % among those given an opioid prescription in a study funded by the Veterans Administration [96]. The risk was in fact substantially higher with higher doses of morphine above 100 mg, being almost ten times higher than if one was prescribed up to 20 mg per day and also the risk was also substantially increased in those with a history of substance abuse and those on combined regular and p.r.n. prescription. Even accepting the lower overall risk of 0.04 %, this worked out at one death in 2500 patients.

The authors worked out that the approximate average death rate per thousand chronic patient-months was approximately

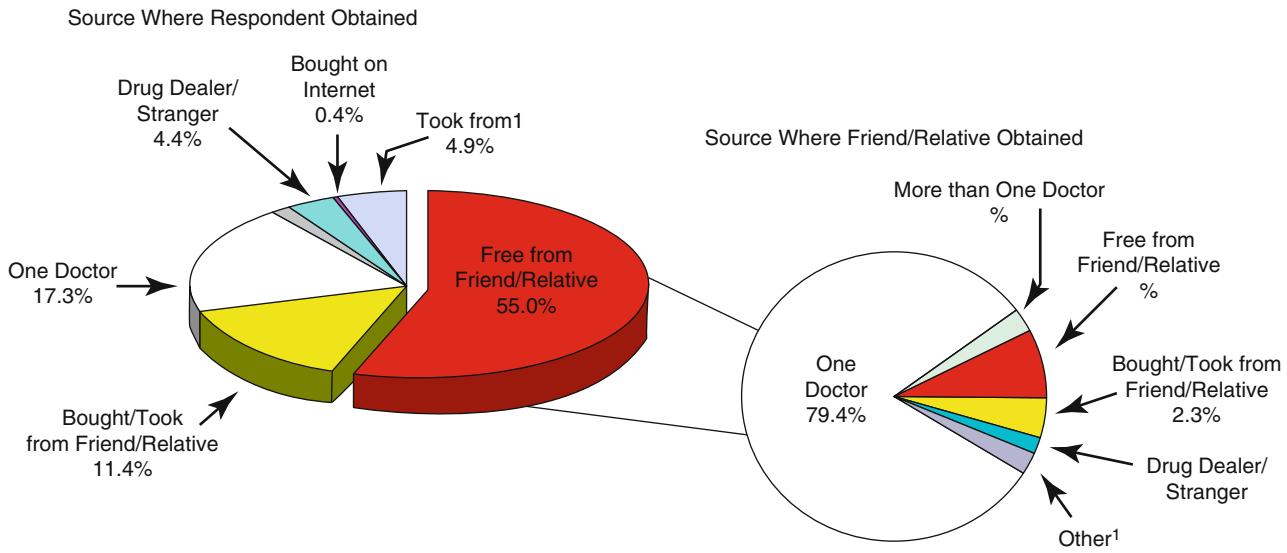


Fig. 12.6 Sources of drugs

one. That is, one patient would die every month for every thousand patients taking an opioid prescription. By any accounts this is an extraordinarily high death rate, even higher when one takes into account doses above 100 mg of morphine equivalent, substance abuse, and the type of prescription.

Increasing Opioid Consumption Associated with Other Health Burdens

The Drug Abuse Warning Network (DAWN) exists to provide information to government agencies about emergency department visits related to opioid poisoning. Even codeine, which is reported to have a decrease in prescriptions this decade, increased in misuse. Hydromorphone led the way with the highest increase between 438 %, followed by oxycodone, fentanyl, hydrocodone, and methadone. Prescription opioids revealed in DAWN data mention an increase in adverse events 4 % in 1996 data to 20 % in 2011 [89]. Not surprisingly, patients seeking detoxification also increased during this period. With the increasing liberalization of laws surrounding marijuana, a drug of abuse should be treated no differently than any other molecule of abuse and misuse. This drug has also realized an increase in adverse outcomes.

Unintentional opioid overdoses have exceeded heroin and cocaine deaths combined. Opioids contribute to 1 death every 36 min [92, 93, 98–101]. The societal impact is more complex than most providers realize. For every death, 9 patients are admitted for substance abuse treatment and 161 for abuse and dependence, with an estimated cost burden of $20 billion [102]. Heroin has recently reemerged in certain areas of the country, presumably as opioid availability decreases. Novel combinations of fentanyl and heroin are a fatal combination.

Nonmedical use of opioids for recreational purposes is now considered an epidemic in the United States [103].

Healthy Americans issued a report in October 2013 stating:

> Drug overdose deaths exceed motor vehicle-related deaths in 29 states and Washington DC. Misuse and abuse of prescription drugs costs the country an estimated $ 53.4 billion a year in lost productivity, medical costs and criminal justice costs, and currently only one in 10 Americans with a substance abuse disorder receive treatment [104].

Diversion of Opioid Therapy

Diversion of prescribed opioids is a known problem, particularly among younger patients. No validated risk assessment tool exists and no failsafe way to prevent diversion has been found that resolves or eliminates this risk. The risk of addiction is real. In a study of patients in treatment for opioids, 39 % reported being addicted to prescription opioids before switching to heroin [105].

Addiction and abuse are related problems that are often overlooked. The acute care setting of a primary care office is a high-risk environment to avoid this consequence.

For example, the National Survey on Drug Use and Health found that the numbers of new, nonmedical users of prescription opioids (primarily products containing codeine, hydrocodone, and oxycodone) increased from 600,000 in 1990 to over 5.2 million in 2006, marking it as the drug category with the largest number of new users in 2006 [106].

Diversion of prescribed opioids remains a rising problem with the young people. Among persons aged 12 older who used pain relievers nonmedically, 55 % report they received the drug for free from a friend or a relative, while another 11 % bought the drug from a friend. Diversion of prescribed opioids remains a rising problem with the young people (Fig. 12.6). Among persons aged 12 older who used pain

relievers nonmedically, 55 % report they received the drug for free from a friend or a relative, while another 11 % bought the drug from a friend or a relative. Seven million, 2.7 % of the population, persons aged 12 or older used prescription-type drugs nonmedically in the past month.

Five million of these used pain relievers. There is no validated risk assessment tool that exists to clearly identify and prevent diversion. Chronic pain may be the complaint, but in one study almost 40 % of those addicted to prescription medications eventually switched to heroin [106]

The primary sources of prescription drugs on the street were the elderly, patients with pain, and doctor shoppers, as well as pill brokers and dealers who work with all of the former. The popularity of prescription drugs in the street market was rooted in the abusers' perceptions of these drugs as (1) less stigmatizing, (2) less dangerous, and (3) less subject to legal consequences than illicit drugs. For many, the abuse of prescription opioids also appeared to serve as a gateway to heroin use [107].

Who Is Prescribing These Opioids?

Primary care physicians are responsible for the largest population of patients chronically exposed to controlled substances (Fig. 12.7). It surprises many that the vast majority of opioid prescriptions are from general practitioners, family medicine, and internists. Anesthesiologists and physical medicine, traditionally associated with pain clinics, are responsible for only about 6 % of total prescriptions combined [108].

The Role of the Drug Enforcement Agency

The DEA introduces a mixed message to prescribers treating those with pain. First, the DEA is responsible for the availability of the drug and will acknowledge that the physician is best prepared and trained to determine whether opioids are indicated. The DEA will further point out that the physicians are at risk for providing these medications and may be unwittingly providing controlled substances to inappropriate recipients. The word recipient is used over patient as often is the case of those seeking drugs for distribution. These diverters are neither a patient nor have a truly justifiable chronic pain condition that would warrant controlled substances. If a physician is a partner in diversion, knowingly or not, law enforcement has the option to prosecute.

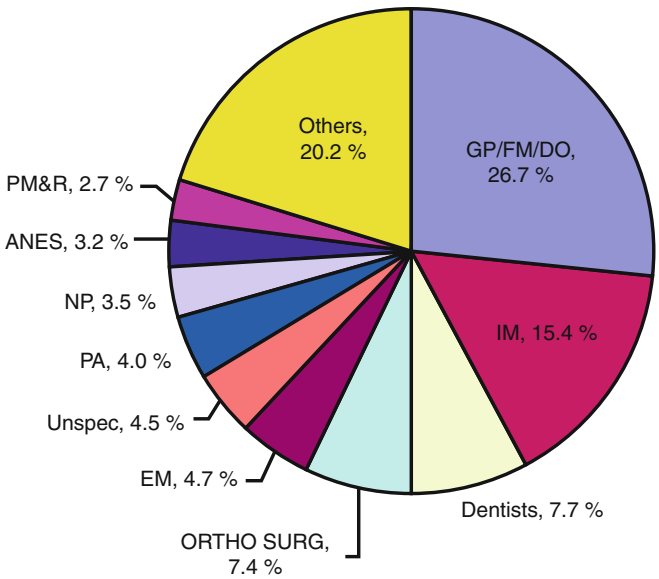


Fig. 12.7 Prescribers of drugs

SS 841 knowingly or intentionally distributing or dispensing a controlled substance

No legitimate medical purpose for the prescription in that the same was not issued/filled in the usual course of professional practice or was beyond the bounds of medical practice.

The conviction will be upheld even if the government does not present compelling evidence that the doctor prescribed with malicious motive or the desire to make a profit.

Abbreviated or no medical history of physical examination is probative on the question of whether a legitimate medical purpose exists.

Prescribing to an individual with a nefarious purpose, even if you are unaware, may implicate the prescriber and result in a legal action. The provider does not have to know or profit from the encounter. It simply has to happen. So the benefits of analgesia and improved function and quality of life are now weighed against the abuse risk, misuse, and addiction threat [109–111].

To the busy family practice physician that has not exercised proper caution, and only performs a brief history or physical that does not support opioid use in the documentation, the risk/reward benefit does not fall in the practitioner's favor.

It is not necessarily the intention to provide substandard care, but time pressures are very real and patient needs and demands can be extensive. A patient or individual that is persistent in aggressively obtaining controlled substances knowingly does so against the physician's common daily practice paradigm. Most physicians are ill equipped to confront a patient that exhibits inappropriate pain behaviors and drug-seeking activity. In some cases, a level of fear and bullying is injected into the practice from a patient that is highly motivated to obtain a controlled substance. Evidence exists that a physician is most likely to be non-confrontational, and accommodating, to diminish conflict. This would include writing a prescription as the most expeditious and safest way to remove this patient burden.

By contrast, evidence exists that poor patient selection is a leading cause of adverse outcome when opioids are utilized to treat painful disorders [112]

The previous data showing a direct relationship between dose of opioid and death rates has led. A group in Washington

State recommends the dosing equivalent not to exceed 120 mg of morphine [113]. The British Pain Society has suggested any patient on doses greater than 120–180 mg be under the care of a specialist pain physician rather than primary care.

Informed Consent in the Chronic Opioid Setting

Informed consent is not an optional endeavor in the clinical setting.

The American Medical Association guidelines state the physician should disclose:

- The patient diagnosis if known
- The nature of proposed treatment or procedure
- The risks and benefits of proposed treatment or procedure
- Alternatives
- The risks and benefits of alternative treatment including non-pharmacologic treatments
- The risks and benefits of not receiving or undergoing the treatment

These guidelines are not requirements, but this list effectively establishes a standard of care by which a physician's disclosures are measured. In general, a physician does not need to advise a patient of every conceivable risk but only the substantial risks must be disclosed. That might be what a physician would reasonably know to be a part of the treatment course and allowing the patient to decide whether they would want to consider moving forward. Informed consent may be verbal, but documentation establishes a better pathway to defend a dispute. Care must be taken that the individual who is providing informed consent is adequately trained to understand the importance of this task. The patient should have a clear understanding of the implications of informed consent and ample time to ask questions and engage in dialogue that addresses the patient's concerns.

