Clinical Case Reports

CASE REPORT

Treatment of complex regional pain syndrome with stellate ganglion local anesthetic blockade: a case report of one patient's experiences with traditional bupivacaine HCl and liposome bupivacaine

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Key Clinical Message

Complex regional pain syndrome (CRPS) is a poorly understood, debilitating disorder characterized by severe chronic pain in an affected limb or region of the body. This case presentation is the first to describe the effectiveness and prolonged duration of the effect of liposome bupivacaine in stellate ganglion block for CRPS.

Keywords

Bupivacaine HCl, liposome bupivacaine, pain, reflex sympathetic dystrophy.

Introduction

Complex regional pain syndrome (CRPS) is a chronic condition characterized by severe pain and motor, sensory, autonomic, and trophic disturbances [1–5]. The severity of symptoms associated with CRPS is unrelated to the severity of the trauma that caused the condition [1, 3, 4, 6]. The classic presentation of CRPS is an exaggerated burning pain, although the pain also has been described as deep pain, provoked by light touch or movement, or similar to an electric shock [2]. Other symptoms include changes in skin temperature and color, edema, sudomotor dysfunction, and tropic changes in nails and bone [2–4, 6]. Motor disturbances include muscle weakness and wasting, impaired voluntary movements, tremors, and dystonic postures or movements [2, 3, 6].

Complex regional pain syndrome has two subtypes. The onset of CRPS type I symptoms, also known as reflex sympathetic dystrophy, typically follows trauma to a limb or lesions in remote body areas [1, 4]. The precipitating traumatic event can be minor, such as a sprain or bruise, or major, such as a bone fracture, surgery, or major coronary event [1]. Symptoms tend to spread to areas of the limb beyond the site of injury or the anatomical distribution of a nerve [1–3, 6]. In CRPS type II, also known as causalgia, injury to a specific major peripheral nerve or one of its major branches is the precipitating event that precedes the onset of symptoms [1, 3, 4]. Areas of pain associated with CRPS type II may or may not correspond to the anatomic distribution of a peripheral nerve [3].

Currently, no single diagnostic test is used to confirm CRPS; rather, diagnosis is based on the patient history, physical examination, and differentiation from other possible causes [7]. The underlying pathophysiology of CRPS is not completely understood, and a number of models have been proposed to describe its etiology [8]. Thus, CRPS treatment is empirical and varies widely [4, 8, 9]; in fact, no definitive treatment exists, and no drug has been approved by the US Food and Drug Administration (FDA) for the treatment of CRPS [7, 8]. In the most recently published treatment guidelines for CRPS type I, a multidisciplinary task force from the Netherlands reviewed the evidence for various treatments and concluded that additional research into therapeutic

interventions was needed [10]. Typically, treatment should be initiated early in the course of disease with an individualized, multidisciplinary approach that includes pharmacologic, interventional, and physiotherapeutic measures to achieve pain relief and restore daily functioning [1, 3–5, 8, 9].

It has been hypothesized that the sympathetic nervous system is involved in the pathophysiology of CRPS in some patients [1, 4, 6, 8]. Therefore, interruption of the sympathetic supply to the painful area is one treatment approach used for CRPS [1, 4, 6, 11]. The use of nerve blocks not only may aid in diagnosis but also may be effective therapy in cases of allodynia, burning pain, and temperature and color changes that do not respond to pain medication and hinder progress during physical or occupational therapy [1, 4, 5, 12]. Stellate ganglion block (SGB) is the blockade of the sympathetic ganglia in the lower cervical and upper thoracic region [12]. CRPS treatment with SGB is a well-established method of nerve blockade [12, 13], but there is no defined protocol for selecting appropriate candidates for this procedure [4]. Spinal cord stimulation and peripheral nerve stimulation may be offered when the response to nerve blocks is short-lived and rehabilitation fails to produce improvement [4]. Destructive interventions, such as surgical, chemical, or radiofrequency sympathectomy, are also used for treatment of CRPS [11]; however, sympathectomy is a controversial approach to treatment because of the possibility of the return of pain, potential for nonresponse or development of new pain syndromes following the procedure, and potential for other complications [5, 11, 12, 14]. Some investigators have recommended that sympathectomy be performed for CRPS only after a spinal cord stimulation trial or nerve block [5, 12].

Liposome bupivacaine (bupivacaine liposome injectable suspension; EXPAREL®, Pacira Pharmaceuticals, Inc., Parsippany, NJ) is a multivesicular formulation of bupivacaine indicated for single-dose administration into the surgical site to produce postsurgical analgesia [15]. Although liposome bupivacaine has been studied in a number of surgical settings [16–20], its use in SGB has not yet been reported. This case report describes the successful off-label use of liposome bupivacaine in SGB for refractory pain associated with CRPS.

