

Case Report

PERIOPERATIVE KETAMINE INFUSION IS EFFECTIVE IN REVERSING OPIOID-INDUCED HYPERALGESIA

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Opioid-induced hyperalgesia (OIH) is a condition of nociceptive sensitization caused by exposure to opioids, which is characterized by a paradoxical response whereby patients receiving opioids for the treatment of pain actually become more sensitive to pain as a direct result of opioid therapy. There is increasing evidence showing OIH presents a clinical challenge in acute, chronic, and cancer pain settings. Both clinical and animal studies have shown that glutamate N-methyl-D-aspartate (NMDA) receptors may play a key role in OIH, and pre-application of ketamine, an NMDA receptor antagonist, or a co-administration of ketamine and opioids, can prevent OIH. However, no reports have shown if ketamine can reverse OIH once it occurs.

We present a case of a 56-year-old male with a past medical history of DM-2 with severe peripheral neuropathy, recurrent osteomyelitis of the left foot, hypertension, dyslipidemia, chronic neck and right arm pain due to cervical spondylosis, status post 4 times of cervical discectomy, and fusion surgeries for cervical radiculopathy. He was prescribed to high doses of opioids (morphine 60 mg, orally every 8 hours and hydrocodone/acetaminophen 10/325 mg, as needed up to 4 times daily) for approximately 10 years. He underwent

left below-knee amputation due to uncontrolled osteomyelitis. The patient had worsening stump pain with an increasing dose of opioids and phantom pain on post-operative day one, and he developed OIH, diagnosed as escalating pain reports with every opioid dose increase. A ketamine infusion (loading dose of 10 mg IV bolus, then 20 mg/hour IV infusion) was used after total cessation of opioid use for post-operative analgesia for 3 consecutive days and the patient recovered from his obvious OIH, with his stump pain and phantom pain well-controlled by opioid administration on post-operative day 5.

In our case, the blockage of NMDA receptors by ketamine might quickly restore the balance between opioid-dependent analgesic systems and NMDA-dependent pronociceptive systems by deactivation of the latter, which may help the patient recover from OIH rapidly. While it is possible that ketamine may help facilitate patients' recovery from OIH in addition to its ability to prevent OIH, this clinical observation must be tested in future prospective studies.

Key words: Opioids, ketamine, opioid-induced hyperalgesia, phantom pain, post-amputation, post-operative

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Opioid-induced hyperalgesia (OIH) is a condition of nociceptive sensitization caused by exposure to opioids, which is characterized by a paradoxical response whereby patients receiving opioids for the treatment of pain actually become more sensitive to pain as a direct result of opioid therapy (1). The type of pain experienced in OIH might be either the same as or different than the original underlying pain (1). OIH can occur in different settings characterized by the opioid dose administered (high doses vs. low doses)

and the pattern of administration (long-term use vs. short-term use) (2). Despite the fact that there has been discussion about clinical importance of OIH, it is becoming an important, challenging factor in acute, chronic, and cancer pain (3). The mechanism underlying OIH is not clear. However, both clinical and animal studies have pointed out that the glutamate N-methyl-D-aspartate (NMDA) receptor, known to play a key role in central sensitization, may be involved in OIH (3,4). Experimental animal studies as well as clinical data have shown that NMDA receptor antagonists, such as ketamine, inhibit central sensitization and prevent OIH (3-7). Although pre-application of ketamine or co-administration of ketamine and opioids demonstrated the benefits of preventing OIH in some studies (3-7), there have been no reports thus far showing that ketamine can reverse OIH or facilitate patients' recovery from OIH once it occurs.

In this report, we present a case of successful use of a ketamine infusion over 3 days in reversing acute development of OIH that evolved rapidly following surgery in an opioid-tolerant patient, wherein we successfully used ketamine to reverse the OIH and made opioid therapy effective again.

CASE DESCRIPTION

The patient gave written permission for the authors to publish the report. A 56-year-old male with a past medical history of DM-2 with severe peripheral neuropathy, recurrent osteomyelitis of the left foot, hypertension, dyslipidemia, and chronic neck and right arm pain due to cervical spondylosis, underwent 4 cervical discectomy and fusion surgeries for cervical radiculopathy over an 18-month period. He visited our pain clinic regularly and was prescribed to high doses of opioids (morphine 60 mg, orally every 8 hours and hydrocodone/APAP 10/325 mg, as needed up to 4 times daily) for approximately 10 years. He underwent left below-knee amputation due to severe diabetic foot neuropathy and toe necrosis associated with chronic, unresolving osteomyelitis. The surgery lasted 108 minutes and was performed under spinal anesthesia (0.5% bupivacaine isobaric 2 mL + fentanyl 25 mcg intrathecal), combined with monitored anesthesia care (midazolam 15 mg in divided doses, ketamine 70 mg IV and Propofol IV infusion at 25 mg/kg/hour).

