

Topical Ketamine Gel: Possible Role in Treating Neuropathic Pain

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ABSTRACT

Neuropathic pain is often resistant to opioids, so other medication classes, such as tricyclic antidepressants, anticonvulsants, and local anesthetics, are often used. Central sensitization, or pain 'wind-up', may perpetuate chronic neuropathic pain even when ongoing peripheral sensory input is absent. Wind-up is thought to cause allodynia, hyperalgesia, and hyperpathia. Receptors such as NMDA, AMPA, and M-glu have recently been identified for their role in central sensitization or pain 'wind-up'. Ketamine has been proposed recently for neuropathic pain secondary to its NMDA receptor activity. The current application as a topical gel stems from the theory that ketamine has peripheral action at both opioid and Na⁺-K⁺ channels. This case study involved 5 patients from 25 to 70 years old (3 RSD, 1 lumbar radiculopathy, 1 post-herpetic neuralgia). Dose used was determined by site and surface area of involvement and ranged from 0.093 mg/kg to 9.33 mg/kg. All five patients reported significant pain relief at initial application and wished to continue treatment. The average numerical analogue scale (NAS) score preapplication was 8.8. The average 15 minutes post application NAS was 1.6. Patients reported alterations in temperature sensation, feelings of relaxation and decreased tension in the area of application, and pain relief. Reduction in numerical pain scores postapplication of ketamine gel ranged from 53-100% using a 1-10 numerical pain intensity scale. No significant side effects were reported. Ketamine Gel may provide clinicians with a new option in the battle against chronic neuropathic pain. Until further information is available and larger trials can be conducted, we can only recommend this type of therapy for refractory cases in which all primary and secondary options have been exhausted.

Neuropathic pain, which is caused by nerve injury or disease leading to abnormal nerve function, can be complex and challenging to treat [1]. Because this type of pain is often resistant to conventional analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, clinicians are required to use adjuvants such as tricyclic antidepressants, anticonvulsants, local anesthetics, and corticosteroids [2,3].

In the last decade, our understanding of the underlying pathophysiology of neuropathic pain has grown dramatically. Central sensitization, or pain "wind-up," is believed to perpetuate chronic neuropathic pain even in the absence of ongoing peripheral sensory input. Wind-up causes allodynia (pain

provoked by a normally non-painful stimulus), hyperalgesia (exaggerated response to pain), and hyperpathia (exaggerated response to a repeated stimulus) [4]. Receptors such as N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and M-glutamate (M-glu) have recently been identified as playing a large role in central sensitization or pain wind-up [5-7]. The amino acids glutamate and aspartate are released in response to noxious stimuli and then bind to NMDA receptors in the dorsal horn of the spinal cord. This interaction is believed to be one of the key steps in the development of pain wind-up [8,9]. Ketamine, an injectable anesthetic, has been studied for its potential role in neuropathic pain syndrome relief [6,9-11]. The proposed mechanism may involve ketamine's noncompetitive inhibition of NMDA receptors.

Despite its potential beneficial effects for neuropathic pain, numerous side effects are reported with

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the use of injectable ketamine, including dissociative reactions, hallucinations, sensation distortion, muteness, sedation, nausea, and vomiting. It is also impractical and invasive for use with ambulatory patients experiencing chronic neuropathic pain.

In 1988, Crowley et al. [11] published a pilot study describing the use of a topical form of ketamine to treat significant allodynia and hyperalgesia associated with chronic neuropathic pain states. The study involved 5 patients ranging from 25 to 70 years of age. All had experienced some trauma that led to their neuropathy. The dose used was determined by site and surface area of involvement and ranged from 0.093 mg/kg to 9.33 mg/kg. All 5 patients reported significant relief of pain and wished to continue the therapy. The average numerical analogue scale (NAS) score preapplication was 8.8. The average 15 minutes postapplication was reported as 1.6. The authors proposed that part of the effect of topical ketamine might lie in interruption of afferent transmission via interactions with local Na⁺-K⁺ channels that may reduce centrally mediated hyperexcitability. They concluded that the positive results obtained in these 5 patients warrant further large-scale, double-blind investigation to determine pharmacokinetics, bioavailability, and more accurate and reproducible outcome measures.

