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The Promising Roles of Intrathecal Magnesium Injection: A Report on Three Cases

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Abstract

Patients with neuropathic pain, such as postherpetic neuralgia, complex regional pain syndrome, failed back surgery syndrome, and phantom limb pain rarely respond to traditional treatments and are more likely to develop chronic refractory pain. Even these patients do not respond to invasive treatment using implantable devices such as spinal cord stimulator and intrathecal morphine pump. This occurs because of central sensitization that involves the N-Methyl-D-Aspartate (NMDA) receptors. The NMDA receptor antagonists are known to be effective in neuropathic pain. And magnesium, a physiological blocker of NMDA receptors, is widely used to treat various chronic pain disorders. Here, we present three cases of the chronic refractory pain patients who were treated successfully with intrathecal magnesium injection.

Introduction

Magnesium is used to treat a variety of diseases, such as preeclampsia, acute asthma, and tachyarrhythmia. In the field of anesthesiology and pain medicine, magnesium has been mainly used to potentiate analgesia and control perioperative pain.

Magnesium is administered via a variety of routes. Jerkovic et al. [1] reports that the oral magnesium administration could be used to reduce postoperative pain intensity. Magnesium also potentiated the effects of intravenous regional anesthesia (Bier block) when combined with local anesthetics [2]. Ever since Haubold and Meltzer [3] first used intrathecal magnesium in humans in 1906, it has also been widely studied as an adjuvant to potentiate spinal anesthesia and to reduce postoperative pain and analgesic requirements [2,4]. Although various drugs, such as epinephrine, clonidine, ketamine, and neostigmine have been added to intrathecal local anesthetics [5], these have been associated with undesirable side effects, including delayed respiratory depression, urinary retention, pruritus, hemodynamic instability, nausea and vomiting [2]. However, intrathecal magnesium is safer and reduces the risk of secondary hyperalgesia and the development of postoperative chronic pain syndromes [6,7].

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Recently, magnesium has been suggested as an alternative treatment option for such neuropathic pain as Post Herpetic Neuralgia (PHN), Complex Regional Pain Syndrome (CRPS), Failed Back Surgery Syndrome (FBSS), and phantom limb pain [2]. When magnesium is administered to patients with neuropathic low back pain, pain intensity is reduced and lumbar spine range of motion improves [8]. Magnesium attenuates preexisting pain hypersensitivity caused by peripheral nociceptive stimuli and prevents central sensitization in two ways. First, magnesium is a Noncompetitive N-Methyl-D-Aspartate (NMDA) receptor antagonist. The NMDA receptor plays an important role in the mechanisms underlying central sensitization (wind-up) and expansion of receptive fields in the spinal cord [9,10]. Second, magnesium inhibits voltage-gated calcium channels, which are reported to be therapeutic targets in neuropathic pain conditions [2,11]. Magnesium for neuropathic pain control has been used, usually via the intravenous route [2]. However, studies in rats have shown that intrathecal magnesium suppresses nociceptive impulses in a neuropathic pain setting, potentiates opioid antinociception, and delay the development of opioid tolerance [12].

Here, we report that intrathecal magnesium injection may be an alternative therapeutic option based on the cases of three chronic neuropathic pain patients who had failed conventional therapy.

Case report

Case 1: CRPS, type 1, 36/F

The patient visited the pain clinic for chronic refractory pain in her entire body that occurred following two back surgeries resulting from three traffic accidents during a six-month period. The patient's pain was higher than Numerical Rating Scale (NRS) 7, and she complained of knife-like and burning pain over her entire body. There were many restrictions on the use of the patient's pain medications (pregabalin, gabapentin, amitriptyline, duloxetine, carbamazepine, nefopam, celecoxib, tramadol, buprenorphine, tapentadol) because of severe side effects and hypersensitivity. Although the patient's pain was effectively controlled with an epidural injection and sympathetic ganglion block, relief lasted less than one day.

Despite repeated treatment for over six months, the analgesic dose was greater than 400 mg when converted to an equivalent oral morphine dose, and the patient was started on an Intrathecal Morphine Pump (ITP). However, the patient had opioid-induced hyperalgesia on a daily dose greater than 2 mg. Therefore, the pain was not properly controlled. For additional pain control, we tried her on a Spinal Cord Stimulator (SCS), and the patient wanted to have stimulators inserted into both the upper and lower extremities. So, we inserted a total of four leads. The patient was satisfied with this pain control. But when using the SCS, the heat generated by its generator of SCS caused severe pain. There was no problem with the generator, but the patient continuously complained that it caused her pain. Thus, she had to use it intermittently. Despite numerous treatments, the patient's pain (NRS 8-10) was not controlled, and the patient said that even the force of gravity cost pain. Afterwards, ketamine and lidocaine intravenous therapy were intermittently administered during outpatient visits, but the patient wanted additional pain control since the injection was effective only briefly.