Case Presentation

A 28-year-old female nurse presented to the clinic 3 months after a job-related injury that occurred at the long-term care facility where she worked. Her left wrist was sprained when a resident grabbed and twisted her left hand.

The patient was a smoker with a history of wheezing due to asthma. She described the pain in her left arm, wrist, and hand as a severe, sharp, cutting-type pain, with cramping and numbness, which was consistent with CRPS. Magnetic resonance imaging and workup revealed no abnormalities. The left wrist showed soft tissue edema but otherwise appeared essentially normal. A triple-phase bone scan was not performed. The diagnostic performance of triple-phase bone scan is variable and may produce false-negative findings, even in the presence of CRPS [21, 22]. A nerve conduction study was expected to yield negative results and was not performed. The pain was most severe in the left wrist and forearm, with hypersensitivity and allodynia from the left elbow to the fingertips. Pain and contracture had spread throughout the left arm, from the fingertips to the nape of the neck, and significant guarding of the left arm was observed. The left upper extremity was warmer, had increased pallor, and had more limited range of motion than the right upper extremity. Hypertonicity, which is commonly observed in CRPS, also was noted. Full flexion and extension at the elbow and abduction at the shoulder were partially restricted; flexion contracture prevented extension of the fingers without pain, except during some occupational therapy sessions.

The use of neuropathic pain agents, including tramadol HCl 50 mg, celecoxib 200 mg, and gabapentin 600 mg, provided slight relief and occupational therapy provided moderate relief. The patient agreed to a multicomponent treatment plan of increasing the gabapentin dosage to 800 mg four times per day, continuing occupational therapy, and undergoing a series of left SGBs. The frequency of injections was based on approval of medical treatment related to workers' compensation insurance.

A left SGB with 0.5 mL bupivacaine HCl 0.5% and 0.5 mL of lidocaine 2% was performed during her first office visit. The patient tolerated the procedure well and reported significantly less joint stiffness during the therapeutic window of the block. Two more left SGBs were performed, one at 9 days after the first block (0.75 mL of bupivacaine HCl 0.5% and 0.75 mL of lidocaine 2%) and the other 26 days later (1 mL of bupivacaine HCl 0.5% and 1 mL of lidocaine 1%). These procedures also were well tolerated, and joint stiffness was reduced, but pain returned within 1 week after each injection. The patient then agreed to a spinal cord stimulator trial and then implantation of a permanent stimulator. However, the patient experienced a device-related infection that required removal of the spinal cord stimulator.

The patient subsequently underwent five more left SGBs, spaced 7 weeks, 16 weeks, 3 weeks, and 1 week apart. The injection schedule was based on workers' compensation insurance approval, the fact that the SGB

treatment plan was interrupted by a trial spinal cord stimulation, and the need to adjust medications during her treatment. The injections consisted of bupivacaine HCl 0.5% (1.5–5.0 mL) with or without 2 mL of lidocaine 2%. As before, pain relief lasted approximately 1 week after each SGB procedure. Fifteen weeks after the last SGB, the patient presented with severe pain (10 out of 10 on a visual analog scale) in her left shoulder, arm, and hand. She had experienced extensive burning pain lasting a few minutes, followed by tingling lasting approximately 1 min and then numbness. The pain was constant, intensified with physical activity, and interfered with sleep. She noted that, overall, her pain was progressively worsening but was somewhat alleviated by pain medication. Hypersensitivity and allodynia extended from the left elbow down to the fingertips. Her left arm had a limited range of motion and severe tenderness, and was cooler and edematous compared with her right arm. Cervical and thoracic ranges of motion were also decreased.

About 4 months later, she received authorization for a left SGB with liposome bupivacaine. During the procedure, liposome bupivacaine 13.3 mg (1 mL) was injected. The treatment goal was to replicate a sympathectomy, for which she was awaiting approval from her insurance provider. At her next follow-up visit, she reported that she had experienced 3 weeks of pain relief (at least 50% reduction in pain) from the SGB with liposome bupivacaine. The patient was surprised at the degree of improvement in her condition and stated that she was able to function with less discomfort during the 3 weeks of pain relief. However, extreme pain (10 out of 10 on a visual analog scale) had returned in her left arm after the 3-week window of relief. As before, the pain was constant and interfered with sleep. Her left shoulder was severely weakened, had extremely limited range of motion (both active and passive), and was sensitive to the touch.

Fourteen weeks later, she received authorization for four additional SGBs using liposome bupivacaine. The procedures were performed 3–5 weeks apart. Injections consisted of 2.0–2.5 mL of liposome bupivacaine (266 mg/20 mL [13.3 mg/mL]). All of these procedures were well tolerated, and there was no adjustment in the dosage of gabapentin during any of the SGBs with liposome bupivacaine. The patient continued to experience approximately 3 weeks (18–21 days) of pain relief with each SGB with liposome bupivacaine.

