Pain Physician 2010; 13:365-368 • ISSN 1533-3159

Case Report

The Use of Sub-Anesthetic Intravenous Ketamine and Adjuvant Dexmedetomidine when Treating Acute Pain from CRPS

Sharanya Nama, BS[1], Daniel R. Meenan, MD, DMD[2], and William T. Fritz, MD[2]

From: [1]Temple University School of Medicine, Philadelphia, PA; and [2]Conemaugh Memorial Hospital, Johnstown, PA.

Nama is a student at the Temple University School of Medicine, Philadelphia, PA. Dr. Meenan is chairman of Aneshesdiology, Department of Surgery, Conemaugh Memorial Hospital, Johnstown, PA. Dr. Fritz is Director of the Acute Pain Services, Memorial Medical Center, Johnstown PA..

Address correspondence:
Daniel R. Meenan, MD, DMD
Conemaugh Memorial Hospital
1086 Franklin Street
Johnstown, PA 15905
E-mail: DMeenan@conemaugh.org

Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: None.

Manuscript received: 04/04/2010
Accepted for publication: 05/28/2010

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Complex regional pain syndrome (CRPS) is a pain condition of the extremities that presents with pain and allodynia, decreased range of motion, swelling and skin changes. There are 2 forms of CRPS — Type I which does not have demonstrable nerve lesions and Type 2, which has evidence of obvious nerve damage. Management of refractory CRPS has been challenging. Some studies have revealed that the N-methyl-D-aspartic acid receptor (NMDAR) may be involved in the etiology of the pain in CRPS and perhaps that a NMDA receptor antagonist like Ketamine is a potential treatment for CRPS. However, the side effect profile of ketamine is concerning, and limiting the adverse effects of the drug is beneficial. Dexmedetomidine is an alpha 2 agonist similar to clonidine with analgesic properties that can be used in combination with ketamine to provide additional analgesia in CRPS.

This case describes the treatment of acute pain symptoms from Chronic Regional Pain Syndrome-Type 1 (CRPS-1) with sub-anesthetic intravenous infusion of ketamine with adjunct dexmedetomidine. A 47-year-old female patient presented with severe pain, burning and allodynia from CRPS-1 refractory to conventional therapy. She was then admitted to a monitored bed, received a sub-anesthetic intravenous infusion of ketamine with adjunct dexmedetomidine for 19 hours and subsequently discharged with complete resolution of her pain and associated symptoms. Here, the synergistic effect of the ketamine and dexmedetomidine together is shown to provide excellent symptom relief while decreasing the total ketamine administered. The combination minimized unwanted side effects and eliminated the need for intensive care unit admission secondary to anesthetic doses of ketamine.

Key words: CRPS; ketamine; dexmedetomidine; NMDA receptor; alpha 2 agonist; analgesia.

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Complex regional pain syndrome (CRPS) is a pain condition affecting an extremity after a local trauma or surgical intervention (1). Symptoms include severe pain, evidence of edema, and vasomotor changes at the site effected such as temperature changes or discoloration (1). There are two variants of the condition based on the presence of nerve damage following an injury. Type I (formerly known as reflex sympathetic dystrophy - RSD), does not have demonstrable nerve lesions and generally develops after trauma. Type 2 (formerly known as causalgia) has evidence of obvious nerve damage and is most commonly caused by severe trauma (2).

Three stages of symptoms may occur in the development of CRPS as time progresses (3). The early acute stage, or stage 1, is characterized by the patient developing limb pain and can occur either following a traumatic event or without any apparent cause. Symptoms

include burning, throbbing pain; diffuse uncomfortable aching, sensitivity to touch or cold and localized edema. The distribution of the pain is not compatible with a single peripheral nerve, trunk, or root lesion. Vasomotor disturbances occur with variable intensity, producing altered color and temperature. The dystrophic stage, or stage 2, is marked by progression of the soft tissue edema, thickening of the skin and articular surfaces, muscle wasting, and the development of brawny skin. This generally lasts from 3 to 6 months. The atrophic stage, or stage 3, is most severe and is characterized by limitation of movement, shoulder-hand syndrome (capsular retraction producing a frozen shoulder), contractures of the digits, waxy trophic skin changes, and brittle, ridged nails. Bone radiography reveals severe demineralization (4).

