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Publication Date

2016

DOI

10.2147/jpr.s110261

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Reduction of central neuropathic pain with ketamine infusion in a patient with Ehlers–Danlos syndrome: a case report

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Objective: Ehlers–Danlos syndrome frequently causes acute and chronic pain because of joint subluxations and dislocations secondary to hypermobility. Current treatments for pain related to Ehlers–Danlos syndrome and central pain syndrome are inadequate. This case report discusses the therapeutic use of ketamine intravenous infusion as an alternative.

Case report: A 27-year-old Caucasian female with a history of Ehlers–Danlos syndrome and spinal cord ischemic myelopathy resulting in central pain syndrome, presented with severe generalized body pain refractory to multiple pharmacological interventions. After a 7-day course of ketamine intravenous infusion under controlled generalized sedation in the intensive care unit, the patient reported a dramatic reduction in pain levels from 7–8 out of 10 to 0–3 out of 10 on a numeric rating scale and had a significant functional improvement. The patient tolerated a reduction in her pain medication regimen, which originally included opioids, gabapentin, pregabalin, tricyclic antidepressants, and nonsteroidal anti-inflammatory drugs.

Conclusion: Ketamine infusion treatment has been used in various pain syndromes, including central neuropathic pain, ischemic pain, and regional pain syndrome. Reports have suggested that ketamine modulates pain by the regression of N-methyl-D-aspartate receptor to a resting state. As such, propagation of nociceptive signal to brain is interrupted allowing for the restoration of physiological balance between pain inhibition and facilitation. The present report shows that this treatment option can be used in patients with refractory central pain syndrome in the setting of spinal cord myelopathy secondary to Ehlers–Danlos syndrome. In addition, as seen in this case, this protocol can potentially decrease the chronic use of pain medication, such as opioids.

Keywords: central neuropathic pain, connective tissue disorders, central pain syndrome, analgesia

Introduction

Ehlers–Danlos syndrome (EDS) is a clinically heterogeneous group of disease that affects one in 5,000 births and is characterized by fragility of soft connective tissues of skin, ligaments, joints, blood vessels, and internal organs.¹ EDS is categorized by clinical and genetic presentations via Villefranche classifications into six subtypes.¹ The most common type of EDS is hypermobility subtype (EDS-HT), which manifests as subluxation and dislocation in the extremities, vertebral columns, costovertebral and costosternal joints, clavicular articulations, and temporomandibular joints.¹ Due to the increasing risk of subluxation and dislocation, acute pain is usually present; however, chronic pain is also a common complication that can significantly impact function, affecting sleep and physical activities.²

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Chronic pain in EDS can be generalized as nociceptive or neuropathic pain. Nociceptive pain is related to soft tissue and joint injuries, which develops from the ongoing stimulation of nociceptors. In other cases, pain is neuropathic and may manifest in a radicular or peripheral nerve pattern, which is likely to be caused by ligament laxity resulting in pressure effects.³ Chronic pain often develops from prolonged nociceptive stimulation resulting in the activation and upregulation of N-methyl-D-aspartate (NMDA) receptor at dorsal horn synapses, which leads to increased pain signals to the brain.⁴ Pain associated with EDS-HT is generally complex in its etiology and can be refractory to various pharmacological and physical interventions.⁵

Physical and pharmacological treatments for EDS-HT pain ranges widely from conservative to invasive measures. Physical therapy involving myofascial release provides short-term relief and includes modalities such as ice packs, heat application, massage, ultrasound, biofeedback, phonophoresis, and electrical stimulation. Assistive devices are also utilized to help with joint stability, and mobility devices may offload the pressure on lower extremity joints.⁶ Medications that contribute to a large aspect of pain management include nonsteroidal anti-inflammatory drugs, muscle relaxants, tricyclic antidepressants, serotonin/norepinephrine receptor inhibitors, antiepileptics, steroids, and opioids.⁵ Patients also undergo surgical procedures such as joint debridement, tendon relocations, arthroplasty, and capsulorrhaphy.⁷ The array of treatment options illustrates the complexity of EDS pathophysiology and the clinical challenge of pain control. In this case report, the therapeutic use of ketamine infusion in an EDS patient with a spinal cord myelopathy that led to refractory central pain syndrome is documented.

