Case Report

Ketamine patient-controlled analgesia for dysesthetic central pain

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Study Design: Case report.

Objectives: To describe the first use of intravenous (IV) ketamine as the sole agent in a patient-controlled analgesic delivery system (ie PCA) in a patient with cervical syringomyelia.

Setting: A tertiary-care university teaching hospital in New York City.

Methods: A 41-year-old tetraplegic female on high-dose opioids suffering from intractable dysesthetic central pain received her best pain relief from a low-dose ketamine infusion after failing trials with multiple neuropathic medications. After several weeks of titrating her infusion rate up and down, she was switched to an IV ketamine PCA device.

Results: The patient was maintained on an IV ketamine PCA for almost 1 year under the following settings: 2.7 mg/h basal rate; 2.7 mg/h demand dose; 15 min lockout period. Although she continues to report some pain, it has dramatically decreased since the ketamine PCA was instituted, enabling us to significantly reduce her opioid dosage.

Conclusions: Ketamine PCA may be a viable treatment option in patients suffering from intractable central pain. The rationale for this treatment, along with dosing guidelines and possible drawbacks, is discussed.

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Introduction

For the large majority of patients, patient-controlled analgesia (PCA) is the preferred delivery method for pain medications in acute and chronic pain conditions.¹ While the intravenous (IV) route is the most common means of administration, patient-controlled epidural analgesia, patient-controlled perineural analgesia, and patient-controlled surgical wound infiltration have also been described.^{2–4} Although opioids are the most frequently used medications in PCA, they are not the only analgesics utilized. Nonsteroidal anti-inflammatory drugs, opioid agonist–antagonists and mixed analgesics like tramadol, with and without magnesium, have also been used successfully.^{5–7}

Use of the anesthetic agent ketamine has also been reported during PCA. Ketamine has been used in conjunction with a variety of different analgesic agents intravenously, epidurally, and during wound infiltration via a patient-controlled delivery system.^{4,8–10} Yet, it has never been reported as a solitary analgesic by any of these routes. We describe a 40-year-old tetraplegic woman with intractable central pain unresponsive to numerous opioid and non-opioid analgesics whose best

pain relief was with a low-dose IV ketamine infusion. After 2 months of titrating the infusion rate up and down every few days based on analgesic efficacy and side effects, she was switched to an IV patient-controlled analgesic infusion using only ketamine that was administered with the assistance of family and nursing staff. The advantages and drawbacks of this technique are discussed.

Case report

The patient is a 41-year-old, 50-kg female with a birth history significant for Arnold–Chiari malformation, lumbar meningocele and spina bifida, for which she has undergone over 60 surgical procedures throughout her life. Notable among her lumbar spine surgeries were an L4–5 meningocele repair at 4 h of life, a ventriculo-jugular shunt at 6 weeks, and a tethered cord release at the age of 17 years that left her unable to ambulate. Her numerous cervical spine and brainstem operative procedures include a C1–3 laminectomy, durotomy and placement of a Cargyle membrane at the age of 19 years, a C1–4 tethered cord release at the age of 32 years that was complicated by the development of a C4–5 syrinx, a syringo-pleural shunt placed 1 year

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later that left the patient tetraplegic, and a vagal nerve stimulator placement at the age of 36 years for intractable seizures. Over the past several years, more than 95% of her time has been spent in an intensive care hospital setting, predominantly as a result of either seizures or recurrent infections. The latter have included multiple bouts of osteomyelitis, meningitis, pneumonia, enteritis, and several large pressure ulcers. She breathes spontaneously through a tracheostomy tube during the day, but requires assist-control ventilation at night. She is fed and receives most of her medications through a gastrostomy tube, with intravenous medications being administered through two indwelling, tunneled catheters. Despite her physical limitations, the patient is usually fully alert and is reported to have an above average IQ score. Communication with her is through lip reading. Her American Spinal Injury Association (ASIA) impairment scale classification is 'A' (complete).