Many guidelines now recommend obtaining separate and specific informed consent for opioid treatment. Warning patients of addiction risks as well as overdose and diversion is important. The Federation of State Medical Board rules state:

> Informed consent documents typically address:
> Treatment agreements outline the joint responsibilities of physician and patient and are indicated for opioid or other abusable medications. They typically discuss:
> The goals of treatment, in terms of pain management, restoration of function, and safety
> The patient's responsibility for safe medication use (e.g., by not using more medication than prescribed or using the opioid in combination with alcohol or other substances; storing medications in a secure location; and safe disposal of any unused medication)
> The patient's responsibility to obtain his or her prescribed opioids from only one physician or practice
> The patient's agreement to periodic drug testing (as of blood, urine, hair, or saliva)
> The physician's responsibility to be available or to have a covering physician available to care for unforeseen problems and to prescribe scheduled refills

There are recommendations for opioid agreements and screening questionnaires. Risk evaluation and mitigation strategies (REMS) training is required for long-acting and sustained-release opioid prescribing. These measures are varied depending on the specific opioid preparation. Standardization of REMS requirements will eventually assist to meet guidelines [114]

Recently, the Federation of State Medical Boards issued a new model policy including the following statement: "Additionally, providers should not continue opioid treatment unless the patient has received a benefit, including demonstrated functional improvement." Most studies of opioids for chronic pain have shown incremental improvements in pain but have failed to show functional improvement. Therefore, it seems as though chronic opioid therapy is unlikely to continue as an accepted treatment for most patients.

Washington State has developed new workers' compensation guidelines in response to an epidemic of overdoses [84]. These guidelines are an attempt to objectify treatment for subjective symptoms. The guidelines restrict the use of chronic opioid therapy to very few special cases. The guidelines reserve opioids for VAS >7 and limit the dose to 120 mg/day of oral morphine equivalents. The duration of treatment is limited to weeks. Continuation of opioids must be associated with a 30 % improvement on a 2-question instrument for pain and function [115].

Specific Comments About Methadone

Methadone is a synthetic opioid that is inexpensive and long acting. Methadone has been used for years to prevent patients in recovery from relapsing and using heroin and other street-borne opioids. Methadone clinics typically require patients to come to the clinic daily to receive a daily dose which prevents overdose. Methadone is associated with its own unique problems including cardiac arrhythmias and the interaction that it has with many drugs through hepatic metabolic pathways. This makes the half-life of methadone variable, introducing the drugs unpredictability to the pain care community. Methadone is considered a drug of enhanced risk in this regard. Methadone is falling out of favor due to deaths associated with its use for chronic pain [116]. National data demonstrate a pattern of increasing opioid-related overdose deaths beginning in the early 2000s. A high proportion of methadone-related deaths was noted. Although methadone represented less than 5 % of opioid prescriptions dispensed, one third of opioid-related deaths nationwide implicated methadone [117]. If used at all, methadone doses should be initiated at low levels and monitored closely.

Specific Comments as Regards Opioid Rotation

Opioid rotation in the presence of benzodiazepines is associated with respiratory arrest. Outpatient spinal opioid trials are as well. Many patients receive psychiatric care in secrecy to avoid insurance premium increases. These patients may not disclose their complete medication list and may be taking centrally acting drugs without the knowledge of the pain physician. Urine drug testing may help to some degree but many drugs are not routinely tested. Opioid rotation, at least at high does, should not be done in one stroke [118, 119]. One opioid can be reduced while another one titrated.

Some centers now recommend benzodiazepine tapering before optimization/rotation of opioid therapy especially in the elderly.

Spinal Opioids

Spinal opioid trials are best done as an inpatient [120, 121].

Many patients take herbal products and the pharmacologic effects of these products are unknown but should be documented as there is growing evidence that they may interact with more standard pharmaceutical agents.

Brief Comments as Regard Serving as an Expert Witness

Before serving as an expert witness, one must feel comfortable holding themselves out as experts. Many fine physicians are not experts and the expert must have a curriculum vitae and enough experience to qualify as an expert in a court of law. Experts must limit their expert opinion to their area of expertise. Being an expert in one area does not qualify one to be an expert in a related but different area. Medical societies may expel members for testifying against other members if the testimony is unprofessional.

Second, before committing to serve as an expert, the records should be reviewed. No conflict of interest should exist between the expert and either party to a lawsuit. For example, one should avoid defending or testifying against a business partner or a business competitor. Testifying against another physician is a difficult task, as is, defending a doctor who has had a serious complication. Each side will have compelling arguments and the expert must be completely comfortable with the testimony they will give. While physicians are given considerable leeway to testify, the expert's reputation is at stake as much as the defendant's. The expert should make certain that the attorney, who calls them to testify, is aware of what the expert is willing to say and what the expert is not willing to say before any trial is scheduled. Experts must be willing to make themselves available once they have committed to a case. Court schedules change and delays are inevitable. Fees for serving as an expert should be in a similar range with what the physician would generate during the same time in practice, plus any expenses for travel, lodging, meals, etc.

The medicolegal aspects of pain management are unlikely to become less complex with time. Physicians need to increase their activity in specialty societies and political action committees in order to avoid the consequences of remaining silent.

Appendix 1: A Summary of Some Potential Complications of Injection and Other Therapies and How to Avoid Them

Procedure	Complication	Mechanism	Potential solution
Thoracic and cervical trigger point injection	Pneumothorax	25–30 G needle Fanning technique	22 G Avoid fanning
Transforaminal	Spinal cord or vertebral artery injection	Sharp needle intravascular or intraneural penetration	Use a blunt needle
Single-shot epidural steroid injection	Subdural injection	Dural laceration from sharp Tuohy or spinal needle	Use of blunt needle, e.g., RX-2 coude
Epidural needle placement	Intracord injection	Initial loss of resistance is deep to epidural space due to inconsistent ligamentum flavum at cervical levels	Entry level at T2 Catheter placement to cervical level :use contrast
Occipital block	Total spinal from injection in foramen magnum, intra-arterial injection and local anesthetic toxicity, occipital nerve injury, hematoma		Use of 20-gauge stealth needle and suboccipital decompression technique. Use of contrast and avoid large volumes
Cervical transforaminal steroid injections	Total spinal, vertebral artery injury, cerebellar hemorrhage, spinal cord infarct	Use of sharp needle	Use of blunt coude needle Avoid particulate steroid
Cervical interlaminar steroid injections	Spinal cord injury, epidural hematoma, epidural abscess, loculation of injectate	Use of sharp needle	Use of blunt needle and RX-2 coude epidural needle
Cervical sympathetic block	Total spinal, pneumothorax, Horner's syndrome, recurrent laryngeal nerve block, brachial plexus block, intravascular injection and seizure, pneumochylothorax	Classic technique	Use of C7 lateral body technique, blunt needle with Bella D needle
Atlanto-occipital block	Ataxia	Central local anesthetic effect	Minimize local anesthetic volume
Cervical 3 facet denervation	Hoarseness	Vagus nerve injury	Avoid bilateral procedure
Bilateral cervical injections	Respiratory arrest	Bilateral phrenic nerve blockade	Avoid bilateral procedure
Cervical facet injection	Total spinal, spinal cord injury	Medial needle placement	Frequent use of anterior-posterior fluoroscopic localization
Intercostal block	Pneumothorax	Plural puncture with sharp needle	Use of fluoroscopy and fixation of needle at skin puncture site
Lumbar sympathetic block	Retroperitoneal hematoma, lymphatic injury	Vascular structure puncture	Use of blunt coude needle
Lumbar transforaminal injection	Paraplegia	Segmental arterial injection	Use of blunt coude and avoid deep foraminal placement Avoid particulate steroid
Lumbar sympathetic block and hypogastric plexus block	Impotence, bladder dysfunction	Autonomic block	Avoid bilateral procedure

References

1. NICE. CG88 Low back pain: Early management of persistent non-specific low back pain. NICE Clinical Guidelines: NICE; London. 2009.
2. Rudol G, Rambani R, Saleem MS, Okafor B. Psychological distress screen as predictor of outcome of epidural injection in chronic lower back pain. Bone Joint J Orthop Proc Suppl. 2013;95(Supp 20):17.
3. Domino J, McGovern C, Chang KW, Carlozzi NE, Yang LJ. Lack of physician-patient communication as a key factor associated with malpractice litigation in neonatal brachial plexus palsy. J Neurosurg Pediatr. 2014;13(2):238–42.
4. Hamasaki T, Takehara T, Hagihara A. Physicians' communication skills with patients and legal liability in decided medical malpractice litigation cases in Japan. BMC Fam Pract. 2008;9:43.
5. Improving Communication, Cutting Risk: MPS New Zealand; 2012 [cited 20 1]. p. 10–1. Available from: http://www.medical-protection.org/newzealand/casebook-january-2012/improving-communication-cutting-risk.
6. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med. 2009;360(5):491–9.
7. Shekelle PG, Wachter RM, Pronovost PJ, Schoelles K, McDonald KM, Dy SM, Shojania K, Reston J, Berger Z, Johnsen B, Larkin JW, Lucas S, Martinez K, Motala A, Newberry SJ, Noble M, Pfoh E, Ranji SR, Rennke S, Schmidt E, Shanman R, Sullivan N, Sun F, Tipton K, Treadwell J, Tsou A, Vaiana ME, Weaver SJ, Wilson R, Winters BD. Making health care safer II: an updated critical analysis of the evidence for patient safety practices 2013. Available from: http://www.ncbi.nlm.nih.gov/books/NBK133363/pdf/TOC.pdf www.ahrq.gov/research/findings/evidence-based-reports/ptsafetyuptp.html.
8. Jackson JZ, HW, ATC, Hahn, CK. Physician assistants; liability and regulatory issues 2012. Available from: http://www.mdmc-law.com/tasks/sites/mdmc/assets/Image/MDAdvisor_FALL_12_ONLINE_FINALrev.pdf.
9. MPS. Clinical negligence claims – what to expect. 2013. Available from: http://www.medicalprotection.org/docs/default-source/pdfs/factsheet-pdfs/scotland-factsheet-pdfs/clinical-negligence-claims.pdf?sfvrsn=8
10. Bolam v Friern Hospital Management Committee. Wikipedia 2014. Available from: https://en.wikipedia.org/wiki/Bolam_v_Friern_Hospital_Management_Committee
11. Manner PA. Practicing defensive medicine – Not good for patients or physicians. AAOS Now. 2007. Available from: http://www.aaos.org/AAOSNow/2007/JanFeb/Clinical/Clinical2/?ssopc=1
12. DeKay ML, Asch DA. Is the defensive use of diagnostic tests good for patients, or bad? Med Decis Making. 1998;18(1):19–28.
13. Cohen H. Medical malpractice liability reform: legal issues and fifty-state survey of caps on punitive damages and noneconomic damages. Received through the CRS Web: The Library of Congress, 2005 Contract No.: Order Code RL31692.
14. Office CB. Medical malpractice tort limits and health care spending. Background paper. Washington, D.C.: The Congress of the United States; 2006.
15. Shearer P. Punitive damage awards, caps and standards. 2007 Contract No.: 2003-R-0743.
16. Association ATR. Collateral source rule reform. Available from: http://www.atra.org/issues/collateral-source-rule-reform
17. Lord Neuberger of Abbotsbury MotR. Proportionate Costs. Fifteenth Lecture in the Implementation Programme; The Law Society 2012. Available from: https://www.judiciary.gov.uk/wp-content/uploads/JCO/Documents/Speeches/proportionate-costs-fifteenth-lecture-30052012.pdf
18. Limitation Act 1980. Wikipedia.
19. Limitation Periods in the UK. Wikipedia.
20. Kalauokalani D. Malpractice claims for nonoperative pain management: a growing pain for anesthesiologists? ASA Newsl. 1999;63(6):16–8.
21. Bird M. Acute pain management: a new area of liability for anesthesiologist. ASA Newsl. 2007;71(8). Available from: http://depts.washington.edu/asaccp/sites/default/files/pdf/Click%20here%20for%20_31.pdf
22. Liau D. Trends in chronic pain management malpractice claims. ASA Newsl. 2007;71(8):10,11,25.
23. Fitzgibbon DR, Posner KL, Domino KB, Caplan RA, Lee LA, Cheney FW, et al. Chronic pain management: American Society of Anesthesiologists Closed Claims Project. Anesthesiology. 2004;100(1):98–105.
24. Sandnes D, Stephens L, Posner K, KB D. Liability associated with medication errors in anesthesia: closed claims analysis. Anesthesiology. 2008;109(A770).
25. Fitzgibbon DR, Rathmell JP, Michna E, Stephens LS, Posner KL, Domino KB. Malpractice claims associated with medication management for chronic pain. Anesthesiology. 2010;112(4):948–56.
26. Fitzgibbon D. Liability arising from anesthesiology-based pain management in the nonoperative setting. ASA Newsl. 2001;65(6):12–5.
27. Domino K, Fitzgibbon D. Clinical lessons in chronic pain management from the Closed Claims Project. ASA Newsl. 2004;68(2):25–7.
28. Rathmell JP, Michna E, Fitzgibbon DR, Stephens LS, Posner KL, Domino KB. Injury and liability associated with cervical procedures for chronic pain. Anesthesiology. 2011;114(4):918–26.
29. Lee L, Posner K, Kent C, Domino K. Complications associated with peripheral nerve blocks: lessons from the ASA Closed Claims Project. Int Anesthesiol Clin. 2011;49(3):56–67.
30. Posner KL, Caplan RA, Cheney FW. Variation in expert opinion in medical malpractice review. Anesthesiology. 1996;85(5):1049–54.
31. Caplan R, Posner R. The expert witness: insights from the Closed Claims Project. ASA Newsl. 1997;61(6):9–10.
32. Domino K. Availability and cost of professional liability insurance. ASA Newsl. 2004;68(6):5–6.
33. Cheney F. How much professional liability coverage is enough? lessons from the ASA Closed Claims Project. ASA Newsl. 1999;63(6):19,21.
34. Huntoon MA, Martin DP. Paralysis after transforaminal epidural injection and previous spinal surgery. Reg Anesth Pain Med. 2004;29(5):494–5.
35. Alturi S, Glaser SE, Shah RV, Sudarshan G. Needle position analysis in cases of paralysis from transforaminal epidurals: consider alternative approaches to traditional technique. Pain Physician. 2013;16(4):321–34.
36. Glaser SE, Shah RV. Root cause analysis of paraplegia following transforaminal epidural steroid injections: the 'unsafe' triangle. Pain Physician. 2010;13(3):237–44.
37. Chang Chien GC, Candido KD, Knezevic NN. Digital subtraction angiography does not reliably prevent paraplegia associated with lumbar transforaminal epidural steroid injection. Pain Physician. 2012;15(6):515–23.
38. Heavner JE, Racz GB, Jenigiri B, Lehman T, Day MR. Sharp versus blunt needle: a comparative study of penetration of internal structures and bleeding in dogs. Pain Pract. 2003;3(3):226–31.
39. Ilkhchoui Y, Koshkin E. A blunt needle (Epimed(®)) does not eliminate the risk of vascular penetration during transforaminal epidural injection. Surg Neurol Int. 2013;4 Suppl 5:S404–6.
40. Scanlon GC, Moeller-Bertram T, Romanowsky SM, Wallace MS. Cervical transforaminal epidural steroid injections: more dangerous than we think? Spine (Phila Pa 1976). 2007;32(11):1249–56.
41. Tiso RL, Cutler T, Catania JA, Whalen K. Adverse central nervous system sequelae after selective transforaminal block: the role of corticosteroids. Spine J. 2004;4(4):468–74.