In an effort to reproduce the results by Crowley et al., we conducted the following open clinical case trial. Because of the minimal dosing data available, therapy was initiated in a low-dose range.

Case 1

DS is a 29-year-old female with a pain diagnosis of Reflex Sympathetic Dystrophy (RSD), brachial/cervical plexus injury, Trigeminal Neuralgia (TMJ), and traction headaches. History of Present Illness (HPI) is significant for injuries s/p Motor Vehicle Accident (MVA). Current medications included oxycodone (long- and short-acting), methadone, diazepam, phenytoin, and lamotrigine. On September 23, 1999 the patient was noted to have significant pain and tenderness from the occipital insertion of the trapezius through the periscapular area on the left and right side. A total of 2 ml (0.37mg/kg based on a weight of 54 kg) of ketamine gel (10mg/ml) was applied over the affected areas on the patient's left side. Lidocaine injection was used in the trigger points on the patient's right side.

Within 5 to 10 minutes postapplication, the patient described feelings of warmth and numbness in the area of ketamine application. The patient described the relief as "relaxation" to the region,

which spread down her left arm at about 10 minutes. At 15 to 20 minutes the patient's NAS was reduced from a preapplication report of 9 to 10 to 4. Although the trigger-point injection provided pinpoint relief, the patient felt that the ketamine gel provided relaxation over a broader area. The only side effects reported were slight light-headedness and sedation, which were not bothersome to the patient. She was sent home with instructions to apply 1 ml (10 mg) of ketamine gel to the affected area 3 times daily, and to return for follow-up in 1 week to determine if there was a continued positive response. Upon follow-up, the patient's dose was increased to 2 ml (20 mg) 3 times daily because of suboptimal response to the 10-mg dose. The patient has continued to receive good results with chronic use of the 20-mg dose.

Case 2

KL is a 27-year-old male diagnosed with right foot, ankle, and calf RSD pain. His current pain regimen consists of methadone, nefazodone, tizanidine, amitriptyline, citalopram, transdermal clonidine, gabapentin, and epidural fentanyl plus bupivacaine.

A 0.1-mg/kg dose of ketamine gel (10 mg/ml) was applied to the anterior and posterior sides of the right ankle. After 15 minutes the patient did not notice any difference in sensation and a repeat application of 10 mg of ketamine gel (0.1 mg/kg) was applied to the same area. Within 15 minutes of the second application (a total of 0.2 mg/kg from both applications) the patient described a numbing sensation with decreased tenderness in the region. Forty-five minutes after the second application, the patient noted increased flexibility with a sensation of warmth and numbness. Throughout the entire observation period the NAS level remained at 4 of 10.

Case 3

SG is a 30-year-old female diagnosed with postherpetic neuralgia. She complained of severe causalgia in left upper chest and breast area. Her pain regimen consists of oxycodone (long- and short-acting), gabapentin, and tizanidine. The patient has had problems tolerating Neurontin, which has prevented titration to a higher dose. A total of 20 mg of ketamine gel (10 mg/ml) was applied to the left chest and breast area. The patient's NAS before application was 8 with the presence of significant allodynia and hyperalgesia. Ten minutes postapplication, the patient described a warming sensation in the area of application. By 30 minutes postapplica-

Table 1 Responses of case studies

Patient case	Pain diagnosis	Ketamine dose (mg/kg)	NAS (preapplication)	NAS (postapplication)	Reduction in pain (%)
1	RSD	0.37	9–10	4	55–60
2	RSD	0.20	4	4	0
3	Postherpetic neuralgia	0.32	8	3	63
4	Post laminectomy syndrome, radiculopathy	0.24	8.5	0 (calf) 4 (back) 1–2 (hip)	100 53 76–88
5	RSD	0.13	8	8	0

NAS, numeral analogue scale; RSD, Reflex Sympathetic Dystrophy.

tion, a marked decrease in sensitivity to touch was noted and a NAS rating of 3 was obtained. The duration of relief postapplication was 2.5 hours.