Discussion

To the author's knowledge, the current case report is the first published description of liposome bupivacaine use in SGB for patients with CRPS type I. The diagnosis of CRPS was strongly supported by clinical presentation, the main criterion to identify the condition [23–25]. The patient also responded to treatment for CRPS.

Overall, based on the author's clinical experience with SGB and other blocks, liposome bupivacaine provides an equal degree of analgesia but appreciably longer duration of analgesic effect compared with bupivacaine HCl. A series of eight SGBs with traditional bupivacaine HCl in this patient provided an average of 5–7 days of pain relief. In contrast, a series of five SGBs with liposome bupivacaine provided approximately 18–21 days of pain relief after each block, with similar tolerability and greater patient satisfaction compared with traditional bupivacaine HCl.

The duration of pain relief with traditional bupivacaine HCl in SGB observed here (5–7 days) was similar to that observed in a double-blind crossover study that included a comparison of sympathetic ganglion blockade (SGB, $n = 4$; lumbar sympathetic block, $n = 7$) with local anesthetic (bupivacaine HCl/lidocaine) versus normal saline [26]. In that study, patients served as their own controls, receiving a block with normal saline and a block with local anesthetic 7–10 days apart. The mean duration of pain relief was 6 days with traditional bupivacaine HCl/lidocaine versus 12 h with normal saline.

The mechanism of pain relief with liposome bupivacaine in SGBs has not been studied. Given the pharmacokinetics of traditional bupivacaine HCl (half-life of about 3 h [27]) and liposome bupivacaine (half-life of about 34 h [15]), it is unlikely that either agent was able to maintain a blockade of sympathetic activity from the stellate ganglion per se for the 1 week (bupivacaine HCl) or 3 weeks (liposome bupivacaine) of pain relief experienced by the patient. Instead, the blockade of sympathetic outflow from the stellate ganglion may have been a short-lived event that "reset" dysfunctional pain pathways, resulting in a prolonged, quiescent period of decreased firing of nociceptive fibers and restoration of daily functioning.

Liposome bupivacaine is currently approved by the FDA for administration into the surgical site to produce postsurgical analgesia [15]. The benefits and risks of liposome bupivacaine use in SGBs have not been studied in clinical trials, and its use in this setting is considered experimental. Off-label use should be approached with caution.

For the patient in this case report, the treatment sequence consisted of a series of SGBs using traditional bupivacaine HCl, followed by SGBs with liposome bupivacaine, which allowed for a meaningful comparison of the two formulations with the patient serving as her own control. In terms of quality of life, an extended duration of relief from the constant, debilitating pain of CRPS would be expected to have a positive impact on daily functioning, sleep, and ability to complete routine

activities. For this patient, SGB with liposome bupivacaine resulted in improved satisfaction over an extended period compared with traditional bupivacaine HCl. The reduction in discomfort allowed her to return to normal daily functioning for about 3 weeks after SGB with liposome bupivacaine.

Administration of SGB should always be considered early in the management of CRPS because it may abort or help reverse progression if used proactively. The encouraging results of SGB with liposome bupivacaine that were observed in this case study suggest that SGB containing liposome bupivacaine instead of bupivacaine HCl may potentiate and/or prolong the treatment response in patients who respond to SGB.

The cost of treatment for CRPS can be a significant financial burden for some patients. From a health economics perspective, a treatment that provides a prolonged duration of pain relief from CRPS would be expected to reduce the number of scheduled reimbursable injections and may therefore translate into decreased patient costs.

Conclusion

This is the first published report to describe the use of liposome bupivacaine in SGB for the treatment of CRPS. Liposome bupivacaine produced three- to fourfold longer pain relief compared with bupivacaine HCl, which produced up to 1 week of pain relief. Large-scale, randomized, controlled studies are needed to confirm the safety and efficacy of liposome bupivacaine in SGB for the treatment of CRPS.

Acknowledgments

Conflict of Interest

Dr. Ferrillo participated as a paid consultant for Pacira Pharmaceuticals, Inc. in a pain medicine roundtable discussion regarding the study design of a Phase I trial for a pain management protocol using liposome bupivacaine.

References

1. Wasner, G., M. M. Backonja, and R. Baron. 1998. Traumatic neuralgias: complex regional pain syndromes (reflex sympathetic dystrophy and causalgia): clinical characteristics, pathophysiological mechanisms and therapy. Neurol. Clin. 16:851–868.

2. Dowd, G. S., R. Hussein, V. Khanduja, and A. J. Ordman. 2007. Complex regional pain syndrome with special emphasis on the knee. J. Bone Joint Surg. Br. 89:285–290.

