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CASE REPORTS

Recurrent Cellulitis Associated with Long-Term Intrathecal Opioid Infusion Therapy: A Case Report and Review of the Literature

Xiulu Ruan, MD,* HaiNan Liu, MS,† J. Patrick Couch, MD,* Frank Wang, MD,‡ and Srinivas Chiravuri, MD§

*Physicians' Pain Specialists of Alabama, Mobile, Alabama;

†Department of Urology, QiLu Hospital, Shandong University, Jinan, China;

‡Department of Internal Medicine, College of Medicine, University of South Alabama, Mobile, Alabama;

§Department of Anesthesiology, Center for Interventional Medicine, University of Michigan Health Systems, Ann Arbor, MI

Reprint requests to: Xiulu Ruan, MD, Physicians' Pain Specialists of Alabama, 2001 Springhill Avenue, Mobile, AL 36607, USA. Tel: 251-478-4900; Fax: 251-478-1996; E-mail: xiuluruan@yahoo.com.

Abstract

Background. Lower-limb edema is recognized as an untoward side effect of intrathecal opioid therapy. Cellulitis, an acute, spreading pyogenic inflammation of the dermis and subcutaneous tissue, predisposed by persistent leg edema, can become problematic in patients on intraspinal opioid infusion therapy.

Objective. To present a case of recurrent cellulitis in an elderly lady with persistent leg edema associated with intrathecal morphine/hydromorphone infusion therapy.

Case Report. Sixty-one-year-old woman with intractable chronic low back pain and bilateral leg pain treated with an intrathecal infusion of morphine up to 5 mg/day over 3 months with satisfactory pain control developed progressive lower extremity edema, complicated by recurrent cellulitis, requiring repeated hospitalization and intravenous antibiotic treatment. Switching to intrathecal hydromorphone helped minimally. Intrathecal baclofen and clonidine infusion resulted in complete resolution of leg edema and pain relief over the following 12 months.

Conclusion. Intrathecal Baclofen and Clonidine may be used as alternatives to provide spinally mediated antinociception when intraspinal opioid fails due to pharmacological side effects such as persistent edema.

Key Words. Intraspinal Drug Delivery; Intrathecal Morphine; Intrathecal Hydromorphone; Edema; Cellulitis

Spinal analgesia, mediated by opioid receptors, requires only a fraction of the opioid dose needed systemically. By infusing a small amount of opioid into the cerebrospinal fluid in close proximity to the receptor sites in the spinal cord, profound analgesia may be achieved. Intraspinal drug delivery of opioid(s), via an implanted pump and catheter, is increasingly used in a subset of patients with intractable, chronic pain who have failed to respond to conventional treatment, or could not tolerate systemic opioid due to side effects [1–5]. Prior to the permanent pump implantation, an intraspinal analgesic infusion trial is usually done, to document efficacy of IDD therapy, and to make sure that the patient is without intolerable side effects. Generally, 50% pain reduction, or patient's subjective report of "significant pain relief" during the trial, or demonstrable improved functional level during the trial, constitutes a positive trial [1]. Morphine, the only FDA-approved opioid for intrathecal administration, is considered effective, inexpensive, and well tolerated by majority of patients, yet, clinically relevant side effects associated with long-term intrathecal morphine administration have become evident [6,7]. These include pruritis, nausea, vomiting, constipation, edema, sexual dysfunction, urinary retention, and respiratory depression [6,7]. Leg edema associated with intrathecal opioid therapy has been increasingly recognized as a problematic complication [6,8,9].

Cellulitis is an acute bacterial infection of the dermis and subcutaneous tissue that is associated with inflammation [10,11]. We are reporting this case of recurrent cellulitis because it is a rare occurrence and can lead to severe morbidity.

