Case report

The efficacy of postoperative perineural infusion of bupivacaine and clonidine after lower extremity amputation in preventing phantom limb and stump pain

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Received 10 May 2006; revised 20 July 2006; accepted 31 July 2006

Abstract We report the efficacy of perioperative infusion of clonidine and bupivacaine for above-knee amputation in a patient with a history of phantom limb pain in the same extremity after a previous below-knee amputation. The patient underwent general anesthesia. Before transection, the sciatic nerve was infiltrated with 0.25% bupivacaine 5 mL and clonidine 50 μg. After the nerve was severed, a 20-gauge epidural catheter was inserted into the nerve sheath and externalized laterally through a separate skin incision. Before closure, 0.25% bupivacaine 10 mL and clonidine 50 μg was injected, and 0.1% bupivacaine and clonidine two μg/mL was infused at 10 mL/h for the first 96 hours postoperatively. There were no incidents of hypotension, bradycardia, or sedation during the infusion period. The mean postoperative pain score (from 0 to 10) for 96 hours was 1.2 ± 0.7. The patient required a total of 10 mg of oxycodone postoperatively. The patient did not report either stump or phantom pain for 12 months after surgery.

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Keywords: Amputation; Above-the-knee; Analgesia; Perineural; Clonidine; Pain; Neuropathic; Phantom limb

1. Introduction

Pain after amputation is a significant problem among amputees. Phantom limb pain may appear in up to 85% of patients and is usually resistant to a wide variety of treatments [1-4]. The mechanisms underlying this pain syndrome are still unknown. Complex multifactorial interactions involving peripheral nerves, central nervous system (CNS), sympathetic system, psychologic overlay [1-4], and genetic predisposition [5] have all been implicated. Peripheral nerve transection results in an afferent nociceptive barrage that initiates spinal cord hyperexcitability with expansion of the receptive fields of dorsal horn neurons that respond to the nearest intact afferents [6]. These neuroplastic changes are believed to be responsible for the development of postsurgical chronic pain syndromes, including phantom limb and stump pain [7,8]. It is believed that regional anesthesia, by preventing the establishment of central sensitization, may play a role in reducing the incidence of acute and chronic pain.
Postoperative perineural bupivacaine infusion

addition, because the surgical neurogenic inflammatory response may provide a source of nociceptive input into the CNS for a prolonged period, a continuous infusion of local anesthetic postoperatively may prevent the establishment of central sensitization [7]. Although perioperative epidural block may prevent the development of phantom limb pain [9-11], its use in the setting of anticoagulation is contraindicated. The perineural administration of clonidine, an α2-adrenergic receptor agonist, reduces neuropathic symptoms after nerve injury in a rat model [12]. Peripheral nerve block for intraoperative and postoperative analgesia with local anesthetics and clonidine not only prolongs and intensifies the block but may also help in preventing sensitization induced by nerve injury during surgery [13].

We report the efficacy of perioperative infusion of clonidine and bupivacaine for above-knee amputation (AKA) in providing effective postoperative analgesia and eliminating both stump and phantom limb pain in a patient with a previous history of this chronic pain syndrome in the same extremity.

2. Case report

A 68-year-old, 81-kg man presented for elective left AKA due to ischemic necrosis secondary to peripheral vascular disease. He had a left below-knee amputation two years earlier, after which he reported stump and phantom pain. His medical history was significant for hypertension, diabetes, chronic atrial fibrillation, and a St Jude aortic valve necessitating daily warfarin therapy. Warfarin was withheld 6 days before AKA surgery, and he received subcutaneous enoxaparin 80 mg (one mg/kg) every 12 hours until the day before surgery. The patient underwent uneventful general anesthesia. Intraoperatively, the sciatic nerve trunk was dissected and infiltrated with 0.25% bupivacaine 5 mL and clonidine 50 μg before transection. Afterward, a 20-gauge, multiorificed, epidural catheter was inserted into the nerve sheath and sutured in place. The catheter was then externalized laterally through a separate skin incision. Before closure, 0.25% bupivacaine 10 mL and clonidine 50 μg were administered through the catheter. Bupivacaine 0.1% and clonidine 2 μg/mL were infused at 10 mL/h for the first 96 hours postoperatively. Enoxaparin 80 mg was initiated every 12 hours for 24 hours after surgery. Pain scores, vital signs [blood pressure (BP), heart rate (HR), respiratory rate] and sedation scores were recorded every 4 hours. Pain scores were recorded on a numerical rating scale (NRS) from 0 to 10 (0 = no pain, 10 = worst imaginable pain), whereas sedation scores were measured on a numerical scale of 1 to 5 (1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, and 5 = asleep and not responsive to any stimulus). Intravenous (IV) fentanyl 25 μg every 5 minutes as needed was prescribed while the patient was in the postanesthesia care unit (PACU), and oxycodone 5 to 10 mg every 4 hours as necessary was prescribed while he was on the surgical ward. There were no incidents of hypotension (blood pressure, <20% baseline), bradycardia (HR, <60 bpm), or excessive sedation (score, >3) during the infusion period. The 96-hour mean NRS pain score was 1.2 ± 0.7, and the mean sedation score was 1.8 ± 0.3. The patient required no fentanyl in the PACU, but he did receive a total of 10 mg oxycodone postoperatively for the first 96 hours during the infusion. The patient reported the absence of both stump and phantom pain at monthly intervals during the first 12 months postoperatively.

3. Discussion

We report the efficacy of a perioperative perineural infusion of bupivacaine and clonidine for analgesia after AKA in a patient with a previous history of phantom limb and stump pain in the same extremity. This technique provided excellent postoperative analgesia with minimal supplementary opioid use while preventing the recurrence of both stump and phantom limb pain.