42. Sullivan WJ, Willick SE, Chira-Adisai W, Zuhosky J, Tyburski M, Dreyfuss P, et al. Incidence of intravascular uptake in lumbar spinal injection procedures. Spine (Phila Pa 1976). 2000;25(4):481–6.
43. Tharakan L, Gupta S, Munglani R. Survey of current UK practice in use of fluoroscopy, contrast material and steroids in neuraxial injections. Pain News. 2012;10(1):24–31. Available from: http://www.rajeshmunglani.com/documents/5surveyneuraxialblocks.pdf
44. Lirk P, Kolbitsch C, Putz G, Colvin J, Colvin HP, Lorenz I, et al. Cervical and high thoracic ligamentum flavum frequently fails to fuse in the midline. Anesthesiology. 2003;99(6):1387–90.
45. Chien GC, McCormick Z, Araujo M, Candido KD. The potential contributing effect of ketorolac and fluoxetine to a spinal epidural hematoma following a cervical interlaminar epidural steroid injection: a case report and narrative review. Pain Physician. 2014;17(3):E385–95.
46. Makris A, Gkliatis E, Diakomi M, Karmaniolou I, Mela A. Delayed spinal epidural hematoma following spinal anesthesia, far from needle puncture site. Spinal Cord. 2014.
47. Smith HS, Racz GB, Heavner JE. Peri-venous counter spread – be prepared. Pain Physician. 2010;13(1):1–6.
48. Chiapparini L, Sghirlanzoni A, Pareyson D, Savoiardo M. Imaging and outcome in severe complications of lumbar epidural anaesthesia: report of 16 cases. Neuroradiology. 2000;42(8):564–71.
49. Smith AD, Jull G, Schneider G, Frizzell B, Hooper RA, Sterling M. Cervical radiofrequency neurotomy reduces central hyperexcitability and improves neck movement in individuals with chronic whiplash. Pain Med. 2014;15(1):128–41.
50. Cheng J, Abdi S. Complications of joint, tendon, and muscle injections. Tech Reg Anesth Pain Manag. 2007;11(3):141–7.
51. Kornick C, Kramarich SS, Lamer TJ, Todd Sitzman B. Complications of lumbar facet radiofrequency denervation. Spine (Phila Pa 1976). 2004;29(12):1352–4.
52. Chinosornvatana N, Woo P, Sivak M, Sung C-K. Iatrogenic unilateral vocal fold paralysis after radiofrequency lesioning for cervical facet joint denervation. Laryngoscope. 2009;119(Supplement S1):S29.
53. Texas Medical Disclosure Panel Informed Consent Chapter 601 2012 [cited 2014]. Available from: https://www.dshs.state.tx.us/hfp/pdf/TMDP_RulesChapter601.doc.
54. Munglani R. Numbers needed to heal, numbers needed to harm, numbers needed to kill: reflections on opioid therapy and the primary duty of medicine. Pain News. 2013;11(1):5.
55. Sullivan MD, Ballantyne JC. What are we learning with long term opioid therapy? Arch Intern Med. 2012;172:433–4.
56. Krueger AB, Stone AA. Assessment of pain: a community-based diary survey in the USA. Lancet. 2008;371(9623):1519–25.
57. (IOM). IoM. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: The National Academies Press; 2011.
58. Pizzo PA, Clark NM. Alleviating suffering 101--pain relief in the United States. N Engl J Med. 2012;366(3):197–9.
59. Donovan MI, Evers K, Jacobs P, Mandleblatt S. When there is no benchmark: designing a primary care-based chronic pain management program from the scientific basis up. J Pain Symptom Manage. 1999;18(1):38–48.
60. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. Lancet. 1999;354(9186):1248–52.
61. Smith BH, Elliott AM, Chambers WA, Smith WC, Hannaford PC, Penny K. The impact of chronic pain in the community. Fam Pract. 2001;18(3):292–9.
62. Picavet HS, Schouten JS. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. Pain. 2003;102(1–2):167–78.
63. Cousins MJ, Lynch ME. The Declaration Montreal: access to pain management is a fundamental human right. Pain. 2011;152(12):2673–4.
64. International Pain Summit Of The International Association For The Study Of Pain. Declaration of Montreal: declaration that access to pain management is a fundamental human right. J Pain Palliat Care Pharmacother. 2011;25(1):29–31.
65. Rocha BA. Principles of assessment of abuse liability: US legal framework and regulatory environment. Behav Pharmacol. 2013;24(5–6):403–9.
66. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain. 1986;25(2):171–86.
67. Braden JB, Young A, Sullivan MD, Walitt B, Lacroix AZ, Martin L. Predictors of change in pain and physical functioning among post-menopausal women with recurrent pain conditions in the women's health initiative observational cohort. J Pain. 2012;13(1):64–72.
68. Mackey S. The IOM, pain report revisited: setting the stage for what's next in transforming pain care, education and research. Pain Med. 2014;15(6):885–6.
69. Pfeifer GM. Transforming pain care: an IOM report. Am J Nurs. 2011;111(9):18.
70. Simpson KH. Opioids for persistent non-cancer pain: recommendations for clinical practice. Br J Anaesth. 2004;92(3):326–8.
71. Recommendations for the appropriate use of opioids for persistent non-cancer pain: a consensus statement. Rev. ed. ed. London: The Pain Society; 2005.
72. Society BP. Opioids for persistent pain 2010. Available from: http://www.britishpainsociety.org/book_opioid_main.pdf.
73. Kenan K, Mack K, Paulozzi L. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000–2010. Open Med. 2012;6(2):e41–7.
74. Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. Pain Physician. 2014;17(2):E119–28.
75. Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: part I--evidence assessment. Pain Physician. 2012;15(3 Suppl):S1–65.
76. Okie S. A flood of opioids, a rising tide of deaths. N Engl J Med. 2010;363(21):1981–5.
77. Nuesch E, Rutjes AW, Husni E, Welch V, Juni P. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev. 2009;(4):CD003115.
78. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic non-cancer pain. Cochrane Database Syst Rev. 2010;(1):CD006605.
79. Freynhagen R, Geisslinger G, Schug SA. Opioids for chronic non-cancer pain. BMJ. 2013;346:f2937.
80. Saunders KW, Dunn KM, Merrill JO, Sullivan M, Weisner C, Braden JB, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med. 2010;25(4):310–5.
81. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. JAMA Intern Med. 2013;173(3):196–201.
82. Seal KH, Shi Y, Cohen G, Cohen BE, Maguen S, Krebs EE, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. JAMA. 2012;307(9):940–7.
83. Braden JB, Fan MY, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Trends in use of opioids by noncancer pain type 2000–2005 among Arkansas Medicaid and Health Care enrollees: results from the TROUP study. J Pain. 2008;9(11):1026–35.