Meanwhile, we noted that magnesium had been used for spinal anesthesia to control postoperative pain. The patient had 50 mg of magnesium sulfate injected into the intrathecal space with her consent, although previous 1 g intravenous injections of magnesium had been less effective. Under C-arm guidance, we administered magnesium at the L3-L4 level, avoiding L4-L5 and L5-S1 levels, which had been the previous surgical sites. After about one hour of observation, there were no side effects.

On the next outpatient visit, the patient said that the intrathecal magnesium injections were mainly helpful for reducing pain in the lower extremities. She felt that these injections were effective because they made her hands and feet feel like they were coated (NRS decreased by 3 points). This intrathecal magnesium injection lasted about two to three days longer than other nerve blocks had, and the patient was satisfied enough that she requested continuous magnesium ITP infusion.

Thereafter, we administered intrathecal magnesium four times during a single month and observed no side effects.

Case 2: FBSS, 59/F

This is a patient who had undergone a posterior lumbar spinal fusion surgery at the L4-L5 level for radiating lower back pain in the lower legs following a traffic accident. Even after the operation, the pain persisted in the area. She complained of pain with an NRS of 10 throughout her body. The patient said that her head, hands and feet were cold, and that she felt like she had been hit by a hammer.

Medications had little effect on pain reduction. Epidural injection and sympathetic ganglion blocks were administered. But the effect was insignificant (NRS decreased by 1 to 2 points) and only lasted about two to three days. The patient wanted additional pain control, and after explaining the intrathecal magnesium injection, we administered it with the patient's consent.

We injected 50 mg of magnesium sulfate intrathecally into the L5-S1 spinal level under C-arm guidance. After about 30 minutes of observation, we noted no side effects. The patient had received no benefits from previous 1 g magnesium intravenous injections. Following intrathecal magnesium injections, the patient's upper extremity pain had not been helped much. However, the lower extremity pain that felt like her legs had been hit with a hammer disappeared, and the overall condition of the body improved for about two weeks.

Afterwards, one more injection was administered. No side effects or neurological abnormalities were observed.

Case 3: CRPS, type 1, 46/M

A patient with CRPS in the right foot complained of persistent pain even after the SCS had been inserted. Based on the treatment experience of the above two patients, we intrathecally injected 50 mg of magnesium sulfate with the consent of the patient and administered an additional right lumbar sympathetic ganglion block. There were no side effects following 30 minutes of observation. The patient preferred the feeling of more heat to the feeling of a typical lumbar sympathetic ganglion block. However, there was no difference in NSR compared to the previous same procedure.

Four hours after returning home, a member of the patient's family called and said that the patient was complaining of dizziness. We requested that they closely monitor the patient's symptoms. We called the patient 30 minutes later, and the

patient complained of increasing dizziness, difficulty focusing when walking, blurred vision, and slurred speech. We explained that outpatient-visiting hours were over and advised the patient to go to the emergency room of our hospital. We began to evaluate the cause of the patient's symptoms and eventually found that the patient had been given 500 mg of magnesium intrathecally. This happened because the nurse mistook the amount of magnesium in the preparation of drugs.

The patient was admitted to the emergency room, and we performed a blood test under suspicion of hypermagnesemia with the immediate injection of hydration and 1 g of calcium gluconate. After one hour, the neurological symptoms had improved, but the symptoms did not completely disappear. So, we gave an additional 1 g of calcium gluconate. After two hours, the patient's symptoms had completely resolved, and normal blood magnesium (0.51 mmol/L, 0.45 to 0.70) and calcium (4.84 mg/dL, 4.20 to 5.40) levels were observed. The patient was discharged four hours after the emergency room visit.

The next day, we called to follow up on the patient's symptoms, and the patient told us that there were no specific findings or side effects. No side effects or neurological abnormalities were observed after three months.

Discussion

This report presents two cases of promising treatment outcome after intrathecal magnesium injection in chronic pain patients. In addition, the safety of intrathecal magnesium injection was experienced through one case of magnesium overdose. Patients with neuropathic pain, such as PHN, CRPS, FBSS, and phantom limb pain, are often seen in pain centers. However, such patients rarely respond to traditional treatments and are more likely to develop chronic refractory pain. These patients do not respond to invasive treatment using implantable devices such as SCS and ITP. This presents pain physicians with a very difficult problem. We aim to report on the potential of intrathecal injections as a treatment option for these patients.