Case Report

A 61-year-old woman with intractable chronic low back pain and bilateral leg pain, due to degenerative disc disease, failed back surgery syndrome, and lumbar radiculopathy, was referred to our clinic for intraspinal drug delivery (IDD) therapy, after failing to respond to multidisciplinary pain treatment. Following a satisfactory epidural morphine infusion trial, she underwent placement of permanent intrathecal infusion pump. The intrathecal catheter was introduced at left paramedian L2-L3 under fluoroscopic guidance, with catheter tip located at T12. Satisfactory intrathecal catheter placement was confirmed by observing positive cerebrospinal fluid (CSF) flow and intraoperative myelogram. The intrathecal infusion was initially started with preservative free morphine at 1 mg/day. Over the following 3 months, the dosage was gradually titrated up to 5 mg/day with satisfactory pain control, 2–3/10 on visual analog pain scale (VAS) of 0–10. However, she developed progressive lower extremity edema and was fitted for compression stockings and prescribed diuretics (furosemide 20 mg bid) with limited success. Subsequently, after dose reduction to 3 mg/day, her leg edema improved, so that although she continued to wear compression stockings, she was able to discontinue the diuretic. Over the following 2 months, after her back and leg pain worsened to 6–7/10 on VAS, the intrathecal morphine dose was titrated to 5 mg/day. However, leg edema recurred, which was resistant to furosemide.

Meanwhile, the patient developed sudden onset of warm, tender erythema of bilateral lower extremities with a fever of 101.8°F. Urinanalysis, urine culture, and chest X-ray were unremarkable, and bilateral lower extremity Doppler study was negative for any blood clots.

She was admitted to the hospital with a working diagnosis of severe cellulitis for intravenous (IV) antibiotic treatment, where she was treated for 3 days with aggressive IV furosemide, oral hydrochlorothiazide (HCTZ), compression stockings, and IV cefazolin, with only slight improvement of leg edema but improvement of leg cellulitis. She was discharged home on oral Keflex for a total of 2 weeks of antibiotic treatment (IV + PO). Serial blood cultures after hospitalization came back negative for any bacterial growth, and her low back and leg pain remained "tolerable" on intrathecal morphine 5 mg/day. Two months later, her cellulitis recurred, requiring another hospitalization for 4 days of IV antibiotic treatment, followed by outpatient oral antibiotics 10 days in conjunction with both furosemide and HCTZ.

Subsequent to recurrent edema and leg cellulitis on intrathecal morphine, she was switched to intrathecal hydromorphone, starting at 1 mg/day and titrated to 1.8 mg/day. Her edema lessened, and her pain remained under satisfactory control, 2–3/10 on VAS, and she was able to discontinuecompression stockings and diuretics. Two months later, however, she experienced worsening low back and leg pain, 6–7/10 on VAS, so the intrathecal hydromorphone was increased to 2.6 mg/day, with recurrence of leg edema followed by severe bilateral leg cellulitis, again requiring hospital admission for intravenous antibiotic followed by oral antibiotics. The cellulitis resolved following antibiotics treatment, but the leg edema persisted.

After struggling with recurrent severe cellulitis and persistent leg edema, it was finally decided to switch her intrathecal regimen to clonidine 33 mcg/day and baclofen 67 mcg/da,y resulting in complete resolution of edema, enabling her to discontinue both compression stockings and diuretics. Her pain remained "tolerable" around 2–4/10 on VAS over the following 12 months, requiring only slight dosage elevation of intrathecal clonidine (67 mcg/day) and baclofen (100 mcg/day). She has had no recurrent leg edema or cellulitis.

Discussion

Cellulitis is an acute bacterial infection of the dermis and subcutaneous tissue that is clinically associated with clinical inflammation [10,11]. The area, usually on the leg, is warm, tender, erythematous, and swollen. It lacks sharp demarcation from uninvolved skin. The diagnosis of cellulitis is based on the clinical ground, i.e., the morphologic features of the lesion and clinical settings [12]. Streptococci (Group A, B, G) and *Staphylococcus aureus* are the most frequently isolated pathogens [12]. Bacteremia is uncommon in cellulitis. Previous studies showed that out of 272 patients, initial blood culture was positive only in about 4% [13,14], indicating blood culture not being cost-effective for most patients with cellulitis. Empirical antibiotics with intravenous cephalosporin, followed by oral cephalosporin for total of 7–14 days are usually employed for moderate or severe cellulitis [12].

