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Analgesic Effects of Ketamine Infusion Therapy in Korean Patients With Neuropathic Pain: A 2-Week, Open-Label, Uncontrolled Study

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Abstract

Background: The overexcitation of the *N*-methyl-D-aspartate receptor complex appears to play a critical role in the development of neuropathic pain, and ketamine acts as an antagonist to that receptor. Some publications have reported on the prominent relief of neuropathic pain with intravenous or subcutaneous ketamine infusions or a single-dose intravenous ketamine injection despite adverse effects.

Objectives: The primary objective of this study was to determine the analgesic effect of intravenous ketamine infusion therapy for neuropathic pain refractory to conventional treatments. Secondary objectives included identifying the variables related to the analgesic effect and the pain descriptors susceptible to ketamine infusion.

Methods: This 2-week, open-label, uncontrolled study was conducted in Korean patients with neuropathic pain recruited from the Samsung Seoul Hospital (Seoul, Republic of Korea) outpatient pain management unit. Patients were required to have a pain severity score >5 (visual analog scale [VAS], where 0 = no pain and 10 = worst pain imaginable) over a period of ≥1 month while on standard treatment. The patients were required to have shown no benefit from standard treatment and no pain relief lasting over 1 month. The ketamine infusion therapy was composed of 3 sessions performed consecutively every other day. Midazolam was administered concomitantly to reduce the occurrence of central nervous system–related adverse events (AEs) secondary to ketamine. Each session was as follows: ketamine 0.2 mg/kg and midazolam 0.1 mg/kg were administered intravenously for 5 minutes as a loading dose, followed by a continuous infusion of ketamine 0.5 mg/kg/h and midazolam 0.025 mg/kg/h for 2 hours. AEs were assessed in the following ways: close monitoring of ECG, blood pressure, oxygen saturation, and evaluating the need for treatment of AEs during infu-

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sion and until discharge by an attending anesthesiologist; an open question about discomfort at the end of each session; spontaneous reports about AEs during each session; and the patients' and caregivers' checklist of AEs occurring at home for 2 weeks after discharge. All the descriptors of pain expressed by the patients in Korean were recorded and translated into appropriate English terminology on the basis of the literature on Korean verbal descriptors of pain. Each of the translated pain descriptors was then classified into 1 of 18 sensory items.

RESULTS: The overall VAS score for pain decreased from a baseline mean (SD) of 7.20 (1.77) to 5.46 (2.29) ($P < 0.001$) 2 weeks after treatment in 103 patients (53 males and 50 females; mean age, 52.56 [17.33] years) who completed the study. Variables such as age, sex, and the duration and diagnosis of pain were not found to be associated with analgesic effect. Seven of the 18 pain descriptors were found to have a significant response to ketamine infusion treatment between baseline and 2 weeks follow-up: burning pain ($P = 0.008$); dull, aching pain ($P < 0.001$); overly sensitive to touch ($P = 0.002$); stabbing pain ($P = 0.008$); electric pain ($P = 0.031$); tingling pain ($P < 0.001$); and squeezing pain ($P < 0.001$). A total of 52 patients reported AEs: 33 during infusion and 44 during recovery and up to 2 weeks follow up. The most commonly reported AEs were snoring (15 [15%]) during infusion and dizziness (43 [42%]) during recovery.

CONCLUSIONS: Ketamine infusion therapy was associated with reduced severity of neuropathic pain and generally well tolerated for up to 2 weeks in these patients with neuropathic pain refractory to standard treatment. Variables such as sex, age, and the diagnosis and duration of pain had no association with the analgesic effect of this treatment. Randomized controlled trials are needed to evaluate the efficacy and tolerability of treatment with ketamine infusion. (*Curr Ther Res Clin Exp*. 2010;71: 93–104) © 2010 Excerpta Medica Inc.

KEY WORDS: ketamine, infusion therapy, neuropathic pain, pain descriptor.

INTRODUCTION

Because neuropathic pain is often resistant to NSAIDs and opioids,[1–3] other medication classes, such as antidepressants, anticonvulsants, and local anesthetics, are used.[2,4,5] Central sensitization may mediate chronic neuropathic pain, even when ongoing peripheral sensory input is absent.[6] A wind-up phenomenon leading to central sensitization is postulated to be the cause of allodynia and hyperalgesia.[6–8] Because overexcitation of the *N*-methyl-D-aspartate (NMDA) receptor complex appears to play a critical role in the development of these phenomena, much research has been conducted on the potential analgesic effects of NMDA-receptor antagonists on neuropathic pain.[9–11]

Ketamine, a dissociative anesthetic, acts as a noncompetitive antagonist to the phencyclidine site of the NMDA receptor for the excitatory neurotransmitter glutamate.[12] Despite the reported adverse effects such as drowsiness, disorientation, dizziness, and hallucinations, some publications have been released on the prominent relief of neuropathic pain with intravenous[13,14] or subcutaneous ketamine infusions,[15] or a

single-dose intravenous ketamine injection.[10,16] In a case report and a retrospective study by Correll et al,[17,18] a complete remission of complex regional pain syndrome (CRPS) occurred in some patients who had failed to achieve pain relief from conventional treatments. In a retrospective chart review, Webster and Walker[19] reported that low-dose intravenous or subcutaneous ketamine infusions were well tolerated and effective for nonresponsive neuropathic pain in ambulatory outpatients.

