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Case Report Open Access

Successful Treatment of Intractable Low Back and Pelvic Pain Caused by Advanced Prostate Cancer with Intrathecal Clonidine and Baclofen Infusion

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Abstract

Background: Intrathecal opioid infusion therapy has been increasingly utilized in patients with severe malignant and nonmalignant pain syndromes in the past few decades. By infusing small amount of analgesics directly into the cerebrospinal fluid (CSF) in close proximity to the receptor site in the spinal cord, spinally mediated analgesia may be achieved while sparing some of the side effects due to systemic opioids. Traditionally, the most commonly infused analgesic for intrathecal infusion is an opioid. Morphine represents the only FDA-approved opioid for intrathecal administration, although other opioids may also be used off-label. However, in patients who have demonstrated intolerance to oral opioid(s), alternative analgesics may be tried to achieve satisfactory analgesia.

Objective: To present a case report of a 73-year old male with intractable low back and pelvic pain due to invasive prostate cancer, unable to tolerate any opioid, being successfully treated by intrathecal infusion of clonidine and baclofen.

Case Report: A 73-year-old male with intractable low back pain and pelvic pain due to invasive prostate cancer was referred to our clinic for pain management. The patient had undergone hormonal therapy, radiation therapy, radical prostectomy, and rectal resection. Trial of non-opioid analgesics was unsuccessful in controlling his pain. Multiple opioids trials were complicated by persistent nausea and vomiting. Other interventional techniques were attempted, but only offered short-term efficacy. Intraspinal drug delivery (IDD) therapy was considered and attempted. Considering his intolerance to various oral opioids despite meticulous opioid dose titration, an outpatient continuous epidural infusion of clonidine was conducted, which provided satisfactory analgesia. The patient subsequently underwent permanent IDD pump placement.

Results: The intrathecal infusion of clonidine was initiated at 50 mcg/day. Over the following 4 months, the dosage was gradually titrated up to 350 mcg/day, with satisfactory pain relief. However, he did report frequent drowsiness during daytime, which was felt to be due to intrathecal clonidine. The decision to add low dose baclofen to the intrathecal infusion and simultaneously lower the clonidine dose was made. The intrathecal regimen was changed to clonidine 150 mcg/day and baclofen 50 mcg/day. His daytime sleepiness improved significantly and his pain control remained satisfactory. Over the following 3 months, his intrathecal regimen was further titrated to clonidine 200 mcg/day and baclofen 100mcg/day. He remained on this regimen for over 12 months with satisfactory pain relief and without experiencing excessive sedation. Addition of baclofen to intrathecal clonidine infusion led to improved analgesia without affecting his alertness, probably via a synergistic mechanism.

Conclusion: Under certain circumstance when intrathecal opioid infusion cannot be tolerated, intrathecal clonidine and baclofen may be used as alternatives to provide spinally mediated antinociception.

Keywords: Prostate cancer; Low back pain; Pelvic pain; Intrathecal analgesic infusion pump; Intrathecal clonidine; Intrathecal baclofen

Case Report

A 73-year-old male with intractable low back and pelvic pain for over 3 months was referred to our facility by his urologist for consideration of Intraspinal drug delivery (IDD) therapy. He was found to have advanced prostate adenocarcinoma extending to rectum. After failing to respond to hormonal therapy, radiation therapy, he underwent prostectomy and rectal resection. Two weeks following the aforementioned surgeries, he started to experience worsening pain in the low back and pelvic area with intermittent testicular and rectal pain. Abdominal and pelvic image studies were unrevealing. He described his low back pain being "aching and heavy", while his pelvic pain being "stabbing and throbbing". He also reported "burning" scrotal pain and "lacerating" rectal pain. His low back and pelvic pain levels were usually around 8-9/10 on visual analogue pain scale (VAS) of 0-10. His low back, pelvic, and scrotal pain worsened by standing and walking, while his rectal pain dramatically worsened by sitting. The only relieving factor was to lie in bed on his side. His previous medical history was noncontributory. The only previous surgical histories were radical prostectomy and rectal resection. His family history and review of systems were non-contributory. Trials of NSAIDs (meloxicam, naproxen, celecoxib), anti-convulsants (gabapentin, tiagabine) and tramadol were not successful in controlling his pain. He

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also tried trans-dermal fentanyl patch 25 mcg/hr, which caused severe nausea and vomiting. He was on pregabalin 75 mg tid, duloxetine 60 mg qhs, propoxyphene N-100 qid prn upon presenting to our clinic. We also tried other opioids including oral morphine, oxycodone, hydromorphone, hydrocodone, methadone, and oxymorphone, and tapentadol, all of which resulted in severe nausea and vomiting, despite careful dose titration. Interventional procedures including lumbar and caudal epidural steroid, ganglion impar block were also attempted, without long-term efficacy. IDD therapy was then considered as an alternative therapy. Since the patient was unable to tolerate any opioids tried except propoxyphene, it was decided an epidural infusion trial of non-opioid analgesic be considered. The patient consented to the procedure.