One year ago, the Pain Management Service was consulted to assist in controlling her pain. She described her main complaint as a continuous, burning pain that was present throughout her entire body except the face, but especially in her arms. This pain was usually worse at night. Sometimes, the placement of a bed sheet over her arms resulted in intense dysesthesias. Previous medication trials had been conducted with over half a dozen anticonvulsant medications, mexiletine, several antidepressants, numerous nonpharmacologic therapies such as transcutaneous electrical nerve stimulation (TENS) and biofeedback, and a plethora of different opioids including high-dose methadone, all without benefit. On a verbal scale of 0–10, she rated her pain as averaging an '8', but never less than '6'. Her medication list, most of which she had been taking for months, included fentanyl patches at 250 µg/h, a continuous morphine infusion at 12 mg/h, lorazepam 2 mg IV q6h, acetaminophen 1000 mg PRN, lamotrigine 200 mg BID, phenobarbital 30 mg qD, phenytoin 330 mg BID and tizanidine 8 mg QID. The opioid regimen was used because attempts to increase her narcotics reportedly resulted in mental status changes without conferring additional analgesia. The patient's neurologic exam was remarkable for flaccid paralysis, muscle wasting in all four extremities, and markedly diminished but not fully absent sensation in both legs and arms to pinprick, light touch and cold. A stage II 3 × 1 inch pressure ulcer was present over her left ischial tuberosity. Despite her history of intermittent touch-evoked dysesthesias, neither tactile allodynia nor hyperalgesia was elicited.

Following a detailed review of past interventions, the patient was given a 5 mg IV infusion of ketamine over 10 min, which resulted in a 50% decrease in her pain. According to the patient, this was the best pain relief she had experienced in several years. No adverse psychomimetic effects or hemodynamic changes were noted. The patient was then started on the noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist dextromethorphan, titrated up to 60 mg TID via her gastric tube, which resulted in no pain relief. Placement of an

intrathecal pump and/or motor cortex stimulator were considered, but rejected because of recurrent infections. After several other unsuccessful interventions that included opioid rotation from IV morphine to hydromorphone, and trials with other neuropathic pain medications, a low-dose IV ketamine infusion was begun at 2 mg/h. The patient reported a 30% pain reduction at this dose, such that each time we saw her she requested an increase in her infusion rate. At 4 mg/h, a dose at which the patient reported 50% pain reduction, she began to experience hallucinations, which necessitated titrating the rate back to 2.5 mg/h. Subsequently, her pain increased. The lorazepam was then increased to 2.5 mg IV q6h, which enabled us to once again increase her ketamine. After several weeks of titrating up and down on the ketamine and lorazepam, an IV ketamine PCA was begun at a 2 mg basal rate, a 2 mg bolus dose and a 20-min lockout period. Over the next few days, this was increased to a 2.7 mg basal rate, a 2.7 mg bolus dose and a 15-min lockout period. Presently, she has been on a ketamine PCA at these settings for over 11 months, with no adverse side effects. During waking hours, the hourly dose averages approximately 7 mg/h. In this same time span, we have been able to reduce her total opioid dose by about 25%. Her average pain score is approximately '4' on a scale of 0–10.

Discussion

Syringomyelia is a fluid-filled cavitation of the spinal cord that is often said to be associated with the highest incidence of central pain of any condition.^{11,12} Although the pathogenesis of this rare disorder is unknown, hydromechanical forces are thought to play an important role in cavity expansion. Trauma can be a precipitating event in the development of syringomyelia, even though most cases are idiopathic.¹³ In our patient, the suspected cause of her cervical syrinx was surgery (ie iatrogenic trauma).

There are several different types of pain seen after spinal cord injury (SCI). These include central pain, spasticity-related pain, visceral pain, radicular pain and miscellaneous sources (pressure ulcers, fractures, deep vein thromboses, etc.).¹⁴ By far the most common form is central pain, which tends to occur below the lesion.^{15,16} While pressure ulcers and paraspinal muscle spasm were present in our patient, diffuse, dysesthetic, 'central' pain was the main source of her discomfort.