Although first described in 1649 [1], the etiology of phantom limb pain still remains unknown, and numerous analgesic techniques aimed at relieving the symptoms of this chronic pain syndrome have proved disappointing [1-4]. Three factors may contribute to the development of persistent, postamputation phantom pain by inducing central sensitization at different times relative to surgery: pre-amputation pain, noxious intraoperative stimuli, and acute postoperative pain [7,8,14,15]. Continuous epidural analgesia may be an effective analgesic technique for lower limb amputation. Initial clinical trials showed a beneficial effect on the reduction of phantom and stump pain [9-11], whereas a later study failed to confirm any benefit [16]. Epidural analgesia is contraindicated in the setting of anticoagulation and may result in hypotension, sedation, respiratory depression, pruritus, urinary retention, and motor block. Continuous regional analgesia by perineural block is a potential technique for managing pain after lower extremity amputation [17-21]. This technique may be a safer alternative to epidural analgesia for geriatric patients who have multiple comorbidities. Furthermore, perineural catheters are not contraindicated in the setting of perioperative anticoagulation. However, clinical investigations evaluating the efficacy of continuous perineural analgesia in reducing long-term phantom and stump pain have been equivocal, with some studies reporting efficacy [17,18,21], whereas others showed no long-term beneficial effect [19,20]. Unfortunately, many of these studies had significant design flaws including the fact that they were not prospective, randomized, or blinded; they used either no control group or historical controls; they investigated a heterogeneous study group; and/or they lacked sufficient power to reach a firm conclusion.
All clinical investigations of perineural infusions [17-21] for lower extremity amputation used bupivacaine without the addition of adjuvant medications. The use of clonidine, an \( \alpha_2 \)-adrenergic receptor agonist, as an adjuvant in continuous perineural infusion of local anesthetics may provide a substantial reduction in both acute and chronic pain after lower extremity amputation. Recently, perioperative administration of clonidine at the site of nerve injury was shown to reduce the development of mechanical hypersensitivity and modulate local cytokine expression in a rat model [12]. Clonidine is also effective when used for a wide variety of regional analgesic techniques [13]. Furthermore, clonidine when administered via the neuraxial, IV regional anesthesia, or intra-articular routes, may reduce chronic postsurgical pain [13,22]. We chose to use a clonidine dose of 0.25 \( \mu \text{g} / (\text{kg/h}) \) based on our previous clinical experience during which higher infusion doses (\( \geq 0.3 \mu \text{g} / (\text{kg/h}) \)) produced systemic side effects including sedation and hypotension.

The mechanism for eliminating long-term phantom pain in our patient is interesting because our technique was effective only in reducing some of the peripheral nociceptive afferent impulses during the intraoperative and postoperative periods. In contrast, previous studies using epidural analgesic techniques [9-11] were aimed at eliminating noxious inputs before, during, and after amputation surgery. Pre- amputation pain is a risk factor for the development of postoperative phantom limb and stump pain [8,14,15]. Although our patient experienced preoperative phantom limb (NRS = 5-7) and stump pain (NRS = 3-5) for several years before his AKA, he did not develop chronic pain after surgery. Because the patient received enoxaparin before surgery, we did not use a spinal anesthetic, which might have blunted intraoperative noxious afferent input into the CNS. However, we did anesthetize the sciatic nerve with bupivacaine and clonidine before sciatic nerve transaction. Perineural administration of clonidine at the site of nerve injury reduces the development of mechanical hypersensitivity and modulates local cytokine expression [12]. Although a single injection provided short-term relief, repeated injections for three days provided a sustained reduction in hypersensitivity. Thus, the intraoperative and postoperative infusion of clonidine used in our patient might have contributed to a reduction in neuropathic pain after nerve transection.

It could be argued that this surgical procedure eliminated a possible peripheral source of nociceptive input contributing to his phantom limb and stump pain. However, no obvious gross pathology was identified intraoperatively, which may have contributed to his chronic pain symptoms (eg, neuroma, bone spurs, ischemia, infection, nerve root impingement). In the absence of local specific pathology, revision surgery is not an effective technique in relieving phantom limb or stump pain [1,23,24]. In fact, several authors “strongly advise against repeated local revision surgery in the hope of relieving stump and/or phantom limb pain” because of lack of efficacy [23].

Neuroplastic changes secondary to phantom pain involve not only the peripheral nervous system and spinal cord but the cerebral cortex as well. Animal studies have shown that there is enlargement of somatotopically adjacent areas into the differentiated regions of the cortex [25]. This cortical reorganization may explain some instances in which stimulation of nociceptive afferent neurons in or around the stump produces painful sensations in the phantom limb [26]. The amount of cortical reorganization appears to be directly proportional to the degree of pain [26]. Because our patient had been experiencing chronic phantom and stump pain for two years, one would assume that significant cortical reorganization had already occurred, rendering treatment more difficult. However, local anesthetic conduction block can result in a reduction in the amount of cortical reorganization in the somatosensory cortex [27]. It is possible that the 4-day perineural infusion of bupivacaine and clonidine reduced not only peripheral and central sensitization but also the cortical reorganization responsible for our patient’s phantom and stump pain.

In conclusion, we describe a 4-day postoperative perineural infusion of bupivacaine and clonidine after AKA in a patient with a previous history of phantom limb and stump pain of the operative extremity. This technique provided excellent postoperative analgesia while eliminating both stump and phantom limb pain postoperatively. We are currently enrolling patients in a prospective, randomized, double-blind study to evaluate the efficacy of this technique for lower extremity amputation.

References

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