CASE STUDY

Very-low-dose ketamine for the management of pain and sedation in the ICU

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ABSTRACT

Management of pain in critically ill patients can be very difficult. In the attempt to provide comfort with adequate levels of opioids and sedatives, respiratory depression and cardiovascular instability may become difficult to control in patients with labile hemodynamics and poor cardiopulmonary reserve. The use of medications like ketamine, an anesthetic agent that in subanesthetic doses has been reported to be effective in preventing opioid-induced tolerance and to have analgesic properties, may be of help, especially in patients who develop tolerance, leading to rapidly escalating doses of opioids and sedatives. The case report presented here shows how a very low dose of ketamine can be helpful for the management of pain and sedation in critically ill patients, especially when they are ready to be weaned from mechanical ventilation, and very high doses of opiods and sedatives do not permit it.

Key words: pain, sedation, opioids, tolerance, critical care

INTODUCTION

Management of pain is a major problem in critically ill and trauma patients.[1,2] In a study by Whipple et al.,[1] assessing treatment of pain in 17 patients with multiple trauma wounds, 95 percent of house staff and 81 percent of nurses reported adequate analgesia for their patients whereas 74 percent of patients rated their pain as either moderate or severe and not adequately treated.

Fears of depressing spontaneous ventilation, inducing opioid dependence, and precipitating cardiovascular instability can lead to inappropriate treatment of pain and sedation, which can affect overall patients' care.[3] In patients ready to be weaned from the ventilator and who may have developed opioid tolerance leading to escalating requirements, the use of medications that minimally affect hemodynamic parameters and spontaneous ventilation such as the N-methyl-D-aspartic acid (NMDA) receptor antagonist ketamine has been reported to be potentially useful.[4]

Ketamine has been reported to be effective in preventing and reversing morphine-induced tolerance in animals and humans,[5,6] particularly in patients with chronic benign or cancer pain,[7,8] leading to a significant reduction of the total daily dose of opioids needed to maintain adequate analgesia.

We describe the case of a patient with multiple injuries of the lower extremities, septic shock, ventilator-associated pneumonia, and adult respiratory distress syndrome, weaned from the ventilator and eventually extubated with the help of a pain and sedation medication regimen, which included a very small dose of ketamine.

CASE REPORT

A 61-year-old morbidly obese (124 kg) male patient with known history of coronary artery disease, status post five vessel coronary artery by-pass graft, congestive heart failure, hypertension, and obstructive sleep-apnea, was involved as a restrained driver in an high-speed motor vehicle accident during which he sustained complex open fractures of the lower extremities and soft tissue injuries. After the initial evaluation in a local hospital, he was transferred to our trauma center.

The initial work-up demonstrated the presence of complex left femur and distal tibia fractures and a right tibia fracture. No other remarkable injuries were observed. After adequate volume resuscitation, the patient underwent irrigation, debridement, and surgical fixation of the fractures. At the end of the surgical procedure, because of the prolonged duration of the operation, the extent of the injuries sustained, and the associated comorbidities, the patient was left intubated and transferred to the intensive care unit (ICU). A sedation and pain medication protocol with intravenous (IV) lorazepam (2-4 mg q 1 h as needed), propofol infusion

(20 mcg/kg/min), and IV morphine (2-5 mg q 1 h as needed) was initiated.

On postoperative day 1, evidence of a non-ST elevation myocardial infarction associated with atrial fibrillation and acute renal failure secondary to rhabdomyolysis was observed. Cardiology and renal consultations were obtained, anticoagulation with IV heparin was instituted, and two direct cardioversions for the treatment of atrial fibrillation were performed. Furthermore, continuous veno-venous hemofiltration for the treatment of acute renal failure was also initiated. The propofol infusion was discontinued, and management of sedation and pain was achieved with a lorazepam infusion (2 mg/h) and a fentanyl infusion (300 mcg/h). In spite of the aggressive treatment, the patient's condition continued to deteriorate and evidence of a clinical picture of septic shock, ventilator-associated pneumonia, and adult respiratory distress syndrome soon developed; a Swan-Ganz catheter was placed, hemodynamic support with vasopressors was given, and lung protective ventilation was started. Appropriate antibiotic therapy for treatment of a methicillin resistant *staphylococcus aureus* infection was also initiated. The lorazepam and fentanyl infusion rates were increased according to the patient's needs and, at one point, reached the 20 mg/h and 1,000 mcg/h, respectively.