Chronic refractory pain refers to chronic pain that does not respond to conventional treatment [13]. This occurs because of central sensitization that involves the NMDA receptors. Stimulation of peripheral nociceptors induces the release of such neuropeptides as glutamate and aspartate in the dorsal horn of the spinal cord [7]. Glutamate is the main excitatory neurotransmitter in the autonomic nervous system of most mammals. The NMDA receptor, one of the glutamate receptors, plays critical physiological roles in synaptic function, including synaptic plasticity, learning, and memory [14]. Activation of NMDA receptors leads to calcium and sodium influx into the cells with an efflux of potassium. This has been demonstrated to be essential for inducing and maintaining central sensitization and wind-up [9]. The NMDA receptor channel complex contains binding sites for noncompetitive antagonists such as magnesium and ketamine. They abolish hypersensitization by blocking NDMA receptor activation in the dorsal horn by excitatory amino acid transmitters. Ketamine has been found to be more effective than magnesium [10]. However, the adverse effects associated with ketamine infusions, such as sedation, dizziness, psychomimetic side effects, and visual distortions, have limited its widespread clinical use [10]. Magnesium blocks NMDA receptors in a voltage-dependent manner [11]. It prevents and reverses the hyperexcitability of neurons produced by nociceptive afferent inputs [9]. Although in some studies, the administration of magnesium did not demonstrate any direct analgesic benefits or pain reduction, it inhibits calcium ions from entering cells by blocking NMDA receptors, resulting in an analgesic effect [2,15]. Properties of magnesium's natural calcium antagonists are useful in the treatment of chronic neuropathic pain conditions by targeting the calcium channels [2,11]. In animals, calcium channel blockers have demonstrated antinociceptive effects [16].

Although intravenous magnesium's antinociceptive effects are controversial [2], a recent study has shown that intravenous magnesium is as effective as intravenous ketamine in patients with PHN [17]. Thirty patients with severe refractory PHN who did not respond to conservative treatment were enrolled. The effects of ketamine 1 mg/kg and magnesium 30 mg/kg were investigated. After two weeks, the differences in Visual Analog Scale (VAS) reduction were not significant between the groups.

Epidural injection of magnesium reduced the pain intensity of PHN patients. Although this was a case report, 100 mg of magnesium were administered via a left T3 transforaminal route. The VAS was 10/100 throughout the first month of follow-up, and pregabalin had also been tapered [18]. And adding 200 mg of magnesium to a local anesthetic and steroid to be injected in the transforaminal epidural space also improved the pain and the quality of life in patients suffering from lower limb radicular pain due to lumbosacral disc herniation. This improvement could last for up to three months [19]. In our case, patients were injected via the intrathecal route rather than another route because intravenous injection had been ineffective, and they had a history of lumbar surgery, an SCS, or an ITP device inserted.

Although magnesium is a useful NMDA antagonist, it has limited ability to cross the blood-brain barrier (BBB). Even high doses of intravenous magnesium, such as those used in preeclampsia, undergo minimal transfer across the BBB [20]. Unlugenc et al. [5] reported that the addition of magnesium (50 mg) to 10 mg of spinal bupivacaine (0.5%) did not shorten the onset time of sensory and motor blockade or prolong the duration of spinal anesthesia, as can be seen in patients with fentanyl undergoing cesarean section with spinal anesthesia. This suggests that magnesium acted only at the spinal level. An animal study has shown that the poor passage of intrathecally administered magnesium through the BBB indicates that it remains in the cerebrospinal fluid for a considerable time before entering the blood stream [21]. This may explain why intrathecally injected magnesium does not diffuse to supraspinal levels. Similarly, two patients in our case said intrathecal magnesium injection was mainly effective in reducing pain in the lower extremities. However, in our study, one patient said it also was effective for the hands, and the other said it was helpful for the entire body even if 1 mL of magnesium had been injected at the lumbar spinal level. Therefore, the administration of intrathecal magnesium appears to be an attractive option. This also obviates the problems of systemic administration such as respiratory paralysis, hypothermia, and coma, and it solves the problem of transport of the agent across the BBB [22].

There have been several studies on the safety of intrathecal magnesium injections [22]. These have shown no neurological injury associated with magnesium administration. The theoretical toxic dose in a dog study was calculated to be around 60 mg, which is the equivalent to over 500 mg in humans. There have been three cases of accidental magnesium injection in human parturients [22]. One was an epidural injection and two were subarachnoid injections. Up to 1000 mg were injected intrathecally, but there were no neurologic sequelae. In our case, 500

mg was given intrathecally. Although this could have had serious side effects, fortunately it decreased soon after treatments without sequelae.

According to our case report, the objective effect of pain treatment is not very good. However, it can be said that one positive finding is that intrathecal magnesium injections are helpful in relieving severe pain despite having undergone surgery, SCS, or ITP. Intrathecal magnesium injections are also expected to have a greater effect if they are administered before the patient's pain becomes chronic and refractory.

Since this study has limitations as a case study and further investigations are required to determine the efficacy of intrathecal magnesium injection in the management of chronic refractory patients.

Conclusion

Intrathecal magnesium injection may be an effective and safe alternative treatment option for pain control in patients with chronic refractory pain. If the patient's pain becomes chronic and progresses to an undesirable pathway, this should be actively considered.

Competing interests

The authors declare that they have no competing interests.

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