Ketamine is an arylcyclohexylamine congener of phencyclidine (PCP) that is usually employed in medicine as a general anesthesia induction agent. The effects of ketamine on neural transmission are less well described than other anesthetics, but the drug has been reported to possess local anesthetic properties, act antagonistically at muscarinic receptors, as an agonist at opioid receptors, noncompetitively block NMDA and non-NMDA glutamate receptors, and facilitate gamma-aminobutyric acid (GABA_A) signaling.¹⁷ In central pain following spinal cord injury, ketamine has been

shown to be an effective analgesic. In a double-blind, placebo-controlled crossover trial by Eide *et al.*,¹⁸ a ketamine infusion of 6 µg/kg/min was shown to reduce spontaneous and evoked pain, an effect the authors attributed to blockade of NMDA receptors. Other NMDA receptors have not been studied in SCI, but a study by McQuay *et al.*¹⁹ found low-dose dextromethorphan to be ineffective in central poststroke pain. In our patient, neither dextromethorphan nor opioid rotation to methadone, another drug with NMDA receptor antagonist properties, significantly reduced her pain. This discrepancy may be secondary to the non-NMDA antinociceptive effects of ketamine, its psychomimetic properties, or different binding sites on the NMDA receptor.

Considering that a ketamine PCA provided our patient with her best pain relief among trials with over 15 different analgesic medications, continuing this treatment seemed a logical extension. In a case report on a 12-year-old girl with central pain from a spinal cord tumor, the authors treated the patient with high-dose morphine, midazolam and IV ketamine for more than 2 months until her death.²⁰ An additional advantage of using NMDA receptor antagonists in patients on opioids is synergistic analgesia and a reduction in tolerance.^{21,22} The main drawback in using IV ketamine is the possibility of developing psychomimetic effects if too large a dose is administered. These side effects can be prevented by the concomitant use of a benzodiazepine,²³ a class of drugs that have also been used to treat opioid-induced myoclonus.²⁴ Presently the long-term effects of long-standing ketamine use has yet to be fully elucidated.

A final question that needs to be addressed is the optimal settings for PCA ketamine. In most studies that have sought to determine the ideal PCA settings, opioids were used in patients suffering from acute postoperative pain. In this context, the use of a basal (baseline) infusion rate has generally been found not to improve analgesia.^{1,5,25} However, in chronic malignant pain, which tends to be more progressive and steady than postsurgical pain, basal infusions are routinely administered in outpatient settings.^{26,27} Given that our patient's condition was more akin to the former than the latter, her pain was constant and unrelenting, and the sequelae of overmedicating with opioids are more catastrophic than with ketamine, we elected to use a basal rate.

The function of the lockout period in PCA is to prevent overdose. This period should be long enough for the patient to start experiencing side effects of the medication (ie sedation with opioids) and to begin experiencing analgesia. The time need not be as long as, and in fact is usually considerably shorter than, the peak analgesic effect (ie 6–10 min for morphine versus a peak analgesic effect of 15–20 min). Since the half-life and peak effect of ketamine are shorter than that of morphine, a 15-min lockout period does not make sense pharmacokinetically. Comparatively, it should be similar or shorter. However, since our settings were based on practical concerns (although the patient controlled the

delivery of medication, someone had to be present to press the button for her), and 15 min provided her with good pain relief, this was chosen as the lockout period. An additional concern in future patients is that while sedation physically limits the amount of opioids that can be self-administered via PCA, hallucinations and euphoria are not necessarily self-limiting side effects with ketamine.

In conclusion, we report a 40-year-old female with refractory central pain whose best pain relief was with a ketamine PCA. Clinical studies are needed to determine the best candidates for this treatment, as well as the ideal dosing regimen.

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