84. Franklin GM, Mai J, Turner J, Sullivan M, Wickizer T, Fulton-Kehoe D. Bending the prescription opioid dosing and mortality curves: impact of the Washington State opioid dosing guideline. Am J Ind Med. 2012;55(4):325–31.
85. Naliboff BD, Wu SM, Schieffer B, Bolus R, Pham Q, Baria A, et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. J Pain. 2011;12(2):288–96.
86. Sites BD, Beach ML, Davis MA. Increases in the use of prescription opioid analgesics and the lack of improvement in disability metrics among users. Reg Anesth Pain Med. 2014;39(1):6–12.
87. Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. Pain. 2007;129(3):235–55.
88. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. Pain. 2006;125(1–2):172–9.
89. Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. Pain. 2013;154 Suppl 1: S94–100.
90. Chou R, Huffman LH. American Pain Society; American College of Physicians. Annals of Internal Medicine. 2007;147(7):505–14
91. Nations U. Report of the International Narcotics Control Board for 2004. New York: United Nations; 2005.
92. Warner M, Chen LH, Makuc DM, Anderson RN, Miniño AM. Drug poisoning deaths in the United States, 1980–2008. NCHS Data Brief. 2011;(81):1–8.
93. (CDC) CfDCaP. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. MMWR Morb Mortal Wkly Rep. 2011;60(43):1487–92.
94. Wikner BN, Ohman I, Selden T, Druid H, Brandt L, Kieler H. Opioid-related mortality and filled prescriptions for buprenorphine and methadone. Drug Alcohol Rev. 2014;33(5):491–98. doi: 10.1111/dar.12143. Epub 2014 Apr 16.
95. Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA. 2008;300(22):2613–20.
96. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011;305(13):1315–21.
97. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med. 2010;152(2):85–92.
98. Edlund MJ, Martin BC, Devries A, Fan MY, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. Clin J Pain. 2010;26(1):1–8.
99. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain. 2007;129(3):355–62.
100. Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and medicaid insurance plans: The TROUP Study. Pain. 2010;150(2):332–9.
101. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain. 2007;8(7):573–82.
102. Inocencio TJ, Carroll NV, Read EJ, Holdford DA. The economic burden of opioid-related poisoning in the United States. Pain Med. 2013;14(10):1534–47.
103. Manchikanti L, Helm S, Fellows B, Janata JW, Pampati V, Grider JS, et al. Opioid epidemic in the United States. Pain Physician. 2012;15(3 Suppl):ES9–38.
104. http://healthyamericans.org/reports/drugabuse2013/. 2013.
105. Peavy KM, Banta-Green CJ, Kingston S, Hanrahan M, Merrill JO, Coffin PO. "Hooked on" prescription-type opiates prior to using heroin: results from a survey of syringe exchange clients. J Psychoactive Drugs. 2012;44(3):259–65.
106. Administration SAaMHS. Results from the 2010 National Survey on Drug Use and Health: summary of national findings. Rockville: NSDUH; 2011.
107. Inciardi JA, Surratt HL, Cicero TJ, Beard RA. Prescription opioid abuse and diversion in an urban community: the results of an ultra-rapid assessment. Pain Med. 2009;10(3):537–48.
108. Governale L. Outpatient prescription opioid utilization in the U.S., years 2000 – 2009. Food and Drug Administration; White Oak, Maryland. 2010.
109. State-by-state opioid prescribing policies 2014 [September 2014]. Available from: http://www.medscape.com/resource/pain/opioid-policies.
110. Bolen JR, R. Prescription drug diversion prosecutions – quick reference card US DOJ 2002 [cited 2014]. Available from: http://www.doctordeluca.com/Library/WOD/OxyDrugcardProsecutorCheatSheet02.pdf.
111. Brushwood DB. Drug enforcement administration liability for false arrest of physician. J Pain Palliat Care Pharmacother. 2009;23(2):156–62.
112. Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: part 2--guidance. Pain Physician. 2012;15(3 Suppl):S67–116.
113. Fulton-Kehoe D, Garg RK, Turner JA, Bauer AM, Sullivan MD, Wickizer TM, et al. Opioid poisonings and opioid adverse effects in workers in Washington State. Am J Ind Med. 2013;56(12): 1452–62.
114. Thompson CA. Long-awaited opioid REMS affects prescribers more than dispensers. Am J Health Syst Pharm. 2011;68(11): 963–7.
115. Boards FoSM. Federation of state medical boards model policy on the use of opioid analgesics in the treatment of chronic pain. Washington DC. July 2013.
116. Prevention CfDCa. Prescription painkiller overdoses: methadone 2014. Available from: http://www.cdc.gov/features/vitalsigns/methadoneoverdoses/.
117. Webster LR, Cochella S, Dasgupta N, Fakata KL, Fine PG, Fishman SM, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. Pain Med. 2011;12 Suppl 2:S26–35.
118. Fine PG, Portenoy RK, Rotation AHEPoERaGfO. Establishing "best practices" for opioid rotation: conclusions of an expert panel. J Pain Symptom Manage. 2009;38(3):418–25.
119. Centre MGDNP. Practice toolkit. Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. Michael G. DeGroote National Pain Centre: Michael G. DeGroote National Pain Centre. Available from: http://nationalpaincentre.mcmaster.ca/opioid/
120. Rathmell JP, Miller MJ. Death after initiation of intrathecal drug therapy for chronic pain: assessing risk and designing prevention. Anesthesiology. 2009;111(4):706–8.
121. Coffey RJ, Owens ML, Broste SK, Dubois MY, Ferrante FM, Schultz DM, et al. Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain. Anesthesiology. 2009;111(4):881–91.

Part IV

Molecular Neurolytic Technique

Intrathecal Substance P-Saporin for the Treatment of Intractable Cancer Pain

13

Hugh Nymeyer, Douglas A. Lappi, Denise Higgins, Carl E. Noe, and Arthur E. Frankel

Introduction

Pain that is refractory to current medical treatments is a worldwide medical problem. Twenty percent of people have chronic pain [1]. Fifty percent of patients with cancer have pain, and 15 % of cancer patients have moderate to severe pain despite treatment [2].

The World Health Organization's analgesic ladder for cancer pain [3, 4] recommends a 3-step analgesic ladder including: (step 1) nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen with or without adjuvants, (step 2) weak opioids with or without NSAIDs and adjuvants, and (step 3) strong opioids with or without NSAIDs and adjuvants. Guidelines for the treatment of cancer pain [5–7] endorse a step-wise approach that has also been used for chronic non-cancer pain [8].

A number of other therapies for managing pain besides NSAIDs and opioids do exist. Oral tricyclic antidepressants, selective serotonin/norepinephrine reuptake inhibitors, calcium channel $\alpha_2\delta$ ligands (gabapentinoids), topical capsaicin, and lidocaine are used as non-opioid co-analgesics [9–11] and carbamazepine and oxcarbazepine for cranial neuralgias, particularly trigeminal neuralgia [9]. Localized inflammatory pain can be treated with oral and injectable steroids [12]. Radiotherapy [13] is highly effective for bone pain and drugs that modify the bone remodeling process, e.g., bisphosphonates and denosumab are also used [14]. Local anesthetic nerve blocks are highly effective for regional pain [15]; however, they block other sensations and motor functions rather than pain selectively, and they are short acting. Continuous nerve blocks with local anesthetic infusions may be efficacious for the control of localized cancer pain [16]. Intrathecal pumps [17] are used to deliver opioids, local anesthetics, or the N-type voltage-gated calcium channel blocker ziconotide for cancer pain when systemic opioid-related side effects are dose limiting. Finally, neurolytic blocks [18] and cordotomy [19, 20] are used for selected patients. However, these pain control measures are limited to treating pain of a specific character or location. NSAIDs and opioids continue to be the mainstay of pain control for the majority of patients.

The side effects and limitations of NSAIDs and opioids are well known [21, 22]. In a retrospective study [23] of 593 cancer patients treated by a university pain service, patients reported (as a percentage of total time) impaired activity 74 %, mood changes 22 %, sedation 14 %, constipation 23 %, nausea 23 %, dyspnea 16 %, dysphagia 11 %, and urinary problems 6 %, despite aggressive side-effect prophylaxis. Pain relief was inadequate in 14 % of patients. Another retrospective analysis reported 9 % of cancer patients had inadequate pain control at their last therapy [24], and another study of palliative care patients reported 12 % had inadequate pain control over the course of treatment [25]. Another study found that in patients with neuropathic pain only one in three has at least a 50 % reduction in pain using standard therapy [26].

In this work, we discuss SP-SAP, a new approach to pain therapy. SP-SAP is a targeted therapy: the targeting molecule substance P (SP) binds specifically to the NK1 receptor which allows the cellular toxin saporin (SAP) to enter and eliminate only those cells. Intrathecal SP-SAP is selectively toxic to projection fibers that ascend in the spinal cord to supraspinal centers while selectively sparing non-nociceptive sensory and motor pathways.

H. Nymeyer, PhD • A.E. Frankel, MD (✉)
Hematology/Oncology Division, University of Texas Southwestern, 5323 Harry Hines Blvd., Dallas, TX 75390-8852, USA
e-mail: arthur.frankel@utsouthwestern.edu

D.A. Lappi, PhD • D. Higgins, BS
Advanced Targeting Systems, 10451 Roselle St., #300, San Diego, CA 92121, USA

C.E. Noe, MD
Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX 75235-9068, USA

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6_13

SP-SAP: Animal and Human Tests

SP was discovered in 1931 by von Euler and Gaddum [27] as a vasodilator and peristaltic inhibitor in brain and intestinal tissue. SP was then identified as an oligopeptide [28] but the sequence remained unknown until 1971 [29]. SP is in a class of tachykinin peptides sharing a common C-terminal sequence motif and widely expressed in the body [30]. The neurokinin-1 receptor (NK1R) is the native SP receptor and is a highly conserved G-protein-coupled receptor with two isoforms, a long form and a truncated form, that are differentially expressed in tissues [31–37]. High sequence homology among the tachykinins and the measured in vitro binding constants [38–40] suggest that there may be biologically relevant cross talk among the different tachykinins and their receptors.

SP was postulated to be a neurotransmitter in afferent neurons [41, 42] and, more specifically, in nociceptive fibers for multiple reasons. First, SP is more abundant in the dorsal spinal nerve roots compared to the ventral nerve roots [41, 42]. Secondly, in the spinal cord, SP is concentrated in unmyelinated fibers in Lissauer's tract and in the dorsal horn [43–45]. SP density is greatest in superficial dorsal horn lamina I and the outer regions of lamina II of the spinal gray matter. However, deeper dorsal horn laminae III, IV, and V, the lateral spinal nucleus, lamina X, and the medial edge of the dorsal horn also contain SP, but at a less intense density [46]. Thirdly, ligation of the dorsal roots in the cat depletes SP in the dorsal horn [45], indicating that SP is synthesized by sensory afferent fibers and transported to axon terminals in the dorsal horn, where it is stored in vesicles [47]. As expected for a nociceptive neurotransmitter, high temperature [48, 49], pinch [50], noxious chemicals [50, 51], capsaicin [48, 52], and direct C-fiber stimulation [48, 53, 54] induce the release of SP in the spinal cord, and SP release is blocked by opioids [55]. Also, direct iontophoric application of SP depolarizes neurons slowly in the dorsal horn [56, 57]. Finally, intrathecal injections of SP evoke behaviors associated with pain in animal models [58–60].

In the dorsal horn gray matter, the highest percentage of NK1R+ neurons is in lamina I [61] and is consistent with the association of SP and nociceptive signaling via lamina I projection fibers. However, a significant background level of NK1R throughout the spinal gray matter is present and high levels of NK1R are in several ventral motor nuclei and the intermediolateral nucleus [62–67]. This indicates a mismatch between SP and NK1R densities that had been previously observed throughout the central nervous system [62, 68, 69]. The SP and NK1R mismatch, the absence of co-localization of NK1R at synaptic clefts, the demonstrated ability of SP and other peptides to diffuse long distances throughout the spinal cord parenchyma, and the lack of known peptide reuptake mechanisms led to the concept that SP may act primarily via *volume transmission* [70] rather than purely via synaptic transmission. Agnati et al. [71] have reviewed volume transmission. It is now recognized [72] that while SP modulates pain sensation, it is not the primary pain neurotransmitter.

SP is endocytosed when it binds to many different NK1R+ cells. This has been shown in cultured non-neural cells [73–75] and also in neurons [76, 77]. After endocytosis, bound SP is lysosomally degraded and the NK1R is returned to the cell membrane [78]. This feature of the SP/NK1R system provides the opportunity to selectively target NK1R+ cells by covalently bonding SP to a cellular toxin that otherwise cannot enter neurons but that can survive intact and enter via NK1R-mediated endocytosis and lysosomal processing. Examples of such conjugates are DAB_{389}SP-Gly, a conjugate of SP and diphtheria toxin [79]; SP-SAP [80]; SSP-SAP [81] (which covalently links a proteolytically resistant SP-like peptide with SAP); BoNT/A-LC:SP [82], which covalently links the botulinum neurotoxin A light chain and SP; and SP-PE35 [83], which covalently links SP to a *Pseudomonas* exotoxin that selectively targets cholinergic and nitric oxide synthase interneurons. This selective targeting of a particular neural cell, i.e., an NK1R+ cell, for destruction has been described as "molecular neurosurgery" [84].

SAP is a 30 kDa ribosome-inactivating protein, found in seeds of the soapwort plant *Saponaria officinalis* [85], that induces apoptosis via N-glycosidase activity on the large ribosomal subunit [86]. SAP alone has a weak ability to enter cells and consequently is relatively nontoxic unless covalently attached to targeting agent recognized by a cell surface marker. A non-covalent mixture of SP and SAP is 500 times less toxic than the conjugated SP-SAP molecule as measured by the median effective dose for inducing cell death [80]. Similarly, NK1R binding and internalization is necessary for lethality. SP-SAP is 500 times less toxic to a cell that does not express NK1R compared to one that does express NK1R by the same measure [80].

Because of this 500-fold difference in toxicity, SP-SAP can selectively target cells that express high levels of NK1R while sparing other cells in the vicinity. In neonatal spinal cord neurons in culture, a 10^{-7} M mixture of SP and SAP produced no visible cellular damage but 10^{-7} M SP-SAP produced widespread cell death secondary to NK1R endocytosis [87], with full lethality observed only after 10 days. Similarly, large differences in toxicity between SP, isolated toxin, and SP-toxin conjugates have also been observed in DAB_{389}SP-Gly [79] and SSP-SAP [81].