Clinical condition improved during the following two weeks. The hemodynamic support with vasopressors was discontinued; however, several attempts of weaning the patient from the ventilator were unsuccessful, in part, because of the high doses of opioids and sedatives utilized. By postoperative day 15, a pain service consultation was requested. At that time, the sedation and pain medication protocol included fentanyl infusion (500 mcg/h plus boluses as needed) and lorazepam infusion (3 mg/h plus boluses as needed). The pain service recommended starting methadone 25 mg every 6 hours and a low-dose ketamine infusion (0.8 mcg/kg/min); the fentanyl infusion rate was reduced to 375 mcg/h while the lorazepam infusion was kept at the same rate of 3 mg/h. The following day, the ketamine infusion was increased to 1.3 mcg/kg/min while no adjustments of the fentanyl and lorazepam infusion rate was made. Three days after the initial consultation, the lorazepam and fentanyl infusion rates were reduced to 1.5 mg/r and 200 mcg/h, respectively. The ketamine infusion was reduced to 0.6 mcg/kg/min one day later and discontinued altogether in the next two days. The lorazepam infusion was also decreased to 1 mg/h and eventually discontinued several hours later. The patient was extubated after the ketamine and lorazepam infusions were discontinued. The fentanyl infusion was discontinued two days later. A schedule for the tapering of methadone was started. Tapering continued throughout the patient's ICU stay until he was transferred to the General Medicine ward on hospital day 29.

Two surgical revisions were performed by the orthopedic trauma team during the remainder of the hospital course, and the patient tolerated both procedures very well with no complications. He was eventually discharged to a rehabilitation facility on hospital day 45. At the time of discharge from the hospital, he was on methadone 10 mg/d and oxycodone as needed for breakthrough pain.

DISCUSSION

Ketamine is a noncompetitive NMDA receptor antagonist that, when given at a bolus dose of 2 mg/kg, produces a dissociative anesthetic state with loss of consciousness, analgesia, sympathetic stimulation with tachycardia and hypertension, excessive salivation, and, if used alone, emergence phenomena including vivid dreams and psychomimetic effects such as delirium and hallucinations.[9] The incidence of the psychomimetic side effects is less common in children and in patients who are premedicated with benzodiazepines.[9]

The administration of a low dose of oral or parenteral ketamine (0.3-0.5 mg/kg) has been reported to be helpful in numerous pain conditions including postherpetic neuralgia,[10] phantom limb pain,[11] central pain,[12] and cancer pain.[13] In a published report,[14] seven out of nine patients reported a significant improvement of their neuropathic cancer-related pain when a small dose of oral ketamine (0.5 mg/kg three times daily) was added to their pain medication regimen. Despite ketamine's reported beneficial effect on pain, psychomimetic side effects, although less frequent, still represent a significant problem for patients using it at a subanesthetic dose such as the one used in the aforementioned report.[14]

Subhypnotic doses of ketamine administered as infusions have been used for critically ill patients in whom it is difficult to maintain an adequate level of analgesia and sedation with opioid and benzodiazepine infusions.[15] These low-dose infusions (<5 mcg/kg/min) are reported to be rarely associated with the adverse effects of ketamine.[16]

The doses of fentanyl and lorazepam needed to manage pain and sedation in our patient had reached alarming levels, and the need of vasoactive drugs to support the patient's hemodynamics did not warrant a further increase of opioids and sedatives; meanwhile, the pain relief service was consulted and it was clear that tolerance to the medications used had developed, and the possibility of opioid-induced hyperalgesia was also of concern. Ketamine's reported ability to provide analgesia when used in low-dose infusions,[8,16] and to reverse opioid tolerance,[8] further confirmed our decision to use it. Certainly, the use of methadone in relatively high doses has played an important role in the management of this patient, but it is also important to remark that the high doses of fentanyl and lorazepam used may have not been

adequately replaced with methadone alone if a small dose of ketamine had not been utilized.

Although the presence of side effects was difficult to assess in our patient, there was no indication of unwanted psychomimetic effects. Certainly, the large doses of lorazepam contributed to minimize the chance of such unwanted effects.

This case report illustrates how a low-dose ketamine infusion may be of help in the management of pain and sedation in critically ill patients who require escalating doses of opioids and sedatives and who may have developed tolerance to the medications used.

It is our opinion that this report of the beneficial effects of ketamine in providing pain relief in well-defined circumstances, and reversing opioid tolerance when used in low-dose infusions, should not increase its indiscriminate use; however, using ketamine when the clinical situation allows it, especially when the patient is ready to be weaned from mechanical ventilation and high doses of opioids and sedatives may not permit it, appears to be warranted.

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