Case presentation

Permission was obtained from the patient to use her information for publication of this case report. A 27-year-old Caucasian female with a history of EDS resulting in an incomplete L1 ischemic myelopathy with paraplegia and subsequent visceral neuropathy and central pain syndrome presented with severe generalized chronic body pain, primarily in bilateral lower extremities. The pain was distributed 60% and 40% to her lower extremities and spine, respectively. It was rated 7–8 out of 10 on the universal numeric rating scale and was described as aching, burning, and throbbing that worsened with movement. Her muscle strength of the bilateral lower extremities was 0 out of 5 limited by pain. Her home medications included ketamine 40 mg orally three times a day, pregabalin 150 mg in the morning and 450 mg at night,

tizanidine 2 mg every 8 hours, baclofen 15 mg three times a day, duloxetine 60 mg twice a day, extended-release morphine 230 mg in the morning and 260 mg at night, and morphine 30 mg every 4 hours as needed for pain. She had previously trialed and failed multiple pharmacologic interventions, including gabapentin, tricyclic antidepressants (amitriptyline and nortriptyline), nonsteroidal anti-inflammatory drugs, and other opioids. Due to her unsatisfied pain control regimen and desire for better relief, a 7-day continuous ketamine intravenous (IV) infusion under controlled generalized sedation was offered to her in the intensive care unit to modulate her central pain.

The patient with a body weight of 106.6 kg began infusion with fentanyl 0.25 mcg/kg/h to prevent opioid withdrawal and midazolam 90 mcg/kg/h and propofol 20 mcg/kg/min for sedation. The infusions were titrated to a Richmond Agitation and Sedation Score of –4, after which ketamine infusion was started at 0.3 mg/kg/h. Within 24 hours, ketamine was rapidly titrated up by 0.3 mg/kg/h every hour until the goal of 2 mg/kg/h was reached. The infusion dose was maintained until day 7 when the patient reached her goal of <4 out of 10 in pain severity. Then, ketamine was titrated down at a rate of 0.5 mg/kg/h every 4 hours until 0.5 mg/kg/h was reached. She was then weaned off over the next 4 days until she was transitioned to oral ketamine 30 mg every 8 hours. Fentanyl, midazolam, and propofol were stopped several hours after ketamine treatment.

These infusions were given by a pump and were controlled separately. Fentanyl, midazolam, and propofol were adjusted to maintain Richmond Agitation and Sedation Score at –4, except when the patient was intermittently awakened to assess the pain level. The awakening was performed by standard sedation holiday protocol during which fentanyl, midazolam, and propofol infusions were held. The patient was allowed to wake up for an hour, after which infusions were restarted and titrated back up.

During the infusions, she remained on oral medications given through a nasogastric tube: baclofen 10 mg three times a day, pregabalin 150 mg in the morning and 450 mg at night, tizanidine 2 mg every 8 hours, and venlafaxine 37.5 mg twice a day. Her other home medications were held. She received nutrition and fluids through nasogastric tube and intravenously. Renal function was assessed daily through chemistry panel and nursing monitoring of urine output.

When the patient woke up following the completion of her ketamine IV infusion treatment, she reported a dramatic pain improvement with an average score of 3 out of 10 on the numeric rating scale. Reexamination on the same day

revealed the muscle strength of 1 out of 5 in bilateral hip flexors, 3 out of 5 in knee extensors, 1 out of 5 in dorsiflexion, 1 out of 5 in extensor hallucis longus, and 3 out of 5 in plantar flexion. She was able to get out of her wheelchair for the first time in years. The patient's renal function remained normal throughout the hospital stay, and she did not demonstrate any signs of opioid-induced neurotoxicity, such as myoclonus.

Some of the patient's pain medications were retitrated up after the sedation and ketamine treatment were stopped. The medications were chosen on the basis of the patient's as needed use. Overall, she also had a significant decrease in the amount of her pain medications including opioids. Her regimen included pregabalin 150 mg in the evening and 450 mg at bedtime, venlafaxine 37.5 mg extended release once a day, baclofen 10 mg three times a day, fentanyl patch 37 mcg every 72 hours, hydromorphone 8 mg every 4 hours as needed for pain, and ketamine 100 mg IV infusion twice a week. The basis of the follow-up ketamine infusion was determined by how long the effect lasted and when the pain began to return. At the time of discharge, her pain remained 0–4 out of 10. On follow-up at 6 months after discharge, the patient reported improvement in her mentation and her pain remained stable on the same regimen.

Discussion

EDS can result in compression myelopathies of the spinal cord through various mechanisms. Connective tissue disorders are commonly seen in patients with spontaneous cerebrospinal fluid leak in the cervical and thoracic regions, which may result in injury with upper extremity paresthesias.⁸ Additionally, EDS can cause hypermobility of spinal joints, resulting in subluxations and dislocations, scoliosis and kyphotic changes, and pannus formation that may invade and compress the spinal canal.⁹ Spinal cord injuries (SCIs) can significantly obscure nociceptive and neuropathic pain in EDS.