Case 4

KWC is a 34-year-old female diagnosed with post laminectomy syndrome (lumbar region), radiculopathy (lumbar), and myofascial pain. Her current pain regimen consists of hydrocodone/acetaminophen, tramadol, diclofenac, nortriptyline, and gabapentin. She complained of severe low-back pain that had a stabbing-like quality. A total of 20 mg (0.24 mg/kg) of ketamine gel (10 mg/ml) was applied to the midline lumbo-sacral area, right calf, and right thigh/hip. The patient's NAS was rated as 8.5 in the calf, back, and hip before application. By 30 to 40 minutes postapplication, the patient described significant decrease in pain with an NAS rating of 0 in her calf, 4 in her back, and 1 to 2 in her hip.

Case 5

TG is a 39-year-old female diagnosed with RSD of the right arm. Her current pain regimen consists of transdermal fentanyl, clonazepam, and morphine. A total of 10 mg (0.13 mg/kg) of ketamine gel (10 mg/ml) was applied to the right wrist. After 30 minutes, the patient's pain status remained unchanged with an NAS rating of 8. The only sensation noted was a change in temperature or feeling of warmth in the area of application. The patient had to leave the clinic and was unable to try a higher dose.

Results

As shown in Table 1, there was a consistent pattern of response that emerged in all 5 cases. Patients first felt a temperature change, followed by a muscle relaxation and increased flexibility in the region of application, and finally pain relief. The range in

pain reduction for the patients in cases 1, 3, and 4 was 53% to 100%. All patients with the exception of the second patient had a level of pain rated as severe preapplication of the ketamine gel. Previous studies have identified a correlation between severity of pain and interference with quality of life. Based on this information and patient report, one could conclude that the treatment had a positive impact on quality of life for the patients in cases 1, 3, and 4 [12]. This may explain why the patient in case 2 did not perceive a reduction in pain, because it was already mild at the start of application. This patient did describe an increase in flexibility and relaxation in the region of application and therefore rated the response favorably. For the patient in case 5, there was no reduction in pain. The only response noted was a change in temperature in the region of application. Until further studies can be conducted to assess response, proper dosing range, dose-response relationship, it is not possible to fully determine if the lack of response was because of suboptimal dosing. This was the only patient in the group to receive <0.2 mg/kg.

Discussion

The use of ketamine as an adjuvant for neuropathic pain has been proposed in recent literature secondary to activity at NMDA receptors located in the central nervous system (CNS) [6,10,13,14]. These receptors are believed to play a key role in development of tolerance to opioid analgesics with chronic use and central sensitization or wind-up.

The current application as a topical gel stems from the theory that ketamine has peripheral action at both opioid and Na⁺-K⁺ channels [11]. We conducted this case trial to determine if results from the previous study by Crowley et al. [11] could be reproduced, thereby warranting larger randomized studies.

During our case trial, we observed what appears to be a dose-response relationship with the use of

ketamine gel. At lower doses (0.13 mg/kg) the patient described alterations in temperature sensation. As the dose was titrated upward (0.2 mg/kg), feelings of relaxation and decreased tension in the area of application were reported to follow the temperature change. At a dose of 0.37 mg/kg, feelings of pain relief followed those listed previously. In some patients the relief provided by ketamine spread over a larger area than that of the application.

Despite the small case trial size, we believe the positive results obtained were similar to those in the Crowley et al. study [11]. A larger randomized trial should be conducted to further identify potential benefit and the role topical application of ketamine may have in the treatment of chronic neuropathic pain. The only side effect noted during our study was slight sedation at the 0.37-mg/kg dose. The patient reporting this side effect was also receiving high-dose opioid analgesics and, therefore, it is impossible to tell if this was a side effect of the ketamine, opioid analgesics, or both. Lower doses did not produce any negative effects.

Ketamine gel may provide clinicians with a new option in the battle against chronic neuropathic pain. Until further information is available and larger trials can be conducted, we can only recommend this type of therapy for refractory cases in which all primary and secondary options have been exhausted.

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