Based on these reports, we developed a protocol of ketamine infusion therapy (KIT) used in this study. Our objectives were to determine the analgesic effect of this KIT to be used as a treatment option in refractory neuropathic pain and evaluate the variables influencing its effect. The theoretical concept of a mechanism-based analysis of neuropathic pain presumes that a specific symptom predicts a specific underlying mechanism.[20] Taking this concept into account, we also assessed which descriptions of pain were more responsive to KIT.

PATIENTS AND METHODS

Consecutive patients (aged 20–85 years) with neuropathic pain were recruited from the outpatient pain management unit at Samsung Seoul Hospital (Seoul, Republic of Korea) from October 2006 to September 2008. The institutional review board of Samsung Seoul Hospital approved the study, and written informed consent was obtained from each patient prior to study participation.

To be included in the study, the patient's mean daily pain intensity had to be >5 on an 11-point visual analog scale (VAS) (where 0 = no pain and 10 = worst pain imaginable) over a period of ≥1 month while on standard treatments. In addition, the patients had to have not benefited from standard treatments and had no pain relief lasting over 1 month. Standard conventional treatments included: nonmedical (eg, physical therapy); pharmacologic monotherapy, or concomitant therapy with NSAIDs, antidepressants, benzodiazepines, anticonvulsants, low- or high-potency opioids, lidocaine patch, or capsaicin cream; or interventional procedures (eg, selective nerve blocks, epidural analgesia, peripheral nerve blocks, sympathetic ganglion blocks, spinal cord stimulation).

Exclusion criteria were severe psychiatric disease, a history of apoplexy, previous cardiac arrhythmia, abnormal ECG, angina pectoris, insufficient respiratory function, insufficient kidney function, pregnancy, present or past drug or alcohol abuse, and an inability to give informed consent. The patients continued their previously prescribed medications including NSAIDs, opioids, antidepressants, and anticonvulsants if the prescription dosage had been unchanged for >1 week before and during the entire study period.

The inclusion criteria were evaluated by 3 attending physicians (C.J.L., T.H.K., and W.S.S.) who also ascertained that subjects did not have any other medical condition that would affect their ability to safely take part in the study. It was clearly addressed that the patient's participation was completely voluntary and could be terminated at any time of request. Patients who did not consent to undergo KIT were continued on their previously prescribed medication.

Our KIT protocol consisted of 3 sessions of ketamine infusion, and each session was performed consecutively every other day. Patients were fasted for ≥9 hours prior to

each session of KIT and each patient received KIT at approximately the same hour of the day for each session. On the study day, patients were placed in a quiet room and monitored with a 3-lead ECG, a peripheral pulse oximeter, and an automated blood pressure (BP) device. An intravenous route was accessed in the nondominant or nonsymptomatic arm for intravenous fluid and drug administration, and oxygen (6 L/min) was given via a facial mask. Benzodiazepines have been demonstrated to attenuate the potential central nervous system (CNS) adverse events (AEs) associated with ketamine.[21] In the present study, midazolam was administered concomitantly with ketamine. In the presence of an anesthesiologist, IV ketamine* 0.2 mg/kg and IV midazolam 0.1 mg/kg (Bukwang Pharmaceutical Co., Seoul, Republic of Korea) were administered for 5 minutes as a loading dose, followed by a continuous infusion of ketamine (0.5 mg/kg/h) and midazolam (0.025 mg/kg/h) for 2 hours using a programmable pump. Patients were determined to have recovered completely from KIT if they were no longer sleepy, attained full orientation to time, place, and person, and were not in need of treatment for AEs. On complete recovery, the patients were discharged from the outpatient recovery unit ≥1 hour after the end of each session of KIT and not without an accompanying reliable guardian or caretaker. AEs were assessed in the following ways: close monitoring of ECG, BP, oxygen saturation, and evaluating the need for treatment of AEs during infusion and until discharge by an attending anesthesiologist (J.G.K., B.S.S., and S.H.L.); an open question about discomfort at the end of each session; spontaneous reports about AEs during each session; and the patients' and caregivers' checklist of AEs occurring at home after discharge. AEs were recorded based on whether they occurred during or after infusion, regardless of session. Multiple AEs were possible in a single patient but repeated AEs were only recorded once.