A tunneled lumbar epidural catheter was placed at L5-S1 with catheter tip advanced to L4 under fluoroscopic guidance. Satisfactory catheter placement was confirmed by epidurogram. The proximal tip of the catheter was then tunneled subcutaneously and connected to a Microject™ patient-controlled epidural analgesia (PCEA) pump (Codman, Raynham, MA, USA). The PCEA pump was connected with a reservoir bag containing preservative free clonidine 20 mcg/ml. The pump was programmed to deliver a basal rate of 0.8 ml/hr. The bolus dose was 0.3 ml with 30 minute lock-out interval. The patient was instructed how to use the pump and discharged home. During the rest of the outpatient infusion trial, the infusion rate was further increased to 1.0 ml/hr with the bolus dose increased to 0.4 ml. The infusion trial lasted 9 days and was beneficial in controlling his pain. The patient reported more than 60% pain reduction with improved standing, walking, and sitting tolerance. He did experience some transient drowsiness initially that completely resolved. He did not feel the need to use any extra boluses while on epidural clonidine infusion at 1.0 ml/hr.

The patient subsequently consented for the permanent intrathecal pump implantation. The intrathecal catheter was inserted at right paramedian L5-S1 with catheter tip located at L3 confirmed under fluoroscopy. A non-programmable Codman 3000 constant-flow rate infusion pump was placed in the right mid quandrant below the right rib cage and above the right iliac crest. The intrathecal infusion initially consisted of preservative free clonidine 50 mcg/day. Over the following 4 months, the intrathecal regimen was gradually titrated up to 350 mcg/day, with satisfactory pain relief, pain reported to be at 3/10 from the initial 8/10 on visual analogue pain scale (VAS) of 0-10. However, he reported excessive drowsiness during daytime, noted by his family member. His blood pressure was stable at 120s/70s. Because of the frequent sedation during the day felt to be mostly due to intrathecal clonidine, the decision to add low dose baclofen to the intrathecal infusion and simultaneously lower the clonidine dose was made. Subsequently, his intrathecal regimen was further changed to clonidine 150 mcg/day and baclofen 50 mcg/day. His daytime sleepiness resolved and, his pain levels remained to be around 3-4/10. Over the following 3 months, his intrathecal regimen was further adjusted to clonidine 200 mcg/day and baclofen 100 mcg/day. He remained on this regimen for over 12 months with satisfactory pain relief, without other significant side effects.

Discussion

The discovery of highly specific opioid receptors in the central nervous system, especially the spinal cord in 1970s, made possible for spinal administration of opioid to obtain spinally mediated antinociception. Intraspinal infusion of opioid has been increasingly utilized since 1980s in patients with intractable, nonmalignant pain who have failed to respond to conventional treatment or could not tolerate systemic opioid therapy due to side effects [1-6]. By infusing small amount of opioid directly into cerebrospinal fluid in close proximity to the receptor sites in the spinal cord, one is able to achieve the spinally mediated analgesia sparing some of the side effects caused by systemic opioids.

Prior to the permanent pump implantation, an intraspinal analgesic infusion trial is required to document efficacy of analgesia. In general, if the patient reports ≥50% pain reduction with improved function, the trial is considered 'positive' and a permanent intrathecal infusion pump may be in order. Pain relief that is < 50% or the development of intolerable side effects constitutes a 'negative trial". Morphine represents the only FDA-approved opioid for intrathecal administration, although other opioids may also be used off-label for such purpose. Krames advocated the equianalgesic conversion of oral morphine to intrathecal morphine being 300:1 [1], which has been widely accepted. Since our patient had failed multiple oral opioid trials, in spite of careful dose titration and opioid rotation, a non-opioid analgesic epidural infusion trial was considered and consented by the patient.

Although Ziconotide has been advocated as one of the Line 1 non-opioid agents for intrathecal infusion when intrathecal opioid cannot be tolerated or ineffective [7]. We did not consider trying Ziconotide based on the manufacture's recommendation that Ziconotide should only be used with programmable infusion pumps such as Medtronic SynchroMed (Prialt package insert). The intrathecal infusion pumps we normally implant are non-programmable Codman constant-flow rate infusion pumps which was the case in our patient.

Although bupivacine is listed as adjunct agent in line 2,3,4, it was advocated to be used only in conjunction with opioids (morphine/hydromorphone or fentanyl) rather alone [7], since we did not plan to use intrathecal opioid in our patient due to opioid intolerance, we did not try intrathecal bupivacine infusion in our patient.