One of the complications of SCI is central pain syndrome, which occurs in ~40% of patients.¹⁰ It manifests as spontaneous pain characterized by severe hyperalgesia and allodynia. The underlying mechanism is poorly understood; however, the proposed features include deafferentation with the formation of neuronal hyperexcitability and imbalance of stimuli and central sensitization.¹¹ Pharmacological management of central pain syndrome is challenging as noted by the limitation and ineffectiveness of present therapies.¹¹

In this case study, our patient trialed an array of pain medications but failed to find adequate pain relief. This failure is commonly seen as most EDS patients undergo multidrug

pain regimens for the management of pain that hinders the daily activities.⁵ More invasive therapies such as surgery involving the extremities and abdomen have been reported to be favorable in only a third of patients and often yield limited results associated with increased complications.⁵ A survey of 44 patients with a total of 214 procedures for pain and symptom instability demonstrated overall pain relief in 50% of cases, shoulder stabilization in 47%, and knee stabilization in 54%.¹² However, complications were reported in 11% and 6% of cases for wound-healing problems and postoperative infections, respectively.¹² Another study involving total knee replacements illustrated a 70% satisfaction rate in EDS patients compared with 90% in those without EDS.¹³ These shortcomings in treatment portray the need for novel effective conservative means to adequately control pain in patients with EDS-HT.

Ketamine, a noncompetitive NMDA receptor antagonist, is primarily used for the induction and maintenance of general anesthesia, usually in combination with other sedatives. It has also been used in the management of central neuropathic pain, ischemic pain, and complex regional pain syndrome.¹⁴ IV ketamine produces a predictable peak concentration and clinical effects within 1 minute of administration and is rapidly distributed into the peripheral tissues, with return of coherence in 15 minutes.^{15,16} It has a relatively short alpha (2–4 minutes) and beta (2–4 hours) half-life and a systemic clearance equal to that of liver blood flow (60–147 L/h/70 kg), thus resulting in low bioavailability of oral ketamine.¹⁷ Additionally, IV ketamine infusion surpasses oral ketamine treatment regimens because only 8%–24% of oral ketamine reaches the systemic circulation.¹⁷ Therefore, a 2.4 times larger dose of oral ketamine is required to generate an equivocal area under the plasma drug concentration–time curve of that by IV ketamine.¹⁷ The IV route is also preferred for lengthy procedures as it allows for convenient repeated dosing.

Previous randomized controlled trials on the effects of ketamine have shown much longer effects with prolonged treatment. Patients with fibromyalgia treated with ketamine over 30 minutes had analgesia for no more than 45 minutes.¹⁸ In contrast, Complex Regional Pain Syndrome Type 1 patients treated for 100 hours in one study and for 10 days with daily 4-hour infusions in another study experienced long-term pain relief up to 3 months.^{19,20} These reports suggest that long-term infusions are needed to sustain analgesia after the completion of treatment. The effects are believed to be a result of long-term NMDA receptor desensitization in the central nervous system.¹⁹

Although the exact mechanism of pain relief following ketamine treatment is unclear, one proposed hypothesis implicates the regression of the NMDA receptor to resting state.²¹ By regression of the NMDA receptor to this stage, the nociceptive signal propagation to the brain is subsequently impaired allowing for the restoration of the physiological balance between pain inhibition and facilitation.²¹ A study of nine patients with central dysesthesia pain after SCI presented with the reduction in both continuous and evoked pain following ketamine infusion, suggesting the relation between central NMDA receptor activation and central dysesthesia pain after SCI.²²

Ketamine infusion protocols should be reserved for pain refractory to other therapies given the risks associated with ketamine use. Adverse effects of ketamine include hallucinations, memory defects, somnolence, dizziness, agitation, nausea/vomiting, cardiovascular stimulation, and hepatotoxicity.⁴ Midazolam and fentanyl are often given in conjunction with ketamine to counteract some of these effects: midazolam reduces agitation and fentanyl decreases psychometric and nausea effects.^{23,24}

Of note, opioid-induced hyperalgesia can occur in patients on high-dose opioids and includes symptoms such as allodynia, mental status changes, and myoclonus. This was initially believed to be a possible cause of the patient's pain with subsequent relief after rotation of opioids. However, opioid-induced hyperalgesia is unlikely given that the patient's renal function remained normal and she did not demonstrate any signs of neurotoxicity related to opioids.

Conclusion

Ketamine is an NMDA receptor antagonist with efficacy in central neuropathic pain, ischemic pain, and regional pain syndrome. Central pain syndrome can cause significant disability and impaired quality of life. It occurs in patients with central nervous system pathologies such as SCI, stroke, and brain injury and is known to be difficult to treat with the standard treatment options. By preventing the upregulation of the NMDA receptor, ketamine provides a new approach toward the management of pain in patients with central pain syndrome related to SCI. This case is the first known report of using ketamine infusion to alleviate refractory central pain syndrome in a patient with a spinal cord myelopathy secondary to EDS. Ketamine infusion also has the potential to decrease the long-term need for other pain medications including opioids. More research is needed to establish an evidence-based treatment for pain related to EDS.

Disclosure

The authors report no conflicts of interest in this work.

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