

Randomized Trial

Multi-Day Low Dose Ketamine Infusion as Adjuvant to Oral Gabapentin in Spinal Cord Injury Related Chronic Pain: A Prospective, Randomized, Double Blind Trial

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Background: Severe, intractable, chronic pain is a significant management problem for those involved in the long-term care of spinal cord injury (SCI) patients. Gabapentin, an anticonvulsant, is widely used for treating chronic pain. Ketamine, an NMDA receptor antagonist, has been available in clinical practice for 35 years. Its usefulness in pathological pain states is known. Despite this, no formal research on its effectiveness in treating neuropathic SCI pain exists.

Objectives: This double-blind study sought to determine the safety and efficacy of adding a multi-day low dose ketamine infusion to oral gabapentin for treating chronic pain related to post spinal cord injury.

Study Design: Randomized, controlled, double blind trial

Setting: Hospital, in-patient setting.

Methods: Forty patients diagnosed with neuropathic pain secondary to spinal cord injury were randomized into 2 equal groups. Group I received an 80 mg intravenous ketamine infusion diluted in 500 cc normal saline over a 5 hour period daily for one week and 300 mg of gabapentin 3 times daily. Group II received a placebo infusion and 300 mg of gabapentin 3 times daily (continued) after 300 mg of gabapentin 3 times daily. Using the visual analogue scale, pain was assessed prior to treatment, daily following ketamine or placebo infusions for 7 days, and then weekly for one month after infusion termination. Side effects, specifically those related to ketamine or gabapentin, were reported.

Results: Both groups demonstrated significantly reduced pain scores compared with pre-treatment values ($P < 0.05$). Group I showed significant pain score improvements over Group II at all measurements ($P < 0.0001$) during infusion and 2 weeks after infusion termination. There was no statistical difference between the groups at 3 weeks and 4 weeks after infusion termination ($P = 0.54$ and $P = 0.25$ respectively). Both drugs were tolerated by all patients; no side effects required intervention.

Conclusion: Multi-day low dose ketamine infusion as adjuvant to gabapentin in post-spinal cord injury related chronic pain is safe and efficacious in reducing pain, but the effect compared to placebo ceased 2 weeks after infusion termination.

Limitations: Study size limited to 40 patients.

Key words: Ketamine, Gabapentin, Spinal, Pain, injury, chronic

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Severe, intractable, chronic pain is a significant management problem for those involved in the long-term care of spinal cord injury (SCI) patients (1). Neuropathic pain's mechanism after SCI remains conjectural. An important factor to determine pain's potential mechanism following spinal injury relates to understanding the cascade of pathological, biochemical, and molecular events initiated by ischemic or traumatic insult to the cord (2).

Several mechanisms have been proposed. Among them are: spinal inhibitory loss mechanisms (3); synaptic plasticity (4); spinal and supraspinal microglia activation (5); changes in cell-signaling pathways at spinal and supraspinal sites (6,7); and transient elevation in the excitatory amino acids glutamate and aspartate, which act at the N-methyl-D-aspartate (NMDA) receptors. These are speculated to contribute to central sensitization or the permanent hyper-excitability of neurons in pain pathways (8).

Neuropathic SCI pain is difficult to treat, but evidence supports a treatment algorithm similar to what is proposed for peripheral neuropathic pain (9).

Many approaches have been used for treating neuropathic SCI pain—with varying degrees of success. Among them are: simple analgesics, tricyclic antidepressants (10), anticonvulsants (10,11), systemically administered local anesthetics or their congeners (12,13), and spinal cord stimulation (14).

Gabapentin, an anticonvulsant, is widely used for treating chronic pain (15). It has a high binding affinity for the $\alpha 2\delta$ subunit of the pre-synaptic voltage-gated calcium channels (16), which inhibit calcium influx and the subsequent release of excitatory neurotransmitters in pain pathways.

Ketamine, an NMDA receptor antagonist, has been available in clinical practice for 35 years. Its usefulness in pathological pain states is known. Despite this, no formal research on its effectiveness in treating neuropathic SCI pain exists. This study was designed to evaluate the efficacy and safety of adding multi-day low dose ketamine infusion to oral gabapentin for treating post spinal cord injury related chronic pain.

METHODS

Before conducting the study, hospital ethics committee approval and written informed consent were obtained. The study comprised 40 patients diagnosed with post spinal cord injury neuropathic pain. All patients had been exhibiting these symptoms for over 6

Table 1. Patient characteristics in both groups, data are means \pm SD, range or number .