On post-operative day one, he complained of severe, intolerable left leg stump pain that was throbbing and sharp, worse with movement, and scored as a 10 on the numeric rating scale (NRS, 0-10). The patient also had phantom limb pain into the amputated foot and ankle while using escalating doses of IV PCA hydromorphone and later morphine when hydromorphone escalating doses was noted to worsen pain. At each dose increase, the pain was accentuated as the opioid dose was increased.

The total dose of opioid administered during the first 24 hours was hydromorphone PCA 30 mg IV, hydromorphone 12 mg orally, morphine PCA 30 mg IV, fentanyl 500 mcg IV, and finally, a fentanyl patch at 12 mcg/hour (total 24 hour dose=288 mcg), which translates to an equivalent dose of oral morphine of 650 mg with the reduction for incomplete cross-tolerance taken as 30% (Table 1).

On post-operative day 2, opioids were discontinued due to lack of efficacy despite increasing the dosage, and ketamine (loading dose of 10 mg IV, followed by an infusion rate of 20 mg/70kg/hour) was used in place of opioid infusions for 3 consecutive days.

The stump pain and phantom pain were improved immediately with a score of 3 out of 10 on the NRS for stump pain and much reduced phantom pain (NRS = 1/10) on day 3. On post-operative day 5 (72 hours after starting use of ketamine), the infusion rate of ketamine was decreased by 5 mg/3-4 hours until it was discontinued. His previously used analgesia using fentanyl patch was then re-started at 12 mcg/hour/72 hours and was increased by 25 mcg every 3-5 days until a dose of 75 mcg/hour was attained. On post-operative day 7, he felt moderate stump pain (NRS = 4/10) but had no phantom pain. On day 20, he was discharged home with a fentanyl patch 75 mcg/72 hours with mild stump pain (NRS = 1-2/10), but without any phantom limb pain whatsoever. On day 29, the patient was re-evaluated at our pain clinic; his fentanyl patch had been discontinued due to intractable pruritis, and he was prescribed morphine 60 mg every 8 hours and morphine sulfate 15 mg every 4 hours as needed, with intermittent burning sensation at the stump of the amputated leg and without complaints of phantom pain.

DISCUSSION

It is well-known that hyperalgesia can occur after prolonged exposure to opioids and this condition has been designated as opioid-induced hyperalgesia (OIH). It should be noted that OIH is not a common occurrence in most instances; however, when it does occur it may be unrelated to the initial starting dose of opioids used to manage acute pain, regardless of the level of tolerance development due to chronic opioid dosing. The hallmark however, is consistent worsening of the pain with increased dosing of opioids. Opioids have been used to control pain following amputation (8). On day one post-surgery in the present case, the patient suffered both severe stump pain and phantom pain, which could not be controlled by escalating doses of opioids, and indeed, both of which reportedly worsened at every dose escalation. Although tolerance can also follow prolonged usage of opioids (9), we consider that this increasing pain with increasing opioid dosing represented OIH instead of tolerance based upon the rapid pain escalation commensurate with every dose increase, which is not characteristic of the more gradual process of habituation and tolerance. With the development of tolerance the efficacy of opioids decreases, whereas the pain can be relieved by increased opioids, which is different from OIH in which increasing opioid doses aggravate pain (1,9).

Phantom pain is defined as pain wherein patients feel pain in a body part that is no longer present following amputation (10). Fifty percent of patients suffer from phantom pain within the first 24 hours following amputation and this pain is generally opioid and adjuvant analgesic medication resistant (10). In this present case, we discontinued all opioids and instead used a ketamine infusion from days 2 to 4 post-operation, resulting in the patient becoming in a state of profound relaxation. Concomitantly, both the stump pain and phantom pain were well-controlled.

Ketamine infusion has been used in chronic pain states and for providing post-operative analgesia (11,12). In a double-blind, prospective, randomized clinical trial (5) performed on 45 patients undergoing fusion for treating lumbar spondylolisthesis, ketamine infusion (0.5 mg/kg/hour) was shown to be more efficient in post-operative pain reduction during the first

Table 1. Opioid use during the first 24 hours, with doses converted to oral morphine equivalents, with a reduction for incomplete cross-tolerance taken as 30% (based on "Equivalent Opioid Calculator" <http://www.clinicalcalc.com/Opioids/> accessed October 5, 2015).