The selective cytotoxicity of SP-SAP has been demonstrated in the central nervous system (CNS) of experimental animals. SP-SAP injected in rat striatum was observed to induce a dose-dependent cytotoxicity [80]. Similarly, when SP-SAP was injected intrathecally into rat spines at the L4 level, it reduced NK1R levels in laminae I/II by a statistically significant 85 %. In contrast, unconjugated SAP injections showed no statistically significant difference compared to injected saline. Twenty-eight days after treatment, SP-SAP

showed no detectable effect on bystander neurons including preganglionic sympathetic neurons, motor neurons, astrocytes, microglia, SP-expressing cells in the dorsal root ganglion (DRG), or SP expression levels in laminae I/II, indicating that SP-SAP did not target SP-secreting afferent fibers [87]. In multiple studies, NK1R+ cell counts are strongly depleted in laminae I/II after SP-SAP treatment, e.g., 85 % [87], 59 % [88], 68 % [89], greater than 58 % [90], and 90 % [91]. Many studies have also observed comparable depletion of lamina III or combined laminae III/IV NK1R+ cell counts [88–93]. NK1R+ cell counts have also been found to be depleted by one half to one third in laminae IV and V [94].

The lack of cytotoxicity in deeper lamina, particularly the ventral horn motor neurons as quantified by acetylcholine–acetyltransferase staining, has been speculated to be due to the short half-life of SP-SAP in the CNS (less than 15 min [92, 95]) and the time required to diffuse to deeper lamina [87]. Also, other neurons and non-neural tissues express NK1R, and it seems plausible that SP-SAP would show cytotoxicity to these other tissues at sufficiently high concentration. For example, SP-SAP has been shown to be cytotoxic to cells transfected with the NK1 receptor [80], and DAB389SP-Gly has been shown to be cytotoxic to cells naturally expressing or transfected with the NK1 receptor [79].

In order for SP-SAP to useful as a therapy for the reduction of acute pain, the safety and efficacy profile of SP-SAP must be understood. Unfortunately, interpreting analgesic testing in animal models is fraught with difficulties [96] for a number of reasons. First, there are different types of pain, and each may respond differently to different therapies. Pain may vary in its origin, intensity, character, method of transmission, and the behaviors elicited. Second, pain is only inferred indirectly via those behaviors, and pain behaviors can be triggered and modified by other factors besides pain, e.g., anxiety, aggression, conditioning, and non-pain reflexes, which can mask the pain response. Third, most animal pain models measure a nociceptive or sensory threshold rather than pain intensity, which makes them limited models for clinical pain in humans.

Despite these limitations, a number of methods to induce and measure different mechanisms of pain in animals have been developed and are in wide usage [96]. An accepted model of acute pain is the formalin test that involves injecting the dorsal surface of a rat paw with a 0.5–15 % solution of formalin. The level of pain is assessed by changes in posture with respect to the paw. The formalin test produces a biphasic response, a first phase that occurs about 3 min after injection and a second phase that occurs 20 min post injection. Both phases respond to opioids, but only the later phase responds to NSAIDs. Other algogenic agents, including capsaicin or complete Freund's adjuvant (CFA), have been used in lieu of formalin in acute pain models.

The formalin test is used for acute or tonic pain; however, injections of a chemical irritant, e.g., carrageenan, capsaicin, or CFA, into the plantar surface of a rat's paw will also induce inflammation leading to thermal hyperalgesia and mechanical allodynia. Mechanical allodynia is measured by the threshold force associated with paw withdrawal. von Frey hairs or an array of plastic monofilaments with a spectrum of stiffness are used to quantify mechanical allodynia. Thermal hyperalgesia is commonly assessed by the latency for paw withdrawal from a hot surface. Different chemical inflammatory agents can be used in animal models to produce pain states with different mechanisms and differentiate between neurogenic and non-neurogenic allodynia and hyperalgesia. Variations of these three tests, the formalin test, the thermal hyperalgesia test, and the mechanical allodynia test, have been used to study targeted pain therapies such as SP-SAP.

Several have consistently confirmed the safety and efficacy profile of intrathecal spinal injections of SP-SAP in small animals. Intrathecal injections (5×10^{-11} mol) into the lumbar spine region of rats produced no observable changes in body weight, alertness, or behavior during a 1-month observation period. However, this injection reduced pain behaviors in response to subsequent capsaicin injections [87], including an 85 % reduction in mechanical hyperalgesia, a 60 % reduction in thermal hyperalgesia, and a 75 % reduction in acute pain quantified by lifting and guarding of the injected paw. Reductions in mechanical hyperalgesia and thermal hyperalgesia were evident 3 days post SP-SAP injection and remained throughout the 28-day period.

A follow-up study that delivered 10^{-11} mol of SP-SAP intrathecally to the lumbar spine region (20 % of the dose in the prior-study) showed similar analgesic effects on a wide variety of pain tests administered 30 days after treatment occurred [88]. Significant reductions were observed in late-phase pain behaviors induced by subcutaneous formalin injections, mechanical allodynia from subcutaneous carrageenan injections, mechanical allodynia from CFA injections, and mechanical allodynia created by nerve ligation. Results were stable over 200 days until the termination of the study. These magnitudes of reductions in pain were reproduced in similar studies of intrathecal SP-SAP by Suzuki et al. [97] and Khasabov et al. [89], in a study of intrathecal DAB_{389}SP-Gly [79], in a study of the effects of intracisternal injections of SP-SAP on oral capsaicin induced pain [98], in a study of the effects of intracisternal injections of BoNT/A-LC:SP on taxol-induced thermal hyperalgesia [82], in a study of carrageenan-induced hyperalgesia [93], in a study of mechanical injury to the zygapophyseal joints of rats pretreated with SSP-SAP [94], and in a study of opioid-induced and incision-induced hyperalgesia [99].

Both lumbar spine injections of SP-SAP [90] (175 ng; approx. 5.9×10^{-12} mol) and SSP-SAP [100] (various doses up to 100 ng; approx. 3.4×10^{-12} mol) have been used with a different set of animal pain models to test the efficacy of NK1R-targeted toxins. In the formalin test model, a

significant reduction in late-phase response was observed after intrathecal treatment with SSP-SAP [100]. In a hot plate testing model, significant reductions were observed in the latencies to the onset of pain behaviors such as licking and guarding [90, 100]. Finally, in an operant escape test model in which a rat could voluntarily partition its time between a box with a hot floor and an unpleasant brightly lit box, the injections significantly reduced the time spent in the brightly lit box [90, 100]. This suggests that real reductions in thermal pain are occurring after SP-SAP treatment rather than just reductions in nociceptive reflexes.

SP-SAP treatment has been tested specifically in a model of neuropathic pain. Mechanical hyperalgesia was induced in the model of ligation of the L5 and L6 spinal nerves; then after several weeks, SP-SAP was administered and shown to reduce the perception of pain [88]. SP-SAP treatment has also been tested in a model of spinal cord injury induced by intraspinal injections of quisqualic acid, an agonist for the AMPA glutamate receptor. Quisqualic acid induces pathological spinal changes resembling spinal cord injury and a biting behavior and excessive grooming, indicative of pain [101]. Intrathecal SP-SAP treatment has been shown to delay the onset of excessive grooming, to decrease the area of excessive grooming, and to decrease the severity of excessive grooming; these changes occurred whether treatment occurred at the time of injury or after the onset of excessive grooming [102].

Key findings are produced from these studies. First, both pain behaviors and hyperalgesia can be mediated by spinal circuits, spinal-bulbar-spinal circuits, and circuits involving the cortex. Each type of circuit can be differentially modified by intrathecal SP-SAP treatment. For example, intrathecal SP-SAP treatment showed no significant effect on the time spent in licking or guarding behaviors after standing on a hot plate [90] (as opposed to the latency for the onset of licking or guarding). SSP-SAP treatment showed only a weak effect at low temperatures [100]. It is suggested that licking and guarding, being largely spinal or possibly bulbar reflexes present in decerebrate rats [103, 104], are less affected by the injections, unlike higher cortical responses to pain . NK1R+ neurons mediate not only local effects in the spinal cord, e.g., windup of wide dynamic range neurons [89, 97] and long-term potentiation of wide dynamic range neurons [105], but also non-local effects involving brainstem or cortical circuits (e.g., mechanical allodynia, thermal hyperalgesia, and formalin-induced pain) [97, 106, 107]. It is also possible that intrathecal SP-SAP treatment differentially modifies the affective and sensory components of pain [108, 109].

Second, intrathecal SP-SAP does not abolish pain transmission as much as it modifies pain sensitivity, hyperalgesia, and allodynia. Targeting NK1R+ neurons affects behavioral responses to intermediate temperature challenges (42–48 °C), but responses to the highest temperatures are unaffected by SP-SAP or SSP-SAP injections, as measured behaviorally [100] or through direct electrophysiological measurements of projection fibers [97]. Also, signaling of spinal neurons in response to 10 μg of applied capsaicin is reduced after SP-SAP treatment, but signaling is identical between SP-SAP-treated and SP-SAP-untreated rats when 100 μg of capsaicin is applied [89]. This is consistent with data from preprotachykinin-A (cleavage products of which include SP, neurokinin A, neuropeptide K, and neuropeptide γ) and NK1R knockout mice, which show a reduction in most middle-intensity responses to pain but preserve normal high-intensity pain responses [110, 111] (however, see Zimmer et al. [112]). Preservation of acute pain sensation is an attractive property of SP-SAP therapy, as it would preserve the protective effects of responses to acute pain.

The complexity of measuring pain using animal models, the possibility of off-target effects due to the ubiquity of the NK1R, the complexities of dosing an intrathecally administered drug, and the possibility of induced hyperalgesia prompted SP-SAP testing in larger animals prior to human testing. Two pharmacokinetic and pharmacodynamic studies of intrathecal SP-SAP were recently reported in canines [92, 95]. Both studies used intrathecal lumbar catheters to deliver a single bolus of SP-SAP of different amounts with at least 28-day medical and behavioral observation followed by examination of the spinal cord. The studies consistently observed the depletion of NK1R-expressing cells in the ventral horn with injections of 15 μg (approx. 5×10^{-10} mol) or more of SP-SAP without significant long-term medical, behavioral, or histological changes outside of the dorsal horn gray matter.

The studies consistently detected a population of NK1R+ cells in ventral horn motor neurons, which could account for the loss of posterior muscle tone and pelvic-limb paraparesis that was observed in one study with intrathecal injection of 150 μg [95]. Three of six canines at the 150 mcg dose showed a loss of tail muscular tone, loss of pelvic-limb proprioceptive reflexes, and loss of withdrawal reflexes. All six canines at the 150-mcg dose showed a significant loss of ventral horn NK1R+ staining and, in some, widespread pathological changes in the upper spinal cord and brain.

While behavior changes were not observed in the other study using injection of 45 or 150 μg, CNS infiltrates were observed in the 150 μg group, suggesting that similar changes were occurring there. NK1R+ cells have been found in the ventral horns of all mammals examined.

Brown and Agnello [113] recently reported the results of a double-blinded randomized controlled companion animal trial of intrathecal SP-SAP to assess efficacy in the treatment of bone pain in 70 canines. Injections were given at the L5–L6 junction for hind-limb pain or at the cisterna magna for forelimb pain. All canine subjects were treated with a fixed standard-of-care pain therapy at the time of randomization.

Primary study endpoints included: (i) the time to unblinding, which occurred either upon canine death or upon request by the owner for a modification of pain treatment, and (ii) the total number of canines unblinded at 6 weeks post randomization due to death or owner request. Four secondary endpoints were based upon (i) the Canine Brief Pain Inventory (BPI) estimation of pain severity (as answered by the blinded owners of the dogs), (ii) the Canine BPI estimation of pain interference (similarly answered), (iii) change in lameness as evaluated by an orthopedist blinded to both treatment group and visit, and (iv) daytime activity counts. Secondary endpoints were evaluated 2 weeks post randomization. Significant reductions in pain in the SP-SAP-treated animals were observed in both time to unblinding ($P=0.002$) and number of canines unblinded ($P=0.001$). Each secondary endpoint showed improvements in the SP-SAP-treated arm relative to the control arm; however, secondary endpoints did not reach the level of statistical significance.