	Group I	Group II
Age (years) : Mean (SD)	48.6 \pm 10.1	48.7 \pm 9.7
Height Cm : Mean (SD)	165 \pm 8	166 \pm 9
Weight Kg : Mean (SD)	70 \pm 13	73 \pm 12
Male / Female	16/4	17/3
Duration of pain (months) : Mean (range)	8 (6 - 17)	9 (7- 18)
Level of injury		
C5-C8	2	1
T1-T12	6	5
L1-L5	10	12
S1-S5	2	2
Injury status		
Complete	8	6
Incomplete	12	14
Cause of SCI		
Motor vehicle accident	4	6
Fall	15	14
Sport accident	1	-

months. A physical examination determined if sensory disturbance was present, including loss, reduction, or increased responsiveness in sensation to pinprick and light touch. The study's inclusion process continued until the requested number of patients was reached. Patients who had SCI at or above the C-4 level were excluded because of the risk of respiratory arrest. Other exclusion factors were: preexisting hypertension, angina, congestive cardiac failure, hepatic impairment, renal impairment, and an allergy to any drugs used in the study. Table 1 illustrates that the study groups showed no statistically significant differences regarding age, weight, height, gender, pain duration, injury level, injury status, and injury causes ($P > 0.05$).

The study followed a double-blind design. The patients were randomized into 2 equal groups. Forty envelopes were prepared; 20 were coded as Group I and 20 were coded as Group II. The sealed envelopes were opened by a blinded chief nurse not participating in the study or data collection for the patients to indicate the group in which they were assigned. The envelopes, infusion bottles containing either ketamine or placebo, and coding of these materials were prepared by an anesthesiologist in cooperation with the hospital's pharmacy. This anesthesiologist did not participate in the study, evaluate the patients or the data, or report the findings. No other medical or nursing staff were aware of the treatment administered to each patient. Group I received an 80 mg ketamine infusion diluted with 500

Table 2. VAS for pain before treatment, daily for 7 days and weekly for one month after stopping infusion in Group I and Group II.

Time of measurements	Group I	Group II
Pre treatment	84.25±10.92	83.75±11.22
1st day of infusion	27.3 ± 8.9*	72.3±5.4§‡
2nd day of infusion	26.25±6.4*	65.4±6.2*‡
3rd day of infusion	23.3±3.8*	60.6±3.9*‡
4th day of infusion	21.2±1.9*	44.7±5.3*‡
5th day of infusion	21.5±4.9*	40.2±2.8*‡
6th day of infusion	18.4±3.2*	42.3±1.9*‡
7th day of infusion	14.0 ±5.6*	42.5±14.5*‡
1 week after stopping of infusion	21.50±6.39*	43.00±4.05*‡
2 week after stopping of infusion	22.4±7.54*	44.00±4.61*‡
3 weeks after stopping of infusion	43.4±5.6*	42.5±3.2*
4 weeks after stopping of infusion	42.2±4.4*	43.5±2.3*

* significant difference in comparison to pre-treatment , P value <0.0001.

§ significant difference within group II 1st day value in comparison to pre-treatment $p=0.0002$.

‡ significant difference between groups, P value <0.0001.

No significant difference between groups in 3rd, 4th week values $P=0.54$, 0.25 respectively.

cc of normal saline over a 5-hour period daily for 7 days and 300 mg of gabapentin 3 times daily (continued). Group II received a placebo infusion of isotonic saline 0.9% over 5 hours daily for 7 days and 300 mg of gabapentin 3 times daily (continued).

Each patient received 2-5 mg of midazolam prior to infusion to avoid hypertensive response and muscle pain. During infusion, each patient was monitored with pulse oximetry, non-invasive blood pressure measurement, and ECG. Throughout the week of infusion, patients were monitored for ketamine side effects, including hypertension, tachycardia, hallucinations, nightmares, and headaches. Patients were asked to report any gabapentin side effects, including dizziness, drowsiness, and peripheral edema (swelling of extremities).

STATISTICAL ANALYSIS

Data were presented in the form of mean ± S.D. Comparison of data parameters regarding patient characteristics was performed by Student's t-test. The Mann-Whitney-U test was used to compare the two groups' pain scores. Power of significance was considered significant if ($P < 0.05$).