Clonidine is a centrally acting alpha$_2$-adrenoreceptor agonist. It is believed to act at the alpha$_2$- adrenoreceptors in the dorsal horn to modulate afferent nociceptive input by pre and postsynaptic mechanism [8-10]. Clonidine has been shown to be effective in treating neuropathic pain, including complex regional pain syndrome (CRPS) [11-12]. Hassenbusch et al. [13] demonstrated the tolerability and efficacy of intrathecal clonidine in the treatment of chronic pain through a phase I/II study. Clonidine represents the only FDA-approved nonopioid intraspinal analgesic [14], specifically, for severe cancer pain.

Based on the above information, in view of his intolerance to opioids, we decided to perform the epidural infusion trial with clonidine. After the successful 9-day outpatient epidural clonidine infusion trial, a permanent intrathecal infusion pump was implanted.

He was initially doing well with intrathecal clonidine infusion, only requiring periodic infusion dose increase (up to 350mcg/day) over the first 4-months following pump implantation, although this daily dose is much lower in comparison with the dose range reported by Garber & Hassenbusch [14]. In their study, thirty-two patients (majority of them with CRPS) being treated with intrathecal clonidine of average duration of 4.9 months, the dose range was 100-960 mcg/day, with most patients' doses between 480-900 mcg/day. Unfortunately, in our patient, further intrathecal clonidine dose escalation was not chosen because of the excessive daytime drowsiness reported, which was

suspected to be due to intrathecal clonidine administration. At this point, after discussing with the patient, the decision of adding baclofen and decreasing clonidine was made.

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 (SCI), multiple scleroisis (MS), traumatic brain injury (TBI), etc [15]. 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 [16-17]. Only recently, the antinociceptive effects of intrathecal baclofen, independent of motor blockade, have been suggested [18-19]. Zuniga et al. [18] reported two cases of advanced CRPS successfully treated with intrathecal baclofen. A recent review by Slonimski et al. [19] suggests efficacy of intrathecal baclofen for nociceptive and neuropathic pain, particularly in combination with opioid and/or clonidine.

In our patient, addition of low dose baclofen (50 mcg/day) to the intrathecal clonidine infusion, which allowed the intrathecal clonidine dose to be lowered to 150 mcg/day from 350 mcg/day without compromising analgesia, proved to be beneficial as the patient reported satisfactory pain control as well as resolution of his daytime drowsiness, suggesting synergistic analgesia when combining both clonidine and baclofen intrathecally.

Traditionally, however, intraspinal clonidine was mainly used as an adjunct to opioids and local anesthetics [20] as studies showed that it increased both the duration of sensory block and the degree of motor block induced by local anesthetics [21]. In our case, though, the initial intrathecal infusion contained only clonidine, without any opioid or local anesthetics. The subsequent addition of low dose baclofen to the intrathecal clonidine infusion resulted in satisfactory analgesia without significant side effects.

Ruan et al. [22] recently published a case report in "Pain Medicine", in which a 61 year-old lady with failed back surgery syndrome, while on intrathecal opioid infusion, experienced severe leg edema complicated by the development of severe, recurrent cellulitis requiring hospitalization and intravenous antibiotics. Her leg edema responded only transiently to intrathecal morphine dose reduction and opioid rotation (morphine to hydromorphone); she continued to have recurrent leg edema and severe cellulitis until her intrathecal opioid infusion was replaced by intrathecal clonidine and baclofen infusion. Her leg edema resolved completely; she did not experience any recurrent cellulitis. Her low back and leg pain remained at a "tolerable" level 2-4/10 on VAS while on intrathecal infusion of clonidine (67 mcg/day) and baclofen (100 mcg/day) for over 12 months. There are similarities between these two cases: sustained satisfactory analgesia was achieved with intrathecal administration of clonidine and baclofen, independent of any opioid or local anesthetics. We speculate a synergistic mechanism in antinociception when combining intrathecal clonidine with baclofen, although the exact mechanism needs further investigation.

Finally, Intraspinal drug delivery therapy has been increasingly utilized over the past three decades, to treat patients with intractable pain, with intrathecal opioid infusion being the most commonly practiced modality. The significance of this case report is that intrathecal non-opioid analgesics, i.e., clonidine and baclofen, may provide satisfactory analgesia for patients with malignant or nonmalignant pain. With increasing utilization of intrathecal opioid administration for intractable, chronic pain, a wide variety of non-nociceptive side effects may also occur in susceptible patients [23]. In patients who can not tolerate opioid therapy (systemic or intraspinal), intrathecal clonidine and baclofen infusion may potentially serve as a useful alternative for IDD therapy in the treatment of severe chronic pain.

Conclusion

Intraspinal drug delivery therapy has become increasingly popular for intractable, malignant and nonmalignant pain, with intrathecal opioid being most commonly utilized. Our case study suggests a potential alternative intrathecal regimen, i.e., clonidine and baclofen, for intrathecal analgesia in the management of intractable pain, when opioids can not be tolerated due to side effects.