Importantly, similar motor neuron problems, hind-limb weakness and ataxia, were seen in some canines in this study, but only when injections were performed into the cisterna magna at the base of the brain and only at the higher doses, 60 μg for dogs above 30 kg in weight and 40 μg for dogs 16–30 kg in weight. After the observation of paraparesis and ataxia, the remaining five canines that received cisterna magna injections received half-doses. No ataxia or plegia was observed either at the lower dose injections in the cisterna magna or in any of the lumbar injections. Additionally, unlike previous motor dysfunction, onset was slow, occurring over 5–7 weeks. Both the lack of dysfunction and slow onset led the investigators to speculate that this may be an effect of SP-SAP on higher order brain centers rather than direct action on the ventral horns of the spinal cord.

A phase I clinical trial of SP-SAP in human subjects with cancer and pain to assess safety is ongoing (ClinicalTrials.gov identifier NCT02036281) and due for completion in July 2016. SP-SAP is being injected intrathecally via a catheter placed at the L5–S1 interspace in a single bolus with a maximum planned dose of 90 μg. Injections are made inferior to the spinal cord, minimizing the risk of spinal cord injury and reducing the risk related to cephalad spread of SP-SAP. The primary effectiveness outcome assessments are changed in the self-reported pain intensity, bothersomeness, and mood using a number of surveys, including the visual analog scale [114] (VAS) of "bothersome pain," [115] the VAS scale of "pain intensity," [116] the Oswestry Disability Index [117], the EuroQol EQ-5D quality of life index [118, 119], and the Beck Depression Inventory [120, 121] and a daily log of analgesic use.

What can be concluded from the SP-SAP animal trials to date? First, SP-SAP has shown a consistently positive, statistically, and clinically significant effect on pain sensation in canines with reductions in mechanical and thermal allodynia and reductions in acute pain. Second, this effect on pain correlates with reductions in the number of NK1R+ neurons in the dorsal spinal cord known to transmit nociceptive signals. Third, these effects may be permanent, as expected from a targeted neurotoxin. In the two canine safety studies, observations extended up to 90 days [92, 95], and in the canine efficacy study [113], observations extended until the canines succumbed to cancer, which was in some instances several hundred days [113]. No compensatory changes have been observed in any study that would suggest the development of induced hyperalgesia after treatment. Fourth, there are potential side effects and toxicity to SP-SAP due to the fact that NK1R is widely distributed within the central and peripheral nervous systems and outside the nervous system. Mitigating factors are that SAP in isolation has low toxicity and substance P is rapidly hydrolyzed by endogenous peptidases; the mean half-life in the CSF is about 15 min [92, 95], and the mean half-life in plasma is 1.6 min [122]. Injections up to 150 μg in the lumbar region of canines resulted in some observed infiltrates but no frank motor dysfunction over the extended observation periods.

SP-SAP, Knockouts, Knockdowns, and NK1R Antagonists

The successful application of SP-SAP as an analgesic treatment might seem paradoxical in light of the results of NK1R antagonists, NK1R knockouts and knockdowns, and SP knockouts. It was once believed that SP is a primary neurotransmitter for pain signals in the spinal cord and NK1R antagonists were promising candidates as opioid replacements. However, NK1R antagonists showed only weak analgesic effects [123].

Despite the negative results of NK1R antagonists for the treatment of pain, it is critically important to distinguish the effects of SP-SAP, which ablates neurons expressing NK1R, and the effects of specific antagonists to NK1R, NK1R knockouts/knockdowns, or SP knockouts. The former targets and eliminates a whole class of neurons using NK1R as a marker, but the latter merely blocks a single signaling pathway on those neurons. Blocking NK1R-mediated signaling selectively can produce similar behavior to ablating NK1R-expressing neurons with SP-SAP. For example, intrathecal SP-SAP injections [87, 88, 97], NK1R antagonists [124–128], NK1R knockouts [111, 129] and knockdowns [130], and PPT-A knockouts [110, 112] reduce pain behaviors in the formalin test. On the other hand, selectively blocking NK1R signaling can under some circumstances produce results that are greatly at variance with the results of ablating NK1R-expressing neurons with SP-SAP. For example, intrathecal SP-SAP injection reduces allodynia induced by nerve ligation [88] or by CFA injections [88, 97], but PPT-A

knockouts still show wild-type allodynia to both nerve ligation and CFA injections [110]. NK1R knockouts and knockdowns are viable and grossly normal behaviorally [111, 129, 130], but injections of SP-SAP into the forebrain or brainstem can disrupt normal respiratory hypercapnic responses [131] and produce motor dysfunction [80].

Possible Mechanisms of SP-SAP Treatment

The mechanisms by which targeting SP-SAP ablation produces analgesia are not precisely known. First, targeted ablation may simply reduce the number of projecting pain fibers in the spine. While fewer than half of the lamina I neurons are NK1R+ [61, 88, 132, 133], approximately 80 % of the lamina I neurons that project to the thalamus [134] or brainstem [135] are NK1R+, and intrathecal SP-SAP kills the majority of NK1R+ lamina I neurons [87, 88, 92, 95]. Spinal pain reflexes, as measured by the rat tail-flick test, appear unaffected by SP-SAP treatment [90], which is understandable if NK1R+ projection neurons to the brainstem are ablated and local NK1R- interneurons are preserved. The reduction in the number of projection neurons via targeted SP-SAP treatment would be expected to reduce pain sensitivity and intensity. It is unclear if this can explain the differential modulation of nocifensive responses to moderate-intensity versus high-intensity thermal stimuli [90, 100] or the differential neuronal signaling of wide dynamic range neurons to low amounts versus high amounts of capsaicin [89].

Second, targeted ablation by SP-SAP could reduce central sensitization mediated by local spinal neuronal interactions. In a model of capsaicin sensitization, wide dynamic range (WDR) neurons in deep dorsal horn lamina fire more frequently in response to mechanical stimuli and have a lower thermal threshold for firing. Central sensitization and windup of WDR neurons are abolished after SP-SAP treatment [89, 93, 97], an effect seen in NK1R knockouts [105]. Finally, long-term potentiation (LTP) in WDR neurons is also eliminated by SP-SAP treatment [105]. While supraspinal circuits may participate in windup and LTP, intrinsic spinal connections must mediate part of these effects since they are both present in spinal cord slices that lack descending controls [136, 137]. Although SP is involved in peripheral sensitization and NK1Rs are present on the presynaptic afferents in the dorsal horn [138], peripheral sensitization, unlike central sensitization, does not appear to be affected by intrathecal SP-SAP treatment, since such treatment does not visibly deplete SP staining of afferent fibers in the dorsal horn [87].

Third, intrathecal SP-SAP treatment could also disrupt descending pain facilitation pathways that involve the 5-HT3 receptor. In untreated rats, blocking the 5-HT3 receptor with ondansetron prevents mechanical allodynia, thermal hyperalgesia, and late-phase formalin model responses similar to SP-SAP treatment [97]. In SP-SAP-treated rats, ondansetron fails to produce these effects, suggesting that the descending pain facilitation pathway blocked by ondansetron involves NK1R+ neurons in lamina I [97]. Ablation of NK1R+ neurons with SP-SAP also eliminates a noradrenergic descending pain inhibitory circuit, since treatment eliminates the typical increases in WDR activity seen after the α2-adrenoreceptor is selectively blocked [139].

The exact mechanisms of pain reduction in SP-SAP-treated subjects are unknown, and it is likely to be due to a combination of reduction in number of afferent pain fibers, reduction in central sensitization, LTP, and windup of WDR neurons and disruption of descending pro-nociceptive pathways.

There are potential benefits of targeted SP-SAP treatment beyond the direct reduction in pain, hyperalgesia, and allodynia. Opioid tolerance, the requirement for increasing amounts of opioid to get the same biological response, and opioid-induced hyperalgesia, a paradoxical increase in pain sensitivity, are both impediments to long-term pain therapy [140]. NK1R knockout model mice [125], PPT-A knockout mice [128], rats treated with an NK1R antagonist [124–128], and rats administered intrathecal SP-SAP [99, 125, 141] all show reduced opioid-induced hyperalgesia, which includes a 5-HT3-dependent mechanism [124–128]. It is possible that the 5-HT3/NK1R+-dependent mechanism of opioid-induced hyperalgesia is related to the 5-HT3/NK1R+ mechanism that reduces late pain in the formalin test, mechanical allodynia, and thermal hyperalgesia.

Conclusions

New pain therapies are needed that are more effective and have fewer side effects. A single intrathecal SP-SAP injection can be used to selectively target NK1R+ projection neurons in lamina I of the dorsal horn that carry the majority of the afferent pain signals to supraspinal centers. This “molecular neurosurgery” can reduce the number of afferent pain fibers, reduce windup of WDR neurons, reduce LTP, reduce central sensitization, disrupt a spinal-bulbar-spinal pro-nociceptive circuit, and reduce opioid tolerance and opioid-induced hyperalgesia. In animal models, SP-SAP treatment has been shown to reduce pain, reduce hyperalgesia, and reduce allodynia.

Lumbar spine SP-SAP injections in canines produced no detectable side effects using either 15 or 45 μg doses, although some motor dysfunction and CNS infiltrates were observed with 150 μg doses [92, 95]. Similarly, 60 μg doses in the lumbar region of canines above 30 kg weight appeared safe and no motor or behavioral dysfunction was observed [113]. 60 μg doses produced dysfunction in a subset of canines when injected into the cisterna magna near the brainstem but not when injected into the lumbar region.

In a double-blinded test of intrathecal SP-SAP on bone cancer pain in canines [113], SP-SAP was associated with statistically significant reductions in pain

severity as measured by the time to request additional pain therapy (or canine death) and as measured by the total number of such requests. A phase I clinical trial of SP-SAP in human subjects to assess safety is ongoing (ClinicalTrials.gov identifier NCT02036281) and due for completion in July 2016. This is the first phase I trial of a targeted toxin for pain. Patients have been treated with targeted injections of 1, 2, 4, 8, 16, and 32 mcg doses. No toxicity or adverse response has been observed.

Acknowledgments Hugh Nymeyer would like to thank Tracy Nymeyer for her personal and financial support.

Declaration of Conflicting Interests Douglas Lappi and Denise Higgins are officers of Advanced Targeting Systems, which manufactures SP-SAP.