RESULTS

There was no statistically significant difference in pre-treatment pain scores between the groups. As Table 2 illustrates, at all time periods examined, pain scores in both groups were significantly lower compared with

pre-treatment values ($P < 0.05$). Pain scores decreased significantly in Group I as opposed to Group II at all time measurements ($P < 0.0001$); however, there was no statistically significant difference between the groups at the third and fourth weeks after infusion termination ($P = 0.54$ and $P = 0.25$ respectively). After infusion termination, Group I, the group receiving ketamine as adjuvant, saw pain scores increase; at 3 weeks after infusion termination ($P < 0.0001$ in comparison to its values at 2 week), Group I's pain scores were equal with Group II, which received gabapentin only.

Three patients in the ketamine group showed short-lasting delusions soon after ketamine infusion; 2 patients exhibited a 15% increase in base line heart rate during infusion. Gabapentin side effects occurred soon after its ingestion; 2 patients, one in each group, exhibited dizziness; 2 patients in Group I and one patient in Group II complained of feeling tired as well as a lack of coordination. None of these side effects required intervention.

DISCUSSION

Gabapentin's analgesic effects in patients with several neuropathic conditions is well-established. Two prospective studies (17,18) and one retrospective study (19) suggest gabapentin's efficacy for traumatic spinal cord pain.

In the present study, pain relief gained by using multi-day low dose ketamine infusion as adjuvant to

oral gabapentin for 7 days was superior to gabapentin alone. Further, the analgesic effect of ketamine infusion was sustained for 2 weeks after infusion termination. This improvement might suggest that continued treatment (longer than 7 days) or repeated treatments every 2 or 3 weeks might produce a more significant response. This agrees with Christoph et al's (20) findings, which implied that a short block of NMDA receptors in the spinal cord can lead to a long-lasting down-regulation of central hyperexcitability triggered by nerve injury. The effect is a common feature of different classes of NMDA antagonists.

A block of NMDA receptors might lead to unwanted psychotomimetic and hemodynamic effects, thus limiting the use of high doses (21). In this study, a low dose of ketamine was administered over a 5 hour period. The infusion rate, 16 mg/hour, is below doses reported to be associated with psychomimetic effects (22). Ketamine side effects during this study were mild and well tolerated; only 3 patients in the ketamine group exhibited short-duration delusions starting soon after infusion commencement.

Goldberg et al (23), in a study carried out on patients with complex regional pain syndrome, found that a 4-hour ketamine infusion that escalated over 10 days can result in significantly reducing pain while also improving mobility. Interestingly, Schwartzman et al (24) used ketamine infusion for 4 hours daily for 10 days at a rate of 0.35 mg/kg/h. The ketamine-treated group demonstrated consistent decreases for all pain parameters that lasted for the 12 week post-treatment evaluation period.

Another study done by Backonja et al (25) found that administering a single slow intravenous push of ketamine at 250 mcg/kg in patients with chronic neuropathic pain resulted in decreased pain scores. Sotar-Katzenschler et al (26) reported successful treatment of

non-malignant pain with intrathecal S(+)-ketamine. Although the evidence for the treatment of chronic pain is moderate to weak, ketamine has been successfully used in patients when standard analgesic options have failed (27).

Benrath and colleagues (28) concluded that intravenous application of low dose S(+) ketamine did not affect the maintenance of established long-term potentiation when used without opioids in rats. This finding reflects clinical situations where using NMDA receptors antagonist for treating some forms of chronic pain has been unsatisfying (29). However, Burton et al (30) have reported that mechanical allodynia is reduced after administering intrathecal ketamine in a rat, possibly by preventing spinal cord sensitization. They further suggested that this effect was sustained for at least 2 weeks, but diminished after one month.

Neuropathic pain after spinal cord injury is very difficult to adequately control using currently available techniques. The clinical study documented here presents a new way of treating SCI pain by combining gabapentin with intravenous ketamine. While useful, this treatment often resulted in exhaustion for the patients; some patients required a hospital stay or daily visits for 7 days during the infusion period. Are there newer options with fewer side effects that afford longer pain relief durations? It is hoped that this study will stimulate interest for further research especially since even after 4 weeks of stopping the infusions both groups were still experiencing significant reductions in their VAS pain scores compared to pretreatment scores.

CONCLUSION

Even though multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury-related chronic pain was safe and efficacious, its effect was limited to 2 weeks after infusion termination.

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