Management of refractory CRPS has been challenging, and common treatments including steroids, sympathetic block, antidepressants, opioids, physical therapy and even transcutaneous nerve stimulation have had varying degrees of success (5). It is currently unknown what percentage of patients fully recover from CRPS, however a considerable number of patients suffer with chronic disease and diminished quality of life.

The pathophysiology of CRPS remains largely unknown; nevertheless recent studies reveal that the N-methyl-D-aspartic acid receptor (NMDAR) may be involved in the etiology and perseverance of the chronic pain. Through a mechanism termed central sensitization, it appears that NMDA receptors are activated and upregulated in the spinal cord leading to chronic pain states (6). This upregulation of receptors in turn causes enhanced pain signal transmission to the cortex leading to spontaneous pain, allodynia and hyperalgesia (1). Considering the contribution of NMDA receptors to chronic pain, an NMDA receptor antagonist such as ketamine could potentially play an important role in the treatment of CRPS. This was evaluated in a retrospective study by Correll et al (7) which revealed that low-dose infusion of ketamine may be an option for patients with intolerable CRPS. The use of sub-anesthetic doses of ketamine for CRPS has also been studied in a double-blind placebo control trial done by Schwartzman et al (8). In this study, patients had significant improvement of their pain after they were given low dose infusions of ketamine as outpatients for 10 days.

When treating CRPS with ketamine, it is beneficial to minimize the dose of ketamine administered to avoid adverse side effects. To accomplish this goal while additionally supplementing pain control, dexmedetomidine can be added to the treatment regimen. Dexmedetomidine is a selective α2-adrenergic receptor agonist similar to clonidine, but with a much greater affinity for its receptor. There are many desirable effects of using α2-adrenergic receptor agonists including analgesia, cardiovascular stability, sedation and reduced anesthetic requirements perioperatively (9). Clonidine has been shown to provide superior pain relief when used as an adjunct in neuraxial blocks (10). α2-adrenergic receptor agonists such as clonidine and dexmedetomidine, appears to exert their analgesic effect by releasing a centrally acting enkephalin-like substances (11). In addition, because sympathetic neural activity might increase both somatic (12) and sympathetically maintained pain (13), clonidine can reduce nociceptive pathways by inhibiting the release of norepinephrine from prejunctional α-2 adrenoceptors (10).

This case report details the successful treatment of a patient with refractory CRPS-1 using sub-anesthetic intravenous infusion of ketamine combined with adjunct dexmedetomidine therapy.

Case Description

A 47-year-old Caucasian female with a past medical history of CRPS-1 presents to the office with severe pain in the left arm. The patient was initially diagnosed with CRPS-1 approximately 8 years ago after undergoing a left arm lateral epicondylar release for a hyperextension injury. Upon initial diagnosis, she was treated with physical therapy, intravenous lidocaine, and stellate ganglion blocks. She is currently on multiple medications for her symptoms including neurontin, oxycodone, and transdermal lidocane patches. This patient has had 3 hospitalizations during the past year for acute pain symptoms associated with her condition. During these admissions, her pain was managed with sub-anesthetic intravenous infusion of ketamine and dexmedetomidine which did provide some pain relief. During her first admission, she was treated with a sub-anesthetic ketamine infusion for 48 hours with one dose of dexmedetomidine. On each subsequent admission, she received less ketamine and more dexmedetomidine. Our patient was symptom-free for 6 months before the admission in this case report.

On presentation, symptoms included severe, continuous pain of the left upper arm rated 10/10 on the pain scale. The patient also exhibited marked allodynia and burning of the left upper extremity from elbow to wrist. She was however neurologically intact with no motor or sensory deficits. Strength was 5/5 in upper

extremities bilaterally and reflexes were present and equal throughout.

The protocol used was a sub-anesthetic intravenous ketamine infusion developed at Walter Reed Army Medical Center for refractory acute pain, which is used at Conemaugh Memorial Hospital. The protocol requires that the patient have failed first and second line therapies for pain such as opioids, anticonvulsants and antidepressants. Also, this protocol can only be administered by a member of the anesthesiology department. Management calls for 60-120 mcg/kg/hr of 2mg/mL solution of intravenous ketamine. Side effects are minimized with the administrations of lorazepam (1 mg intravenously every 4 hours for unpleasant dreams, mild hallucinations or agitation), scopolamine (1.5 mg transdermal patch for nystagmus, nausea or vomiting) and ondansetron (4 mg intravenously every 4 hours for severe nausea) as needed. The patient is to be placed in a monitored bed where vital signs, including heart rate, blood pressure, respiratory rate and oxygen saturations, can be monitored. Pain and sedation level were also assessed. To increase the efficacy of intravenous ketamine, the patient was also given a bolus dose of dexmedetomidine. Dexmedetomidine was mixed in a 10 mL syringe containing 4 mcg of drug for every 1 mL of saline. The developed protocol permits delivery of up to 40 mcg of dexmedetomidine in a 24-hour period.