References

1. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. JAMA. 1998;280(2):147–51.
2. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol. 2007;18(9):1437–49.
3. Organization WH. Cancer pain relief. Geneva: World Health Organization; 1986.
4. Organization WH. Cancer pain relief: with a guide to opioid availability. Geneva: World Health Organization; 1996.
5. Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F, Group EGW. Management of cancer pain: ESMO clinical practice guidelines. Ann Oncol. 2012;23 Suppl 7:vii139–54.
6. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012;13(2):e58–68.
7. Auret K, Schug SA. Pain management for the cancer patient – current practice and future developments. Best Pract Res Clin Anaesthesiol. 2013;27(4):545–61.
8. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. Lancet. 2011;377(9784):2226–35.
9. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010;17(9):1113–e1188.
10. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc. 2010;85(3 Suppl):S3–14.
11. Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. PM & R. 2011;3(4):345–52, 352 e341-321.
12. Paulsen Ø, Aass N, Kaasa S, Dale O. Do corticosteroids provide analgesic effects in cancer patients? A systematic literature review. J Pain Symptom Manage. 2013;46(1):96–105.
13. McQuay HJ, Collins SL, Carroll D, Moore RA, Derry S. Radiotherapy for the palliation of painful bone metastases. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD001793. DOI: 10.1002/14651858.CD001793.pub2.
14. Sun L, Yu S. Efficacy and safety of denosumab versus zoledronic acid in patients with bone metastases: a systematic review and meta-analysis. Am J Clin Oncol. 2013;36(4):399–403.
15. Falco F, Erhart S, Wargo BW, et al. Systematic review of diagnostic utility and therapeutic effectiveness of cervical facet joint interventions. Pain Physician. 2008;12(2):323–44.
16. Richman JM, Liu SS, Courpas G, et al. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. Anesth Analg. 2006;102(1):248–57.
17. Ver Donck A, Vranken JH, Puylaert M, Hayek S, Mekhail N, Van Zundert J. Intrathecal drug administration in chronic pain syndromes. Pain Practice. 2014;14(5):461–76.
18. Candido K, Stevens RA. Intrathecal neurolytic blocks for the relief of cancer pain*. Best Pract Res Clin Anaesthesiol. 2003;17(3):407–28.
19. Raslan AM, Cetas JS, McCartney S, Burchiel KJ. Destructive procedures for control of cancer pain: the case for cordotomy: a review. J Neurosurg. 2011;114(1):155–70.
20. Bain E, Hugel H, Sharma M. Percutaneous cervical cordotomy for the management of pain from cancer: a prospective review of 45 cases. J Palliat Med. 2013;16(8):901–7.
21. Rainsford K. Profile and mechanisms of gastrointestinal and other side effects of nonsteroidal anti-inflammatory drugs (NSAIDs). Am J Med. 1999;107(6):27–35.
22. McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. J Pain. 2003;4(5):231–56.
23. Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. Pain. 2001;93(3):247–57.
24. Schug SA, Zech D, Dörr U. Cancer pain management according to WHO analgesic guidelines. J Pain Symptom Manage. 1990;5(1):27–32.
25. Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain. 1995;63(1):65–76.
26. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain. 1999;83(3):389–400.
27. Euler U, Gaddum J. An unidentified depressor substance in certain tissue extracts. J Physiol. 1931;72(1):74.
28. v. Euler U. Untersuchungen über Substanz P, die atropinfeste, darmerregende und gefäßerweiternde Substanz aus Darm und Hirn. Naunyn-Schmiedeberg's Arch Pharmacol. 1936;181(2):181–97.
29. Chang MM, Leeman SE, Niall HD. Amino-acid sequence of substance P. Nat New Biol. 1971;232(29):86–7.
30. Steinhoff MS, von Mentzer B, Geppetti P, Pothoulakis C, Bunnett NW. Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. Physiol Rev. 2014;94(1):265–301.
31. Kage R, Leeman SE, Boyd ND. Biochemical characterization of two different forms of the substance P receptor in rat submaxillary gland. J Neurochem. 1993;60(1):347–51.
32. Mantyh PW, Rogers SD, Ghilardi JR, Maggio JE, Mantyh CR, Vigna SR. Differential expression of two isoforms of the neurokinin-1 (substance P) receptor in vivo. Brain Res. 1996;719(1–2):8–13.
33. Baker SJ, Morris JL, Gibbins IL. Cloning of a C-terminally truncated NK-1 receptor from guinea-pig nervous system. Brain Res Mol Brain Res. 2003;111(1–2):136–47.
34. Caberlotto L, Hurd YL, Murdock P, et al. Neurokinin 1 receptor and relative abundance of the short and long isoforms in the human brain. Eur J Neurosci. 2003;17(9):1736–46.
35. Lai JP, Ho WZ, Kilpatrick LE, et al. Full-length and truncated neurokinin-1 receptor expression and function during monocyte/

macrophage differentiation. Proc Natl Acad Sci U S A. 2006; 103(20):7771–6.
36. Lai JP, Cnaan A, Zhao H, Douglas SD. Detection of full-length and truncated neurokinin-1 receptor mRNA expression in human brain regions. J Neurosci Methods. 2008;168(1):127–33.
37. Gillespie E, Leeman SE, Watts LA, et al. Truncated neurokinin-1 receptor is increased in colonic epithelial cells from patients with colitis-associated cancer. Proc Natl Acad Sci U S A. 2011;108(42): 17420–5.
38. Masu Y, Nakayama K, Tamaki H, Harada Y, Kuno M, Nakanishi S. cDNA eloping of bovine substance-K receptor through oocyte expression system. Nature. 1987;329:836–8.
39. Yokota Y, Sasai Y, Tanaka K, et al. Molecular characterization of a functional cDNA for rat substance P receptor. J Biol Chem. 1989;264(30):17649–52.
40. Shigemoto R, Yokota Y, Tsuchida K, Nakanishi S. Cloning and expression of a rat neuromedin K receptor cDNA. J Biol Chem. 1990;265(2):623–8.
41. Lembeck F. Central transmission of afferent impulses. III. Incidence and significance of the substance P in the dorsal roots of the spinal cord. Naunyn Schmiedebergs Arch Exp Pathol Pharmakol. 1953;219(3):197–213.
42. Pernow B. Studies on substance P; purification, occurrence and biological actions. Acta Physiol Scand Suppl. 1953;29(105): 1–89.
43. Hokfelt T, Kellerth JO, Nilsson G, Pernow B. Experimental immunohistochemical studies on the localization and distribution of substance P in cat primary sensory neurons. Brain Res. 1975;100(2):235–52.
44. Hokfelt T, Kellerth JO, Nilsson G, Pernow B. Substance p: localization in the central nervous system and in some primary sensory neurons. Science. 1975;190(4217):889–90.
45. Takahashi T, Otsuka M. Regional distribution of substance P in the spinal cord and nerve roots of the cat and the effect of dorsal root section. Brain Res. 1975;87(1):1–11.
46. Ribeiro-da-Silva A, Hökfelt T. Neuroanatomical localisation of substance P in the CNS and sensory neurons. Neuropeptides. 2000;34(5):256–71.
47. Cuello AC, Jessell TM, Kanazawa I, Iversen LL. Substance P: localization in synaptic vesicles in rat central nervous system. J Neurochem. 1977;29(4):747–51.
48. Go VL, Yaksh TL. Release of substance P from the cat spinal cord. J Physiol. 1987;391:141–67.
49. Duggan A, Morton C, Zhao Z, Hendry I. Noxious heating of the skin releases immunoreactive substance P in the substantia gelatinosa of the cat: a study with antibody microprobes. Brain Res. 1987;403(2):345–9.
50. Duggan A, Hendry I, Morton C, Hutchinson W, Zhao Z. Cutaneous stimuli releasing immunoreactive substance P in the dorsal horn of the cat. Brain Res. 1988;451(1):261–73.
51. Kuraishi Y, Hirota N, Sato Y, Hino Y, Satoh M, Takagi H. Evidence that substance P and somatostatin transmit separate information related to pain in the spinal dorsal horn. Brain Res. 1985; 325(1):294–8.
52. Takano M, Takano Y, Yaksh TL. Release of calcitonin gene-related peptide (CGRP), substance P (SP), and vasoactive intestinal polypeptide (VIP) from rat spinal cord: modulation by α2 agonists. Peptides. 1993;14(2):371–8.
53. Brodin E, Linderoth B, Gazelius B, Ungerstedt U. In vivo release of substance P in cat dorsal horn studied with microdialysis. Neurosci Lett. 1987;76(3):357–62.
54. Klein CM, Coggeshall RE, Carlton SM, Sorkin LS. The effects of A-and C-fiber stimulation on patterns of neuropeptide immunostaining in the rat superficial dorsal horn. Brain Res. 1992;580(1):121–8.
55. Yaksh T, Jessell TM, Gamse R, Mudge A, Leeman SE. Intrathecal morphine inhibits substance P release from mammalian spinal cord in vivo. Nature. 1980;286:155–7.
56. Henry J, Krnjević K, Morris M. Substance P and spinal neurones. Can J Physiol Pharmacol. 1975;53(3):423–32.
57. Randić M, Miletić V. Effect of substance P in cat dorsal horn neurones activated by noxious stimuli. Brain Res. 1977; 128(1):164–9.
58. Piercey MF, Dobry PJ, Schroeder LA, Einspahr FJ. Behavioral evidence that substance P may be a spinal cord sensory neurotransmitter. Brain Res. 1981;210(1):407–12.
59. Hylden JL, Wilcox GL. Intrathecal substance P elicits a caudally-directed biting and scratching behavior in mice. Brain Res. 1981;217(1):212–5.
60. Matsumura H, Sakurada T, Hara A, Sakurada S, Kisara K. Characterization of the hyperalgesic effect induced by intrathecal injection of substance P. Neuropharmacology. 1985;24(5):421–6.
61. Todd AJ, Spike RC, Polgar E. A quantitative study of neurons which express neurokinin-1 or somatostatin sst2a receptor in rat spinal dorsal horn. Neuroscience. 1998;85(2):459–73.
62. Torrens Y, Beaujouan JC, Viger A, Glowinski J. Properties of a 125I-substance P derivative binding to synaptosomes from various brain structures and the spinal cord of the rat. Naunyn Schmiedebergs Arch Pharmacol. 1983;324(2):134–9.
63. Ninkovic M, Beaujouan J, Torrens Y, Saffroy M, Hall M, Glowinski J. Differential localization of tachykinin receptors in rat spinal cord. Eur J Pharmacol. 1984;106(2):463–4.
64. Shults CW, Quirion R, Chronwall B, Chase TN, O'Donohue TL. A comparison of the anatomical distribution of substance P and substance P receptors in the rat central nervous system. Peptides. 1984;5(6):1097–128.
65. Mantyh PW, Hunt SP. The autoradiographic localization of substance P receptors in the rat and bovine spinal cord and the rat and cat spinal trigeminal nucleus pars caudalis and the effects of neonatal capsaicin. Brain Res. 1985;332(2):315–24.
66. Dietl MM, Sanchez M, Probst A, Palacios JM. Substance P receptors in the human spinal cord: decrease in amyotrophic lateral sclerosis. Brain Res. 1989;483(1):39–49.
67. Yashpal K, Dam TV, Quirion R. Quantitative autoradiographic distribution of multiple neurokinin binding sites in rat spinal cord. Brain Res. 1990;506(2):259–66.
68. Quirion R, Shults CW, Moody TW, Pert CB, Chase TN, O'Donohue TL. Autoradiographic distribution of substance P receptors in rat central nervous system. Nature. 1983;303(5919):714–6.
69. Viger A, Beaujouan J, Torrens Y, Glowinski J. Specific binding of a 125I-substance P derivative to rat brain synaptosomes. J Neurochem. 1983;40(4):1030–9.
70. Agnati L, Fuxe K, Zoli M, Ozini I, Toffano G, Ferraguti F. A correlation analysis of the regional distribution of central enkephalin and β-endorphin immunoreactive terminals and of opiate receptors in adult and old male rats. Evidence for the existence of two main types of communication in the central nervous system: the volume transmission and the wiring transmission. Acta Physiol Scand. 1986;128(2):201–7.
71. Agnati L, Zoli M, Strömberg I, Fuxe K. Intercellular communication in the brain: wiring versus volume transmission. Neuroscience. 1995;69(3):711–26.
72. Kandel ER, Schwartz JH, Jessell TM. Principles of neural science, vol. 4. New York: McGraw-Hill; 2000.
73. Larsen PJ, Mikkelsen JD, Mau S, Særmark T. Binding and internalization of a iodinated substance P analog by cultured anterior pituitary cells. Mol Cell Endocrinol. 1989;65(1):91–101.
74. Sjodin L. Cholecystokinin-induced inhibition of endocytosis of receptor-bound substance P in pancreatic acinar cells. J Recept Res. 1992;12(3):323–50.