Edema predisposes patients to cellulitis [15]. Persistent edema after recovery from cellulitis predisposes patient to recurrent cellulitis [15]. The precise pathophysiological and immunological responses in this disposition to cellulitis remain to be poorly understood [16]. Leg edema, associated with intraspinal opioid therapy, has been increasingly recognized along with the increased utilization of this treatment modality for intractable, chronic pain [6,8,9]. It has been widely accepted that the mechanism of spinally opioid-induced edema to be the cephalad migration of morphine in CSF, and subsequent interaction with opioid receptors in the posterior pituitary gland, stimulating vasopressin release [6,7].

Recently, we reported a case of an otherwise healthy elderly female with failed back surgery syndrome who developed severe peripheral edema while on continuous epidural morphine infusion [17]. We also noticed the early research by Huidobro-Toro et al. [18] and Denesh et al. [19]. Huidobro et al. [18], who observed striking difference in urine electrolytes in rats following intraventricular injection of antidiuretic hormone and opioids, respectively; the former being oliguria with high concentration of Na+ and K+, while the latter being very low concentration of urine electrolytes, suggesting spinal opioids selectively activate central opioid receptors to produce changes in urine for-

mation and composition. Denesh et al. [19] demonstrated that centrally administered morphine in conscious rats enhanced renal tubular sodium reabsorption, by opioid receptor-dependent mechanism. So, our speculation is that both centrally mediated renal effect (through alteration of urine electrolyte composition) and centrally mediated vasopressin release may be the underlying mechanism of spinal opioid-induced edema. In our patient, we believed that the recurrent cellulitis was predisposed by lower extremity edema. When she repeatedly developed edema with cellulitis while on intrathecal morphine, we decided to switch her intrathecal opioid to hydromorphone.

Hydromorphone, a semisynthetic derivative of morphine, is considered to be equianalgesic at a ratio of 1:5–1:8 [20,21]. It is more lipophilic than morphine, therefore penetrating the spinal cord more rapidly, leaves less time for it to ascend cephalad in CSF [20,22], and is expected to have less side effects due to rostral spread of the drug in comparison with morphine. Hydromorphone has been increasingly used off-label over the past a few years for long-term intrathecal therapy [23]. Deer et al. recently published the most up-to-date expert panel recommendations on intrathecal drug selection—the "Polyanalgesic Algorithm" [23]. It calls for the selection of intrathecal analgesics for long-term intrathecal infusion in the order from line 1 to line 6 (line 1 agents include morphine, hydromorphone, and ziconotide; line 2 agents include fentanyl, morphine/hydromorphone + ziconotide, morphine/hydromorphone + bupivacaine/Clonidine; line 3 agents include Clonidine, morphine/hydromorphone/fentanyl, bupivacaine +/Clonidine + ziconotide; line 4 agents include sufetanil, sufetanyl + bupivacaine +/Clonidine + ziconotide; line 5 agents include ropivocaine, buprenophine, midzolam, meperidine, ketorolac; line 6 agents include other experimtental drugs) [23]. The switch of intrathecal morphine to hydromorphone did not deviate from the "polyanalgesic algorithm," as hydromorphone is considered a line 1 agent, although the rationale for this switch was due to the edema caused by intrathecal morphine rather than inadequate analgesia.

Her pattern of initial improvement of peripheral edema, followed by recurrence of edema with intrathecal hydromorphone, was previously observed by Anderson et al. [9], who reported their findings in a retrospective review of 37 patients with chronic nonmalignant pain managed with intrathecal hydromorphone. However, there was no cellulitis reported, and to this day, there have been no other reported cases of cellulitis associated with intrathecal opioid infusion therapy. It is quite likely that this is underreported, considering the incidence of peripheral edema due to intraspinal opioid being from 6.1% [24] to 21.7% [25].