3. Stanton-Hicks, M. 2000. Complex regional pain syndrome (type I, RSD; type II, causalgia): controversies. Clin. J. Pain 16:S33–S40.

4. Hsu, E. S. 2009. Practical management of complex regional pain syndrome. Am. J. Ther. 16:147–154.

5. AbuRahma, A. F., P. A. Robinson, M. Powell, D. Bastug, and J. P. Boland. 1994. Sympathectomy for reflex sympathetic dystrophy: factors affecting outcome. Ann. Vasc. Surg. 8:372–379.

6. Kurvers, H. A. 1998. Reflex sympathetic dystrophy: facts and hypotheses. Vasc. Med. 3:207–214.

7. Cossins, L., R. W. Okell, H. Cameron, B. Simpson, H. M. Poole, and A. Goebel. 2013. Treatment of complex regional pain syndrome in adults: a systematic review of randomized controlled trials published from June 2000 to February 2012. Eur. J. Pain 17:158–173.

8. Goebel, A. 2011. Complex regional pain syndrome in adults. Rheumatology (Oxford) 50:1739–1750.

9. Hey, M., I. Wilson, and M. I. Johnson. 2011. Stellate ganglion blockade (SGB) for refractory index finger pain - a case report. Ann. Phys. Rehabil. Med. 54: 181–188.

10. Perez, R. S., P. E. Zollinger, P. U. Dijkstra, I. L. Thomassen-Hilgersom, W. W. Zuurmond, K. C. Rosenbrand, et al. 2010. Evidence based guidelines for complex regional pain syndrome type 1. BMC Neurol. 10:20.

11. Stanton-Hicks, M., R. Baron, R. Boas, T. Gordh, N. Harden, N. Hendler, et al. 1998. Complex Regional Pain Syndromes: guidelines for therapy. Clin. J. Pain 14:155–166.

12. Elias, M. 2000. Cervical sympathetic and stellate ganglion blocks. Pain Physician. 3:294–304.

13. Yucel, I., Y. Demiraran, K. Ozturan, and E. Degirmenci. 2009. Complex regional pain syndrome type I: efficacy of stellate ganglion blockade. J. Orthop. Traumatol. 10:179–183.

14. Furlan, A. D., P. W. Lui, and A. Mailis. 2001. Chemical sympathectomy for neuropathic pain: does it work? Case report and systematic literature review. Clin. J. Pain 17:327–336.

15. Exparel [prescribing information]. 2015. Pacira Pharmaceuticals, Inc., Parsippany, NJ.

16. Gorfine, S. R., E. Onel, G. Patou, and Z. V. Krivokapic. 2011. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Dis. Colon Rectum 54:1552–1559.

17. Smoot, J. D., S. D. Bergese, E. Onel, H. T. Williams, and W. Hedden. 2012. The efficacy and safety of DepoFoam bupivacaine in patients undergoing bilateral, cosmetic, submuscular augmentation mammoplasty: a randomized, double-blind, active-control study. Aesthet. Surg. J. 32:69–76.

18. Golf, M., S. E. Daniels, and E. Onel. 2011. A phase 3, randomized, placebo-controlled trial of DepoFoam(R) bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. Adv. Ther. 28:776–788.

19. Cohen, S. M. 2012. Extended pain relief trial utilizing infiltration of Exparel®, a long-acting multivesicular liposome formulation of bupivacaine: a Phase IV health economic trial in adult patients undergoing open colectomy. J. Pain Res. 5:567–572.

20. Bramlett, K., E. Onel, E. R. Viscusi, and K. Jones. 2012. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. Knee 19:530–536.

21. Lee, G. W., and P. M. Weeks. 1995. The role of bone scintigraphy in diagnosing reflex sympathetic dystrophy. J. Hand Surg. Am. 20:458–463.

22. Schurmann, M., J. Zaspel, P. Lohr, I. Wizgall, M. Tutic, N. Manthey, et al. 2007. Imaging in early posttraumatic complex regional pain syndrome: a comparison of diagnostic methods. Clin. J. Pain 23:449–457.

23. Bruehl, S. 2015. Complex regional pain syndrome. BMJ 351:h2730.

24. Turner-Stokes, L., and A. Goebel. 2011. Complex regional pain syndrome in adults: concise guidance. Clin. Med. (Lond) 11:596–600.

25. Harden, R. N., S. Bruehl, M. Stanton-Hicks, and P. R. Wilson. 2007. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med. 8:326–331.

26. Price, D. D., S. Long, B. Wilsey, and A. Rafii. 1998. 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 14:216–226.

27. Marcaine [package insert]. 2013. Hospira, Inc., Lake Forest, IL.