75. Garland AM, Grady EF, Payan DG, Vigna S, Bunnett N. Agonist-induced internalization of the substance P (NK1) receptor expressed in epithelial cells. Biochem J. 1994;303:177–86.
76. Mantyh PW, Allen CJ, Ghilardi JR, et al. Rapid endocytosis of a G protein-coupled receptor: substance P evoked internalization of its receptor in the rat striatum in vivo. Proc Natl Acad Sci U S A. 1995;92(7):2622–6.
77. Mantyh PW, DeMaster E, Malhotra A, et al. Receptor endocytosis and dendrite reshaping in spinal neurons after somatosensory stimulation. Science. 1995;268(5217):1629–32.
78. Grady EF, Garland AM, Gamp PD, Lovett M, Payan DG, Bunnett NW. Delineation of the endocytic pathway of substance P and its seven-transmembrane domain NK1 receptor. Mol Biol Cell. 1995;6(5):509–24.
79. Fisher CE, Sutherland JA, Krause JE, Murphy JR, Leeman SE. Genetic construction and properties of a diphtheria toxin-related substance P fusion protein: in vitro destruction of cells bearing substance P receptors. Proc Natl Acad Sci. 1996;93(14):7341–5.
80. Wiley RG, Lappi DA. Destruction of neurokinin-1 receptor expressing cells in vitro and in vivo using substance P-saporin in rats. Neurosci Lett. 1997;230(2):97–100.
81. Wiley RG, Lappi DA. Targeting neurokinin-1 receptor-expressing neurons with [Sar9, Met(O2)11 substance P-saporin. Neurosci Lett. 1999;277(1):1–4.
82. Mustafa G, Anderson EM, Bokrand-Donatelli Y, Neubert JK, Caudle RM. Anti-nociceptive effect of a conjugate of substance P and light chain of botulinum neurotoxin type A. Pain. 2013;154(11):2547–53.
83. Saka E, Iadarola M, Fitzgerald DJ, Graybiel AM. Local circuit neurons in the striatum regulate neural and behavioral responses to dopaminergic stimulation. Proc Natl Acad Sci U S A. 2002;99(13):9004–9.
84. Wiley RG, Lappi DA. Targeted toxins in pain. Adv Drug Deliv Rev. 2003;55(8):1043–54.
85. Stirpe F, Gasperi-Campani A, Barbieri L, Falasca A, Abbondanza A, Stevens W. Ribosome-inactivating proteins from the seeds of Saponaria officinalis L. (soapwort), of Agrostemma githago L. (corn cockle) and of Asparagus officinalis L. (asparagus), and from the latex of Hura crepitans L. (sandbox tree). Biochem J. 1983;216:617–25.
86. Stirpe F. Ribosome-inactivating proteins. Toxicon. 2004;44(4):371–83.
87. Mantyh PW, Rogers SD, Honore P, et al. Inhibition of hyperalgesia by ablation of lamina I spinal neurons expressing the substance P receptor. Science. 1997;278(5336):275–9.
88. Nichols ML, Allen BJ, Rogers SD, et al. Transmission of chronic nociception by spinal neurons expressing the substance P receptor. Science. 1999;286(5444):1558–61.
89. Khasabov SG, Rogers SD, Ghilardi JR, Peters CM, Mantyh PW, Simone DA. Spinal neurons that possess the substance P receptor are required for the development of central sensitization. J Neurosci. 2002;22(20):9086–98.
90. Vierck Jr CJ, Kline RH, Wiley RG. Intrathecal substance p-saporin attenuates operant escape from nociceptive thermal stimuli. Neuroscience. 2003;119(1):223–32.
91. Abe T, Ohshita N, Sugiyo S, Moritani M, Kobayashi M, Takemura M. Elimination of neurokinin-1 receptor neurons in caudal nucleus reverses the effects of systemic bicuculline on c-Fos expression in rat trigeminal sensory nucleus: I. High intensity electrical stimulation of the trigeminal ganglion. Neuroscience. 2005;133(3):739–47.
92. Allen JW, Mantyh PW, Horais K, et al. Safety evaluation of intrathecal substance P-saporin, a targeted neurotoxin, in dogs. Toxicol Sci. 2006;91(1):286–98.
93. Choi J, Koehrn FJ, Sorkin LS. Carrageenan induced phosphorylation of Akt is dependent on neurokinin-1 expressing neurons in the superficial dorsal horn. Mol Pain. 2012;8:4.
94. Weisshaar CL, Winkelstein BA. Ablating spinal NK1-bearing neurons eliminates the development of pain and reduces spinal neuronal hyperexcitability and inflammation from mechanical joint injury in the rat. J Pain. 2014;15(4):378–86.
95. Wiese AJ, Rathbun M, Butt MT, et al. Intrathecal substance P-saporin in the dog: distribution, safety, and spinal neurokinin-1 receptor ablation. Anesthesiology. 2013;119(5):1163–77.
96. Le Bars D, Gozariu M, Cadden SW. Animal models of nociception. Pharmacol Rev. 2001;53(4):597–652.
97. Suzuki R, Morcuende S, Webber M, Hunt SP, Dickenson AH. Superficial NK1-expressing neurons control spinal excitability through activation of descending pathways. Nat Neurosci. 2002;5(12):1319–26.
98. Simons CT, Gogineni AG, Iodi Carstens M, Carstens E. Reduced aversion to oral capsaicin following neurotoxic destruction of superficial medullary neurons expressing NK-1 receptors. Brain Res. 2002;945(1):139–43.
99. Rivat C, Vera-Portocarrero LP, Ibrahim MM, et al. Spinal NK-1 receptor-expressing neurons and descending pathways support fentanyl-induced pain hypersensitivity in a rat model of postoperative pain. Eur J Neurosci. 2009;29(4):727–37.
100. Wiley RG, Kline RH, Vierck Jr CJ. Anti-nociceptive effects of selectively destroying substance P receptor-expressing dorsal horn neurons using [Sar9, Met(O2)11]-substance P-saporin: behavioral and anatomical analyses. Neuroscience. 2007;146(3):1333–45.
101. Robert P. Yezierski, Chapter 21 Pain following spinal cord injury: central mechanisms, In: Fernando Cervero and Troels S. Jensen, Editor(s), Handbook of Clinical Neurology, Elsevier, 2006, Volume 81, Pages 293–307.
102. Yezierski RP, Yu CG, Mantyh PW, Vierck CJ, Lappi DA. Spinal neurons involved in the generation of at-level pain following spinal injury in the rat. Neurosci Lett. 2004;361(1–3):232–6.
103. Woolf CJ. Long term alterations in the excitability of the flexion reflex produced by peripheral tissue injury in the chronic decerebrate rat. Pain. 1984;18(4):325–43.
104. Berridge KC. Progressive degradation of serial grooming chains by descending decerebration. Behav Brain Res. 1989;33(3):241–53.
105. Rygh LJ, Suzuki R, Rahman W, et al. Local and descending circuits regulate long-term potentiation and zif268 expression in spinal neurons. Eur J Neurosci. 2006;24(3):761–72.
106. Khasabov SG, Brink TS, Schupp M, Noack J, Simone DA. Changes in response properties of rostral ventromedial medulla neurons during prolonged inflammation: modulation by neurokinin-1 receptors. Neuroscience. 2012;224:235–48.
107. Khasabov SG, Simone DA. Loss of neurons in rostral ventromedial medulla that express neurokinin-1 receptors decreases the development of hyperalgesia. Neuroscience. 2013;250:151–65.
108. Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science. 2000;288(5472):1769–72.
109. Gilron I, Tu D, Holden RR. Sensory and affective pain descriptors respond differentially to pharmacological interventions in neuropathic conditions. Clin J Pain. 2013;29(2):124–31.
110. Cao YQ, Mantyh PW, Carlson EJ, Gillespie A-M, Epstein CJ, Basbaum AI. Primary afferent tachykinins are required to experience moderate to intense pain. Nature. 1998;392(6674):390–4.
111. De Felipe C, Herrero JF, O'Brien JA, et al. Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. Nature. 1998;392(6674):394–7.
112. Zimmer A, Zimmer AM, Baffi J, et al. Hypoalgesia in mice with a targeted deletion of the tachykinin 1 gene. Proc Natl Acad Sci. 1998;95(5):2630–5.

113. Brown DC, Agnello K. Intrathecal substance P-saporin in the dog: efficacy in bone cancer pain. Anesthesiology. 2013;119(5): 1178–85.
114. Scott J, Huskisson E. Graphic representation of pain. Pain. 1976;2(2):175–84.
115. Patrick DL, Deyo RA, Atlas SJ, Singer DE, Chapin A, Keller RB. Assessing health-related quality of life in patients with sciatica. Spine. 1995;20(17):1899–908.
116. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain. 1983;16(1):87–101.
117. Roland M, Morris R. A study of the natural history of back pain: part I: development of a reliable and sensitive measure of disability in low-back pain. Spine. 1983;8(2):141–4.
118. Rabin R, Charro F. EQ-SD: a measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337–43.
119. Oppe M, Devlin NJ, Szende A. EQ-5D value sets: inventory, comparative review and user guide. Dordrecht: Springer; 2007.
120. Beck AT, Ward C, Mendelson M. Beck depression inventory (BDI). Arch Gen Psychiatry. 1961;4(6):561–71.
121. Lee Y, Song J. A study of the reliability and the validity of the BDI, SDS, and MMPI-D scales. Korean J Clin Psychol. 1991;10(1):98–113.
122. Schaffalitzky De Muckadell OB, Aggestrup S, Stentoft P. Flushing and plasma substance P concentration during infusion of synthetic substance P in normal man. Scand J Gastroenterol. 1986;21(4):498–502.
123. Hill R. NK1 (substance P) receptor antagonists--why are they not analgesic in humans? Trends Pharmacol Sci. 2000;21(7):244–6.
124. Hui SC, Sevilla EL, Ogle CW. Prevention by the 5-HT3 receptor antagonist, ondansetron, of morphine-dependence and tolerance in the rat. Br J Pharmacol. 1996;118(4):1044–50.
125. King T, Gardell LR, Wang R, et al. Role of NK-1 neurotransmission in opioid-induced hyperalgesia. Pain. 2005;116(3):276–88.
126. Chu LF, Liang DY, Li X, et al. From mouse to man: the 5-HT3 receptor modulates physical dependence on opioid narcotics. Pharmacogenet Genomics. 2009;19(3):193–205.
127. Liang DY, Li X, Clark JD. 5-hydroxytryptamine type 3 receptor modulates opioid-induced hyperalgesia and tolerance in mice. Anesthesiology. 2011;114(5):1180–9.
128. Sahbaie P, Shi X, Li X, et al. Preprotachykinin-A gene disruption attenuates nociceptive sensitivity after opioid administration and incision by peripheral and spinal mechanisms in mice. J Pain. 2012;13(10):997–1007.
129. Santarelli L, Gobbi G, Debs PC, et al. Genetic and pharmacological disruption of neurokinin 1 receptor function decreases anxiety-related behaviors and increases serotonergic function. Proc Natl Acad Sci. 2001;98(4):1912–7.
130. Naono-Nakayama R, Sunakawa N, Ikeda T, Nishimori T. Knockdown of the tachykinin neurokinin 1 receptor by intrathecal administration of small interfering RNA in rats. Eur J Pharmacol. 2011;670(2–3):448–57.
131. Nattie EE, Li A. Substance P-saporin lesion of neurons with NK1 receptors in one chemoreceptor site in rats decreases ventilation and chemosensitivity. J Physiol. 2002;544(Pt 2):603–16.
132. Brown JL, Liu H, Maggio JE, Vigna SR, Mantyh PW, Basbaum AI. Morphological characterization of substance P receptor-immunoreactive neurons in the rat spinal cord and trigeminal nucleus caudalis. J Comp Neurol. 1995;356(3):327–44.
133. Polgar E, Durrieux C, Hughes DI, Todd AJ. A quantitative study of inhibitory interneurons in laminae I-III of the mouse spinal dorsal horn. PLoS One. 2013;8(10), e78309.
134. Marshall G, Shehab S, Spike R, Todd A. Neurokinin-1 receptors on lumbar spinothalamic neurons in the rat. Neuroscience. 1996;72(1):255–63.
135. Todd AJ, McGill MM, Shehab SAS. Neurokinin 1 receptor expression by neurons in laminae I, III and IV of the rat spinal dorsal horn that project to the brainstem. Eur J Neurosci. 2000;12(2):689–700.
136. Herrero JF, Laird JM, Lopez-Garcia JA. Wind-up of spinal cord neurones and pain sensation: much ado about something? Prog Neurobiol. 2000;61(2):169–203.
137. Ikeda H, Heinke B, Ruscheweyh R, Sandkuhler J. Synaptic plasticity in spinal lamina I projection neurons that mediate hyperalgesia. Science. 2003;299(5610):1237–40.
138. Hu HZ, Li ZW, Si JQ. Evidence for the existence of substance P autoreceptor in the membrane of rat dorsal root ganglion neurons. Neuroscience. 1997;77(2):535–41.
139. Rahman W, Suzuki R, Hunt SP, Dickenson AH. Selective ablation of dorsal horn NK1 expressing cells reveals a modulation of spinal alpha2-adrenergic inhibition of dorsal horn neurones. Neuropharmacology. 2008;54(8):1208–14.
140. DuPen A, Shen D, Ersek M. Mechanisms of opioid-induced tolerance and hyperalgesia. Pain Manag Nurs. 2007;8(3):113–21.
141. Vera-Portocarrero LP, Zhang ET, King T, et al. Spinal NK-1 receptor expressing neurons mediate opioid-induced hyperalgesia and antinociceptive tolerance via activation of descending pathways. Pain. 2007;129(1–2):35–45.

Index

G.B. Racz, C.E. Noe (eds.), *Techniques of Neurolysis*, DOI 10.1007/978-3-319-27607-6