References

1. Krames E (2001) Intraspinal analgesia for nonmalignant pain, in Waldman SD: Interventional Pain Management. (2nd Edition), Sanders, Philadelphia.
2. Raphael JH, Southall JL, Gnanadurai TV, Treharne GI, Kitas GD (2002) Long-term Experience with implanted intrathecal drug administration systems for failed back syndrome and mechanical low back pain. BMC Musculoskeletal Disord 3: 17.
3. Deer T, Chapple I, Classen A, Javery K, Stoker V, et al. (2004) Intrathecal drug delivery for treatment of chronic low back pain: Report from the National Outcomes Registry for Low Back Pain. Pain Med 5: 6-13.
4. Kumar K, Kelly M, Pirlot T (2001) Continuous intrathecal morphine treatment for chronic pain of nonmalignant etiology: Long-term benefits and efficacy. Surg Neurol 55: 79-88.
5. Anderson VC, Burchiel KJ (1999) A prospective study of Long-term intrathecal morphine in the management of chronic nonmaligmant pain. Neurosurgery 44: 289-300.
6. Cohen SP, Dragovich A (2007) Intrathecal Analgesia. Med Clin North Am 91: 251-270.
7. Deer T, Elliot SK, Hassenbusch SJ, Burton A, Caraway D, et al. (2007) Polyanalgesic consensus conference 2007: Recommendations for the management of pain by intrathecal (intraspinal) drug delivery: Report of an interdisciplinary expert panel. Neuromodulation 10: 300-328.
8. Yaksh TL, Reddy SV (1981) Studies in the primate on the analgesic effects associated with intrathecal actions of opiates, alpha-adrenergic agonists and baclofen. Anesthesiology 54: 451-467.
9. Yaksh TL (1985) Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. Pharmacol Biochem Behav 22: 845-858.
10. Kamisaki Y, Hamada T, Maeda K, Ishimura M, Itoh T (1993) Presynaptic alpha2 adrenoceptors inhibit glutamate release from rat spinal cord synaptosomes. J Neurochem 60: 522-526.
11. Rauck RL, Eisenach JC, Jackson K, Young LD, Southern J (1993) Epidural clonidine treatment for refractory reflex sympathetic dystrophy. Anesthesiology 79: 1163-1169.
12. Glynn CJ, Jamous MA, Teddy PJ, Moore RA, Lloyd JW (1986) Role of spinal noradrenergic system in transmission of pain in patients with spinal cord injury. Lancet 2: 1249-1250.
13. Hassenbusch SJ, Gunes S, Wachsman S, Willis KD (2002) Intrathecal Clonidine in the treatment of intractable pain: A phase I/II study. Pain Medicine 3: 85-91.
14. Garber JE, Hassenbusch SJ (2001) Spinal administration of nonopiate analgesics for pain management, in Waldman SD: Interventional Pain Management. (2nd Edition), Sanders, Philadelphia.
15. Francisco GE (2004) The role of intrathecal baclofen therapy in the upper motor neuron syndrome.Eura Medicophys 40: 131-143.
16. Bowery NG, Hill DR, Hudson AL, Doble A, Middlemiss DN, et al. (1980) Baclofen decreases neurotransmitter release in the mammalian CNS by action at a novel GABA receptor. Nature 283: 92-94.
17. Mueller H, Zierski J, Dralle D, Borner U, Hoffmann O (1987) The effect of

intrathecal baclofen on electrical muscle activity in spasticity. J Neurol 234: 348-252.

18. Zuniga RE, Perera S, Abram SE (2002) Intrathecal Baclofen: A useful agent in the treatment of well established complex regional pain syndrome. Reg Anesth Pain Med 27: 99-93.
19. Slonimski M, Abram SE, Zuniga RE (2004) Intrathecal baclofen in pain management. Reg Anesth Pain Med 29: 269-276.
20. Schug SA, Saunders D, Kurowski I, Paech MJ (2006) Neuraxial Drug Administration: A Review of Treatment Options for Anaesthesia and Analgesia. CNS Drugs 20: 917-933.
21. Eisenach JC, De Kock M, Klimscha W (1996) Alpha(2)-adrenergic agonists for regional anesthesia : a clinical review of clonidine(1984-1995). Anesthesiology 85: 655-674.
22. Ruan X, Liu H, Couch JP, Wang F, Chiravuri S (2010) Recurrent Cellulitis associated with long-term intrathecal opioid infusion therapy: A case report and the review of the literature. Pain Med 11: 972-976.
23. Ruan X (2007) Drug-related side effects of long-term intrathecal morphine therapy. Pain Physician 10: 357-365.