Opioid	Route	Dose	Equivalent Dose of Oral Morphine
Hydromorphone	IV PCA	30 mg	420 mg
Hydromorphone	Oral	12 mg	34 mg
Morphine	IV PCA	30 mg	75 mg
Fentanyl	IV	0.5 mg	10.5 mg
Fentanyl	Transdermal	12 mcg/hr	28.8 mg
Total			662.8 mg

24 hours compared to routine morphine administration (5 mg IV), although both were effective methods of pain control. In another randomized, controlled study involving 160 pregnant women undergoing cesarean section with spinal anesthesia, 5 minutes after delivery, patients who received 0.25 mg/kg intravenous ketamine via bolus doses significantly reduced the requirement for analgesics and had fewer side effects caused by opioids, compared with those in the control group who received normal saline solution after delivery (13). Ketamine has also been successfully used in phantom pain (14-16), although a recent case report demonstrated a lack of efficacy when ketamine is used for this purpose (17). In a randomized, double-blind, and crossover study of 20 patients, ketamine (0.4 mg/kg IV), but not calcitonin, was shown to reduce phantom limb pain (14), which was supported by a double-blind, saline-controlled study in which 11 patients had decreased stump and phantom limb pain scores as a response to ketamine (0.1 mg/kg/5 min IV bolus, followed by an infusion rate of 7 µg/kg/min) (16). Recently, ketamine has been found to have antidepressant effects, which are possibly related to the selective blockade of NMDA receptor-associated ion-channels, resulting in increased glutamate release (18,19). Following a single low-dose ketamine infusion (0.5 mg/kg over 40 min) improvement in mood reached a maximum within 72 hours (19). Since the loss of a limb may have a substantial psychological impact and since depression is a significant predicting factor for phan-

tom pain (10), ketamine's antidepressant effect might contribute to the patient's relief from phantom pain.

In the present case, on day 5 post-operatively, we stopped using ketamine and changed back to opioid analgesics again as a prelude to preparing the patient for discharge and found that, unlike the situation on day one, both stump pain and phantom pain could be well-controlled until the patient was finally discharged on day 20 after surgery. We believe that the subsequent and ultimate relief of pain in the present case by opioid use is due to the patient's recovery from OIH. Until we addressed the OIH, there was 0 likelihood of addressing the acute pain related to the amputation or that due to a phantom limb syndrome.

In rats, the hyperalgesia induced by high doses of fentanyl can last up to 10 days (20). Based on our previous experience, once OIH occurs, it normally takes approximately several weeks to a few months to suppress it once opioids are discontinued. Ilkjaer et al (21) reported that hyperalgesia proximal to the wound site was found to be present 3 months after surgery in patients recovering from abdominal hysterectomy. However, in our case, the patient recovered from OIH within 3 days when ketamine was substituted for opioids. Although the neurobiology of OIH is complex, activation of central glutamergic pathways (mainly via NMDA receptors) has been regarded as a key mechanism underlying analgesia (1,9). In rats, Mao et al (22,23) found that an increase in responsiveness of the glutamate NMDA receptor contributes to the

development of OIH as the NMDA antagonist MK-801 prevented it from occurring. This result is also supported by 2 additional animal studies in which ketamine, a clinically-used NMDA receptor antagonist (20), clearly reduced fentanyl- or morphine-induced hyperalgesia (7,20). Célèrier et al (24) proposed a neuroadaptive model in which stability between opioid-dependent analgesic systems (pain inhibitory) and NMDA-dependent pronociceptive systems (pain excitatory) could be broken by repeated opioid administrations, thus increasing the sensitivity and leading to the hyperalgesic state. Similar to animal studies, a human clinical study has also shown that OIH did not occur when a high dose of remifentanyl (0.4 µg/kg/min) was co-applied with 0.5 mg/kg ketamine, while remifentanyl alone did produce OIH (4). This was supported by another clinical study where, when given in combination for 30 minutes, S-ketamine (5 µg/kg/min) abolished remifentanyl-induced (0.1 µg/kg/min) OIH (5). However, no studies thus far have reported whether or not ketamine infusion used as an orphan drug to manage post-operative pain can facilitate patients' recovery from OIH. In our case, blockage of glutamate NMDA receptors by ketamine might quickly restore the balance between opioid-dependent analgesic systems and NMDA-dependent pronociceptive systems by deactivation of the latter, which may help the patient recover from OIH rapidly. While it is possible that ketamine can facilitate recovery from OIH, the clinical observations made in this case report need to be tested in future prospective studies.

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