All patients were required to complete the VAS for pain assessment just before the initiation of the first, second, and third sessions of ketamine infusion (VAS1, VAS2, VAS3, respectively), and at 2 weeks after the third ketamine infusion (VASF). In addition to the patients' characteristics, the following variables were recorded for analysis: primary diagnosis, duration of pain, descriptors of pain before and 2 weeks after KIT, patient satisfaction, and AEs. Patient satisfaction was recorded at the 2-week follow-up as "Yes" or "No."

All the descriptors of pain expressed by the patients in Korean were recorded and translated into appropriate English terminology on the basis of the literature on Korean verbal descriptors of pain (multiple descriptors per patient were possible).[22] Each of the translated pain descriptors was then classified into 1 of 18 sensory items according to the preliminary item set for a neuropathic pain assessment instrument by Krause and Backonja.[23]

Statistical analyses were carried out using SPSS version 12.0 (SPSS Inc., Chicago, Illinois). Data were presented as mean (SD) or number (%) of patients. The changes in the VAS score during the study period were analyzed using a repeated-measures ANOVA with post hoc analysis and a pairwise multiple comparison with Bonferroni

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adjustment. To determine the variables that were related to the change in the VAS score, a binary logistic regression analysis was performed using age, sex, and the diagnosis and duration of pain before KIT. The susceptibility of the descriptor was analyzed using a McNemar test. $P < 0.05$ was considered statistically significant.

RESULTS

One hundred twenty-three Korean patients with neuropathic pain met the inclusion criteria but 15 patients refused to participate; therefore, 108 patients were enrolled in this study. A total of 5 study participants were excluded from the analysis: 2 participants took herbal medications after the first session of ketamine infusion; 1 participant did not take previously prescribed medication after the first session; 1 participant slipped on the way to the hospital for the second session and had an emergency operation; and 1 participant was lost to follow-up without reason after the first session. Accordingly, 103 patients (53 males and 50 females, aged 22–83 years) completed the study. The patients' characteristics and diagnoses are summarized in **Table I**.

The baseline VAS score (VAS1, mean [SD]) was 7.20 (1.77). The VAS2 and VAS3 scores decreased significantly to 6.28 (2.12) ($P < 0.001$) and 5.85 (2.36) ($P < 0.001$), respectively, compared with baseline (**Table II**). The VASF (5.46 [2.29]) was significantly lower than the VAS1 ($P < 0.001$) and VAS2 ($P = 0.003$). Forty-eight patients (47%) had a decrease in the VAS score of >33% at 2 weeks after KIT compared with that of baseline and 19 patients (18%) had a decrease of >50%. The variables, including age, sex, and the diagnosis and duration of pain before KIT, were not found to be associated with the changes in VAS score.

Table III shows the pain descriptors and their response to KIT. The descriptors retrieved from the patients reporting "Yes" for satisfaction at 2-week follow-up were defined as *improved*. The significantly improved descriptors were as follows: burning pain (38%, $P = 0.008$); dull, aching pain (44%, $P < 0.001$); overly sensitive to touch (37%, $P = 0.002$); stabbing pain (47%, $P = 0.008$); electric pain (36%, $P = 0.031$); tingling pain (36%, $P < 0.001$); and squeezing pain (50%, $P < 0.001$).

Fifty-two patients (50%) overall experienced AEs. Thirty-three patients (32%) experienced AEs during the infusion of ketamine. Snoring (n = 15 [15%]) was the most common AE. Other frequent AEs included the following: involuntary movement (7 [7%]); decreased heart rate (>20% decrease in heart rate from preinfusion baseline) (7 [7%]); decreased BP (>10% decrease in mean arterial BP [MABP] from preinfusion baseline) (5 [5%]); and increased BP (>10% increase in MABP from preinfusion baseline) (2 [2%]). These patients presenting AEs were closely monitored, but did not require intervention or treatment because the AEs were considered tolerable and mild. Forty-four patients (43%) reported AEs during recovery after ketamine infusion and at home. The most commonly expressed AEs were dizziness (43 [42%]), nausea (7 [7%]), dry mouth (2 [2%]), and decreased BP (2 [2%]). Among them only 3 patients required intravenous antiemetics for nausea; the other patients did not require treatment for the AEs and recovered spontaneously. Complications related to KIT were not found after 2 weeks, and 56 patients (54%) reported that they were satisfied with KIT at the 2-week follow-up.

Table I. Demographic and clinical characteristics of Korean patients with neuropathic pain (N = 103).

