Correspondence

Emerging applications of low-dose ketamine for pain management in the ED☆☆☆

To the Editor,

1. Introduction

The recent Institute of Medicine report, *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, described inadequate emergency department (ED) treatment of pain as a major public health concern [1-6]. The risks associated with the traditional mainstays of ED pain management—opioids and nonsteroidal anti-inflammatory medications—often limit their utility in ED patients [7,8]. The following report describes 3 distinct clinical scenarios where low-dose ketamine holds promise in ED pain management.

Ketamine has a unique mechanism of action that involves blockade of N-methyl-D-aspartic acid receptors in the central nervous system, including spinal dorsal horn neurons, as well as blockade of peripheral Na+ channels and μ-opioid receptors. At doses of 1 to 4 mg/kg intravenous (IV), ketamine induces profound dissociative anesthesia. Low-dose ketamine (also known as “subanesthetic” or “subdissociative” dose ketamine) refers to doses up to, but generally less than, 1 mg/kg IV [9-11]. The primary limitation of ketamine in clinical use is its dose-dependent psychomimetic effects that include dizziness, confusion, hallucinations, and emergence reactions [12]. In this report, we discuss the use of a very-low-dose ketamine (15 mg IV or approximately 0.2 mg/kg). At this dose range, ketamine continues to produce analgesia, with little to no dissociative effects.

In the ED and prehospital setting, there are small studies suggesting that low-dose ketamine is effective and well tolerated among trauma patients [1-6]. To date, there have been no prospective trials of low-dose ketamine for analgesia in a general ED population [13,14]. Our clinical experience suggests particular promise for very-low-dose ketamine (0.1-0.3 mg/kg IV) among 3 distinct patient groups: (1) awake patients undergoing brief painful procedures, (2) patients with chronic pain on high-dose opioids presenting with intractable breakthrough pain, and (3) patients in whom pain is associated with emotional distress.

2. Illustrative cases

2.1. Case 1

A 25-year-old man presented to the ED with a 15 by 15 cm area of erythema and induration with central fluctuance on the lateral aspect of the left shin. Low-dose ketamine (15 mg IV) was administered with 4 mg IV morphine. Subcutaneous infiltration with local anesthetic was performed 3 minutes later. The patient was able to tolerate extensive subcutaneous infiltration of 10-mL 1% lidocaine with epinephrine into the highly inflamed tissue around the abscess with minimal discomfort. Five minutes after the anesthetic injection, the abscess was incised, explored, and drained without discomfort.

2.2. Case 2

A 57-year-old man with advanced prostate cancer, metastatic to the sacrum, pelvis, and lumbar and thoracic spine, and an acute T-5 pathologic fracture, presented to the ED complaining of severe back pain. During a recent hospitalization, he required 1.5 mg of IV hydromorphone per hour, around the clock. In the ED, after his pain proved refractory to repeated boluses of 2 mg IV hydromorphone, ketamine15 mg IV was administered. After 5 minutes, the patient's pain resolved completely. The patient reported that he had not had a similar complete respite from pain at any point in the previous 6 months of treatment.

2.3. Case 3

A 52-year-old woman presented emotionally upset and tearful. She complained of intolerable pain in her head, chest, and back. Review of the electronic medical record revealed

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23 ED visits in the previous 3 years for pain variously located in the chest, neck, abdomen, pelvis, legs, and arms. During these visits, she underwent 8 computed tomographic scans, 23 x-rays, 9 electrocardiograms, and a pelvic ultrasound. Her ED length of stay averaged 6 hours and 23 minutes with a total time spent in the ED of 151 hours (>6 days). Several providers documented concerns for drug-seeking behavior.

On this visit, the patient was given morphine and lorazepam IV. One hour later, her pain and emotional upset were unchanged. At this point, ketamine 15 mg IV was administered. Twenty minutes postinjection, she reported that her pain had resolved, was noted to have a bright affect, and was discharged uneventfully.

3. Discussion

3.1. Ketamine for injury and procedure-related pain

Case 1 is an example of the role of low-dose ketamine to improve pain management for brief painful procedures. The efficacy of ketamine for burn-dressing changes, for example, is well-established [1,2]. Local anesthetic infiltration of the skin surrounding abscesses and wounds can be very painful in part due to the phenomenon of secondary hyperalgesia. Several studies suggest the addition of ketamine to opioid analgesics acts synergistically to produce greater analgesia than possible with opioids alone [11,14,15].

3.2. Ketamine for intractable breakthrough pain in a patient on long-term opioid therapy

Opioids have a narrow therapeutic window at high doses, and these patients are at increased risk for delirium, hypoventilation, and excessive somnolence [8]. In addition, paradoxical hyperalgesia may occur with escalating doses of opioids, further limiting their utility for chronic pain [15-18]. Ketamine can produce improved quality and level of analgesia for breakthrough pain that cannot be achieved with opioids alone [16,19-22]. This effect is likely due to central inhibition of opioid-induced hyperalgesia and peripheral potentiation of the analgesic effects of opioids [23].

3.3. Ketamine for pain in the context of acute emotional distress

In clinical practice, chronic pain, psychologic distress, and behavioral disorders frequently overlap [24,25]. Ketamine is unique among the analgesics in that it has powerful antidepressant effects and has been shown to influence the affective component or emotional coloring of the pain experience, in addition to the peripheral perception of pain [26-28]. The unique combination of antinociceptive and antidepressive properties of low-dose ketamine, however, provides an intriguing therapeutic option in this difficult-to-treat population [29,30].

3.4. Psychomimetic effects of low-dose ketamine

Because the analgesic properties of low-dose ketamine were first described in 1971, the dose-dependent central nervous system side effects have been the major limiting factor in its widespread use for analgesia [9]. Although most emergency physicians are comfortable giving dissociative dose ketamine to children for procedural sedation or as an induction agent for rapid sequence intubation, many are hesitant to use ketamine in awake adults due to fears of emergence phenomena [31]. For the busy emergency physician, concerns about the risk of an unpleasant reaction to low-dose ketamine may be a significant deterrent given the well-established efficacy of more traditional analgesics.

Although actual emergence phenomena has not been reported with subdissociative doses of ketamine below 0.3 mg/kg, patients do frequently experience dizziness, changes in vision, and a floating sensation. In our experience, these effects occur in the first several minutes after administration and are typically short lived. Some patients find the experience unpleasant; others are not bothered by it, and many seem to enjoy it. The likelihood of experiencing strange symptoms should be discussed with all patients before administration [11,21]. Although these minor unpleasant psychomimetic effects rarely require treatment, small doses of a benzodiazepine typically prove effective [21]. Furthermore, ketamine can exert a powerful analgesic effect at very low doses, and boluses of just 0.1 to 0.15 mg/kg may be effective in many patients while causing fewer side effects [21,32].

4. Conclusion

Low-dose ketamine is a promising analgesic agent for ED use. We believe that with more widespread use and greater familiarity will come a more nuanced approach to patient selection and dosing, as exemplified by the 3 cases that we present here. High-quality, prospective clinical research is now needed to confirm that ketamine adds to the current ED pain management armamentarium and to determine whether specific clinical applications, such as we propose here, are actually effective.
References