Our patient was admitted to a monitored bed and was placed on a ketamine intravenous infusion that was administered as per our institution protocol. The infusion was started at a dose of 100 mcg/kg/hr and continued for 19 hours. Approximately one hour after the start of the infusion, the patient reported her pain had subsided to a subjective rating of 7/10 from a 10/10 preadmission rating. Approximately 6 hours after starting the ketamine infusion, the patient received a one-time bolus of 8 mcg of dexmedetomidine, totaling 2 mL of solution, which resulted in a decrease in pain to 3/10. When the patient was seen the following morning (19 hours later), she reported complete resolution of pain (0/10 pain rating), with elimination of burning and allodynia. At this point, she did not require continued intravenous ketamine infusion or additional doses of dexmedetomidine and was discharged to home on her oral medications within 24 hours of being admitted. Written permission was sought and obtained from the patient to report this case.

Discussion

Physicians in the past have avoided the use of ketamine due to the fear of psychomimetic side effects and emergence reactions that occur as the effects of therapeutic doses of ketamine dissipate following sedation. Emergence reaction may include vivid, unpleasant dreams, extracorporeal experiences, illusions, and can be associated with excitement, confusion or fear (14). The use of anesthetic doses of ketamine to treat CRPS has been reported in the literature by Kiefer et al (15), however this intervention requires admission to the intensive care unit for close monitoring. Along with the increased costs associated with admission to an intensive care unit, there may be significant health risks associated with the ICU also, including adverse events resulting from immobilization, risk of nosocomial infection, need for invasive monitoring, parenteral nutrition, endotracheal intubation, and mechanical ventilation (15). Therefore to minimize these adverse events, our patient with CRPS-1 was treated with sub-anesthetic intravenous infusion of ketamine and adjunct dexmedetomidine, requiring admission to a monitored bed instead of the intensive care unit and thereby reducing the cost of therapy (16).

With our combined protocol, the patient only required 19 hours of the ketamine infusion at 100 mcg/kg/hr, compared to a 50 mg bolus and 120 mcg/kg/hr of ketamine for approximately 48 hours during a previous admission 6 months prior. This decreased ketamine requirement could be attributed to the increase in dose of dexmedetomidine given to the patient. The combination of α-2 agonists with ketamine has been reported in the literature for treatment of pain in different situations. One study by Sollazzi et al (17) found that in morbidly obese patients undergoing bariatric surgery, the concomitant use of ketamine and clonidine at lower doses preoperatively at induction leads to a reduced intraoperative requirement of volatile anesthetics and postoperative requirements of analgesics.

Studies have also been done with the administration of clonidine and sub-anesthetic ketamine for the relief of pain secondary to CRPS with favorable results (18). Additionally, such a synergistic phenomenon when using dexmedetomidine specifically and ketamine has been studied by Mizrak et al (19) in a double blinded study of patients premedicated with dexmedetomidine when undergoing intravenous regional anesthesia for surgery requiring a tourniquet. The study concluded that the addition of dexmedetomidine provides clinical benefit by reducing intra

and postoperative analgesic consumption and reduced incision and tourniquet related pain (12). We believe that the higher affinity of dexmedetomidine to the alpha receptor makes it a superior choice as a adjunct to pain therapy, as also seen in our case study.

Conclusion

Sub-anesthetic ketamine with adjunct dexmedetomidine may be a promising therapeutic option for the treatment of acute exacerbation of CRPS. Our patient experienced total relief of symptoms after a shorter infusion of intravenous ketamine with supplemental dexmedetomidine, and avoided both adverse side effects and admission to the intensive care unit. Future research may investigate an outpatient treatment option with sub-anesthetic intravenous ketamine and adjunct dexmedetomidine for acute pain from refractory CRPS.

Acknowledgments

The authors wish to thank the editorial board of *Pain Physician* for review and criticism in improving the manuscript.

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