Opioid-induced hyperalgesia after implantation of intrathecal morphine pump: a case report

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Opioid-induced hyperalgesia is characterized by an increased pain response to noxious stimuli despite increased use of opioid medications. Here, we report the case of a 43-year-old woman diagnosed with post-laminectomy syndrome who presented with an increasing pain score following a morphine infusion via an implanted intrathecal drug delivery device. Her pain improved after reducing opioid doses and the administration of intravenous ketamine infusion therapy. Thus, the early suspicion of opioid-induced hyperalgesia is essential for patients with increasing pain refractory to augmented doses of opioid medications.

Keywords: Hyperalgesia; Implantable; Intrathecal; Ketamine; Morphine; Opioid

INTRODUCTION

Post-laminectomy syndrome, a relatively common condition caused by back surgery, can decrease patient quality of life. The prevalence of post-laminectomy syndrome is reportedly up to 60% [1]. Because post-laminectomy syndrome can be difficult to treat, the use of a multimodal approach consisting of psychological support, physical therapy, anti-inflammatory medication, oral opioid, and nerve block is necessary. Advanced pain management devices such as spinal cord stimulators and intrathecal (IT) morphine pumps can be used to treat intractable post-laminectomy syndrome [2,3]. Consensus is lacking regarding post-laminectomy syn-

drome management. Narcotic analgesics are often effective for post-laminectomy syndrome patients, although controversy persists regarding their long-term use. Physicians can become embarrassed if a patient's pain score worsens while on opioid management. When opioid-related complications are suspected, various causes such as opioid withdrawal, toxicity, tolerance, and hyperalgesia should be investigated. Distinguishing opioid tolerance from the deterioration of a pre-existing condition is another daunting challenge.

Opioid-induced hyperalgesia (OIH), an uncommon phenomenon observed in patients receiving opioid therapy, occurs after patients use various opioid medications such as remifentanyl, fentanyl, sufentanyl, and oxycodone [4-7]. Di-

verse routes of administration such as oral, intravenous (IV), epidural, and IT are associated with OIH. However, the diagnosis of OIH is often delayed or misdiagnosed because of its low incidence and vague appearance as well as delayed clinical recognition.

Here we present a case of a 43-year-old female who developed OIH after receiving a morphine infusion through an implanted IT drug delivery device. Here, we share our clinical experience successfully managing a case of OIH.

CASE REPORT

The patient, a 43-year-old woman with diabetes mellitus, underwent a lumbosacral fusion operation 6 years prior to treat a herniated disc. At 2 months postoperative, she developed lower back pain radiating to the bilateral lower extremities with a visual analog scale (VAS) score of 8. She was diagnosed with post-laminectomy syndrome and underwent spinal cord stimulator implantation 3 months later. She subsequently underwent a series of neuraxial and sympathetic ganglion blocks that did not effectively resolve her pain. Signs of depression manifested. She recently developed a sleep disturbance because of the increasing pain. Her opioid medication dose was gradually increased to 440 mg of oral oxycodone daily and 100 µg of transdermal fentanyl hourly equivalent to 840 mg of daily oral morphine (8.4 mg of IT morphine daily). Her non-opioid medications included gabapentin, baclofen, afloqualone, duloxetine, quetiapine, clonazepam, and mirtazapine. However, these drugs were unable to mitigate her pain. The patient agreed to undergo the implantation of an IT drug delivery device. The patient provided written informed consent for the publication of this case report, which was approved by the Institutional Review Board of the Veterans Health Service Medical Center (2020-01-014).

After she was admitted to our hospital, she received an effective IT bolus of 0.3 mg of morphine that reduced her VAS pain score to 4. Although it is general practice to taper at least 50% of the dose of previous opioid medications before a trial [2,8], we maintained her original medications because she strongly refused to reduce them due to her extreme fear of enduring more pain than she was already experiencing. IT drug delivery device implantation was scheduled. Under general anesthesia, the catheter was inserted through L4-L5.

The catheter tip was located at the level of the T11 vertebral body. The pump was placed in a subcutaneous pocket in the right abdominal region and connected to the catheter via an extension cable through a subcutaneous tunnel. The initial infusion rate was set to 1.4 mg of morphine daily. Her overall VAS pain score decreased to 4 on the same day.

Three days later, the patient reported pain worsening. The IT infusion rate was gradually increased three times throughout the following 8 days until it reached 2.0 mg of daily morphine. Nevertheless, the pain severity increased to a VAS score of 9. The patient complained of widespread pain involving her trunks and upper extremities. Several diagnostic measures including laboratory findings, X-rays of relevant regions, and a neurologic examination were performed. However, these tests failed to identify any causes of the increased pain score. A contrast study of the implanted device confirmed that it was functionally intact without catheter obstruction. The likelihood of OIH was considered. After the pain physician's decision was explained, her oral and transdermal opioid medication doses were reduced by 50% and her VAS pain score decreased to 4.

The following day, she complained of severe pain with a VAS score of 10. Thus, an IV ketamine infusion was administered. Treatment with 2 mg of midazolam followed by 20 mg of ketamine and 60 mg of ketamine infused over 1 hour immediately decreased her VAS pain score to 6. Three consecutive identical ketamine infusions administered over the next 10 days of the hospitalization ameliorated her VAS pain score to a mean of 4. The patient was discharged on postoperative day 25. Additionally, 200 mg of oxycodone and 50 µg of transdermal fentanyl hourly were prescribed for the patient. She was satisfied with the new quality of life provided by the IT morphine pump device.