Although Ziconotide is listed as a Line 1 agents, we did not use it in our patient for the following reasons: 1) ziconotide can only be used with programmable infusion pump such as Medtronic SynchroMed (Prialt package insert). Ziconotide has a very narrow therapeutic window that requires starting low at 0.5 mcg/day, gradually increasing dosage at no more than 0.5 mcg/day, until therapeutic dose is achieved [26]. This highly meticulous titration process mandates a programmable pump such as Medtronic SynchroMed infusion pump, not the constant-flow rate, nonprogrammable Codman pump in our patient, which we use because it is less expensive and lasts longer [28]. The only way to change drug infusion dose with the nonprogrammable, constant flow rate pump, is by replacing pump medication with different drug concentration during pump refill. 2) Ziconotide is very expensive and has high incidence of side effects, including psychiatric, neurological, cardiovascular, and gastrointestinal symptoms [27].

The main reason that we routinely implant nonprogrammable Codman constant-flow pumps is that they are much less expensive than the Medtronic programmable pump [28]. This is especially true when one considers the effect that programmable pumps require multiple replacement surgeries about every 5 years due to limited battery lifespan [29]. Staats et al. [28] recently conducted a retrospective study in 101 patients who received programmable infusion pumps for management of nonmalignant low back pain, and found out that almost all patients stayed on constant-flow treatment within the normal battery lifespan. They further suggested that programmable infusion pumps be replaced by constant-flow pumps at the first pump replacement surgery.

Although bupivacaine is listed as adjunct agent in line 2, 3, and 4, it was advocated to be used, only in conjunction with opioids (morphine/hydromorphone or fentanyl) rather than to be used alone [23]. We were also concerned about the possibility that intrathecal bupivacaine could worsen leg edema by interrupting the sympathetic outflow, causing venous pooling, which was described by Bridenbaugh et al. [30]. Since we speculated that intrathecal opioids (morphine or hydromorphone) were responsible for causing recurrent leg edema, combining opioid(s) with bupivacaine for intrathecal infusion, obviously, would not solve the problem of leg edema. In our patient, we believed that the spinal opioid-induced edema involves both centrally mediated renal function (resulting in urine electrolyte composition change) and centrally opioid receptor-mediated opioid interaction with posterior pituitary (leading to vasopressin release).

Unfortunately, agents in line 2, 3, and 4 all involve opioids. Faced with these limitations, in view of multiple recurrent lower extremity edema and recurrent cellulitis in our patient while on intrathecal clonidine, is a centrally acting alpha2-adrenoreceptor agonist believed to act at the alpha2 adrenoreceptors in the dorsal horn to modulate afferent nociceptive input by pre- and postsynaptic mechanism [31–33]. Clonidine has been shown to be effective in treating neuropathic pain, including complex regional pain syndrome (CRPS) [34–36]. Hassenbusch et al. demonstrated the tolerability and efficacy of intrathecal Clonidine in the treatment of chronic pain through a phase I/II study [37].

Baclofen, a *gamma*-amino-butyric acid (GABA B) agonist, has been widely used intrathecally in the management of spasticity due to upper motor neuron syndromes, such as spinal cord injury, multiple scleroisis, traumatic brain injury, etc. [38]. The antispastic properties of baclofen are mediated by the suppression of release of excitatory neurotransmitters and inhibition of excitatory afferent terminals involved in monosynaptic and polysynaptic reflex activity at the spinal cord level [39,40]. Only recently have the antinociceptive effects of intrathecal baclofen, independent of motor blockade, been suggested [41,42].

Lastly, we would like to emphasize the importance of adhering to the "polyanalgesic algorithm" when utilizing intrathecal analgesic drug therapy for pain management, as complications do occur, especially with intrathecal baclofen, as serious withdrawal symptoms have been reported [43,44].

Conclusion

Peripheral edema becomes increasingly recognized as a potential side effect of intraspinal opioid infusion therapy. Persistent leg edema predisposes patients to recurrent cellulitis. Opioid dosage reduction or switching to nonopioid analgesics may be required to resolve the edema induced by intrathecal opioid, and to prevent the development of associated cellulitis. Intrathecal baclofen and clonidine may be used as alternative, under certain circumstances, to provide spinally mediated antinociception, when intraspinal opioid fails because of intolerable pharmacological side effects.

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