Can J Anesth/J Can Anesth (2014) 61:86–87
DOI 10.1007/s12630-013-0050-4

CORRESPONDENCE

Ultra-low-dose ketamine infusion for ischemic limb pain

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Received: 21 August 2013 / Accepted: 3 October 2013 / Published online: 12 October 2013

To the Editor,

Ketamine is widely used in acute pain management and has found special application in patients with opioid tolerance, acute hyperalgesia, and chronic neuropathic pain.[1,2] We report the pain management of a patient with ischemic limb pain using an ultra-low-dose ketamine infusion.

A 40-yr-old male (80 kg, American Society of Anesthesiologists' physical status IV) with a complex medical history (diabetes mellitus type 2, diabetic neuropathy, end-stage renal disease on peritoneal dialysis, peripheral vascular disease, and hypertension) presented with worsening ischemia of his right leg. Initially, he underwent below-knee amputation under epidural anesthesia, and the epidural was continued for analgesia for three days after surgery. After the epidural was discontinued, oral multimodal analgesia with acetaminophen (650 mg *po* q4h), pregabalin (50 mg *po* q am), tramadol (25 mg *po* q12h), and nortriptyline (10 mg *po* qhs). In addition, he was prescribed intermittent doses of hydromorphone (0.5 mg *sc* or 1-2 mg *po* q4h *prn*) for breakthrough pain. The patient appeared to be very sensitive to these small doses of opioids - he complained of nausea, vomiting, sedation, and hallucinations. These side effects limited the amount of opioid that could be used, and his pain continued to be inadequately controlled. He remained in hospital for another three weeks with worsening pain due to poor healing of the stump. The patient's pain became difficult to control and he refused any opioid analgesia. At this point, the surgeons re-consulted the Acute Pain Service (APS). On evaluation, the patient reported a pain score (numerical rating score 0-10) of 8/10 at rest and 12/10 with movement. In addition to phantom pain and allodynia, he described pain in the amputated leg as shooting, sharp, and thunder-like. After careful discussion, the APS physician administered a small "test" dose of ketamine (2 mg *iv* q 15 min, 6 mg total). The pain decreased dramatically to 4/10 without any psychomimetic side effects. A decision was made to stop the intermittent opioids and to start a ketamine infusion at 1.5-5 $mg{\cdot}hr^{-1}$. Three days after initiating the ketamine infusion, the surgeons decided to proceed with above-knee amputation due to persistent stump ischemia and infection. Surgery was done under general anesthesia supplemented with a single-shot femoral nerve block. Postoperatively, opioids were not prescribed and the ketamine infusion was re-initiated. The ketamine infusion was titrated to provide analgesia (within the range of 1-5 $mg{\cdot}hr^{-1}$) and continued for four days. Daily ketamine requirement and pain scores are shown in the Figure. The patient was discharged home after one week with minimal pain and no side effects from the ketamine. He continued to take pregabalin (25 mg *bid*) and tramadol (25 mg *prn*) with consistent pain scores of 3/10 at rest and 5/10 with activity. He remained well at follow-up six months after his amputation and returned to the operating room for an uneventful revascularization of his other leg.

The effective treatment of ischemic limb pain remains a clinical and pharmacological challenge. There is evidence suggesting that neuropathic mechanisms play a major role in this type of pain due to ischemia or direct damage to the nerve.[3] One other explanation for neuropathic pain may be the N-methyl-D-aspartate receptor-mediated increases in synaptic excitability of the spinal cord, clinically manifested as hyperalgesia and allodynia. Ischemic limb

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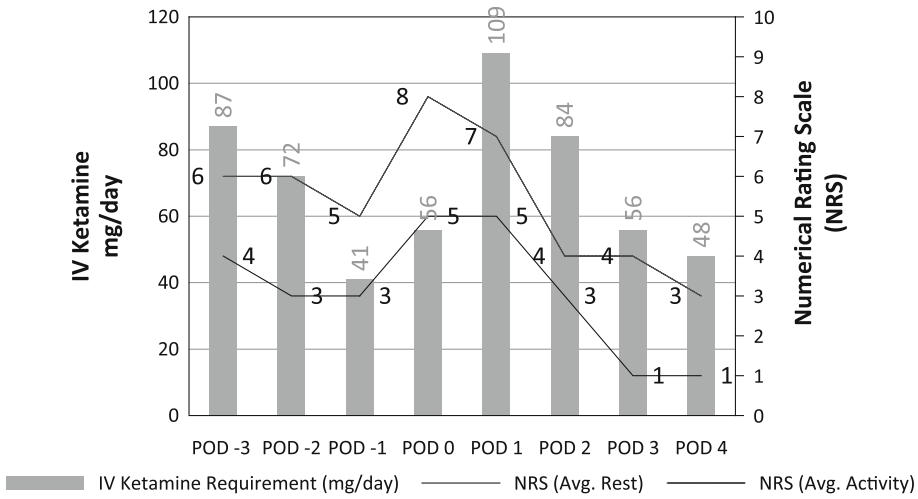

Figure Daily ketamine requirement and pain scores (POD; postoperative day)

pain can be quite severe and prevent activities of daily living. Our patient could not tolerate opioids because of his sensitivity to their side effects, which was probably related to his end-stage renal disease. Other non-opioid drugs useful for similar acute neuropathic pain include pregabalin and systemic lidocaine, both of which require dose reductions in renal failure. Using ketamine in renal failure is not new, and typically no dose adjustment is required in this population.

A common concern with ketamine is determining the smallest effective dose to avoid its psychomimetic effects. For chronic pain, the recommended "low-dose" ketamine infusion is 15-50 $mg{\cdot}hr^{-1}$ (mean 23.5 $mg{\cdot}hr^{-1}$, interquartile range 15-25 $mg{\cdot}hr^{-1}$).[4] More recently, "low-dose" ketamine (three-day infusions of 0.1 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$) have been used successfully to manage pain after major limb injuries sustained in combat.[5] We used less than 5 $mg{\cdot}hr^{-1}$ for a patient with significant comorbidities and found adequate analgesia with no side effects. This "ultra-low-dose" ketamine (0.01-0.05 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$) appears to be a useful option in patients with ischemic limb pain and requires further investigation.

Conflicts of interest and sources of support None declared.

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