DISCUSSION

Post-laminectomy syndrome is a common challenging condition encountered by physicians managing spinal disorders owing to the expanded indications for spinal surgery. Various factors can lead to post-laminectomy syndrome: preoperative factors include smoking, obesity, and depression, while postoperative factors include new-onset foraminal stenosis, recurrent disc herniation, muscular atrophy, muscle spasm, and degenerative changes to the postopera-

tive spine [9].

A multidisciplinary approach is recommended for post-laminectomy syndrome patients. For pharmacological therapy, paracetamol and nonsteroidal anti-inflammatory drugs are recommended for axial back pain [10]. Anticonvulsant drugs such as gabapentin and pregabalin can effectively alleviate neuropathic pain. Gabapentin is superior to naproxen at managing back pain [11]. The use of opioids in post-laminectomy syndrome is quite controversial; in fact, it is currently recommended only for short-term therapy [12]. In neuromodulation therapy, the spinal cord stimulator is the most effective treatment for neuropathic limb pain. Kumar reported that 48% of the spinal cord stimulator group versus 9% of the conventional medical management group achieved at least a 50% reduction in pain score [3].

The IT drug delivery system was first released for cancer chemotherapy in 1988 by Medtronic. The indications for the device were expanded to cancer- and non-cancer-related pain in 1991 [13]. The system consists of an implantable drug storage device and an IT catheter. The drug delivery mode can be programmed by an external device positioned over the implanted pump. The American Society of Interventional Pain Physicians recommends reserving the IT drug delivery system as the last management tool. The IT drug delivery system can reportedly be used for various chronic pain conditions such as post-laminectomy syndrome, compression fracture, spinal stenosis, complex regional pain syndrome, rheumatoid arthritis, connective tissue disorders, and chronic pancreatitis [13]. The device's analgesic response outcomes were reportedly quite favorable (up to 73%) [14].

Various IT drug delivery systems feature complications such as bleeding, infection, catheter malfunction, neurologic injury, cerebral spinal fluid leakage, inflammatory mass, and central hypocortisolism [15]. In the present case, the patient's neuropathic pain could not be controlled with regular pain medications. A spinal cord stimulator was also unable to control her symptoms. High-dose opioids was the only modality that provided short-term pain relief.

Paradoxical hyperalgesia was observed in the absence of a careful dosing strategy in the present case. The general protocol is to taper 50-100% of the previous opioid dosage for several weeks prior to the trial and completely wean opioid medications at least 1 week before implantation [2,8].

However, our patient refused a reduction in the dose of oral opioid medication for IT morphine pump implantation. The increase in opioid dosage using the IT morphine pump might have led to the paradoxical OIH.

In IT morphine pump-implanted patients, clinical conditions related to IT opioid infusion are complicated and difficult to treat. When exacerbation of neuropathic pain is observed in a patient taking high-dose opioids, it is necessary to distinguish among various etiologies such as opioid withdrawal, toxicity, tolerance, and hyperalgesia. Opioid withdrawal resulting from the sudden cessation of opioid infusion can be confirmed with pump testing using contrast dye. It is usually accompanied by other symptoms such as nausea, vomiting, or an altered sense of smell [16]. The presence of myoclonus and rigor after each bolus shot from the IT morphine pump could suggest opioid central toxicity [16]. Exposure to opioids can lead to increased doses over time to maintain an analgesic effect, known as tolerance. Tolerance reflects the desensitization of antinociceptive pathways to opioids. However, OIH reflects a sensitization of the pronociceptive pathways [17]. OIH can be observed in IT morphine pump-implanted patients [16]. Opioid tolerance-related pain could be reduced by increasing the opioid dosage. OIH can be confirmed when exacerbated pain can be alleviated by a dosage reduction or opioid antagonist application. However, distinguishing between opioid tolerance and OIH in clinical practice can be challenging.

In the present case, it was unclear if the cause of the OIH was the oral or IT opioid. It might be reasonable to deduce that additional IT morphine might enhance the sensitization of the pronociceptive pathways to opioids. The mechanisms responsible for the development of OIH are complex and not completely understood. N-methyl-D-aspartate receptors, μ -receptors, and genetic factors are proposed mechanisms [18-20].

The clinical suspicion of OIH is the most crucial part of the diagnosis. In OIH, as a response to escalating opioid doses, the pain score does not improve; rather, it is exacerbated. However, there is no confirmative test for the diagnosis of OIH. Elon suggested clinical criteria for diagnosing OIH [21]. He claimed that the following six criteria must be fulfilled for the diagnosis of OIH: increased pain intensity during opioid medication, no evidence of other disease progression, no evidence of opioid withdrawal, no evidence

of opioid tolerance, no evidence of drug addiction, and a decrease in pain intensity in response to an opioid dose reduction.

Our patient met the above criteria. The exacerbation of her pain was relieved after the opioid dose reduction. Opioid withdrawal, tolerance, and progression of other diseases are other possible causes. She had no opioid withdrawal symptoms such as anxiety, excessive sweating, or lacrimation.

Using multimodal analgesia with non-opioid analgesics combined with an appropriate nerve block and psychosocial techniques can reduce the need for opioids and lower the risk of OIH [18]. Opioid rotation (conversion to other opioids) could also facilitate the management of OIH. A change of IT morphine to sufentanil or ziconotide was reportedly effective at relieving OIH [16,22].

Once the diagnosis of OIH is strongly suspected, patient education and a cautious dose reduction of opioid medications are initial measures. Ketamine infusion therapy is an additional option for OIH [18,19].

In conclusion, a careful oral opioid reduction is essential in cases of IT morphine pump implantation in which sudden exacerbation of the pain score is observed in patients taking high doses of opioid. OIH should be suspected; once diagnosed, it can be managed with opioid reduction, opioid conversion, and ketamine infusion therapy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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