Variable	Value
Age, y	
Mean (SD)	52.56 (17.33)
Range	22–83
Sex, no. (%)	
Male	53 (51)
Female	50 (49)
Duration of pain, mo	
Mean (SD)	25.65 (30.12)
Range	1–144
Diagnosis of pain, no. (%)*	
Postherpetic neuralgia	44 (43)
Complex regional pain syndrome type 1/2	36 (35)/3 (3)
Postthoracotomy pain syndrome	5 (5)
Failed back surgery syndrome	5 (5)
Spinal cord injury	3 (3)
Plexopathy	3 (3)
Trigeminal neuralgia	2 (2)
Diabetic polyneuropathy	2 (2)
Current medication, no. (%)*	
Anticonvulsants	71 (69)
Antidepressants	49 (48)
Tramadol/tramadol + acetaminophen	43 (42)/13 (13)
Benzodiazepines	29 (28)
Opioids/NSAIDs	18 (17)/10 (10)
Capsaicin cream/lidocaine patch/other	2 (2)/3 (3)/4 (4)
No medication	15 (15)
Patients under physical therapy, no. (%)	15 (15)

*Totals may not equal 100% due to rounding.

DISCUSSION

This study found that KIT had an analgesic effect for the treatment of neuropathic pain without serious AEs for up to 2 weeks. There are insufficient data to support the long-term use of ketamine for chronic pain[24]; however, a recent review by Visser and Schug[25] listed articles that reported the analgesic efficacy of ketamine for various types of neuropathic pain such as postherpetic neuralgia, CRPS, spinal cord injury, trigeminal neuralgia, and stump and phantom limb pain. In the present study, the effect of KIT was observed for 2 weeks, which may be inadequate to support its long-term effect.

Table II. The visual analog scale (VAS) scores for pain assessment just before the initiation of the first, second, and third sessions of ketamine infusion (VAS1, VAS2, VAS3, respectively) and at 2 weeks after the third ketamine infusion (VASF) in Korean patients with neuropathic pain (N = 103).

Time	VAS Score, mean (SD)	*P*
VAS1	7.20 (1.77)	–
VAS2	6.28 (2.12)	<0.001*
VAS3	5.85 (2.36)	<0.001*
VASF	5.46 (2.29)	<0.001*; 0.003†

*Compared with VAS1.
† Compared with VAS2.

In the present study, 47 patients (46%) reported that they were not satisfied with KIT. Possible explanations might be that they had pain mechanisms other than NMDA-dependent pathway or our protocol of KIT did not achieve a therapeutic blood level of ketamine in those patients. There are several subunits of the NMDA receptor, and the NMDA receptors containing a specific subunit appear particularly important for nociception.[26] A low blood level of ketamine may block a different subunit from a higher blood level showing analgesic effect.[27] Unfortunately, we did not measure the plasma concentration of ketamine in the present study. On the other hand, Webster and Walker[19] proposed that pain reduction is most likely a product of time and dose and also suggested that the duration of infusion might be more important than the blood level. In randomized clinical trials assessing efficacious medications (eg, antidepressants, gabapentin, and pregabalin) for neuropathic pain, typically <50% of patients experience satisfactory pain relief.[28] It has been suggested that 10% to 15% of patients with neuropathic pain are truly refractory to all forms of pharmacotherapy.[27,29] Considering the inclusion criteria of our study, the satisfaction rate of 54% might be meaningful.

The responder rate in this study was analyzed by definition of a 50% reduction in VAS score compared with baseline[30] or a 33% reduction.[31,32] However, we did not define a "treatment responder" when planning this study because we thought that any reduction of pain compared with baseline might be meaningful to the participants who had been unresponsive to multiple conventional treatments. As a result, 47% of participants had a reduction of >33% of the VAS score, which was similar to that of satisfaction (54%). In addition, because the patients recruited in this study had neuropathic pain resistant to other treatment and a relatively high mean baseline VAS score (7.20), the results might have been different if we had treated the patients with KIT on admission to the pain management unit.[33]

This KIT protocol was designed for outpatients with consideration for tolerability, monitoring and analgesic effects. Webster and Walker[19] reported the tolerability of

Table III. Response to pain descriptors in patients who received ketamine infusion therapy. Data are number (%) of patients (N = 103).

Descriptor*	Frequency at Baseline†	Unimproved at 2 Weeks‡	*P*§
Tingling pain	39 (38)	25 (24)	<0.001
Dull, aching pain	27 (26)	15 (15)	<0.001
Overly sensitive to touch	27 (26)	17 (17)	0.002
Squeezing pain	24 (23)	12 (12)	<0.001
Burning pain	21 (20)	13 (13)	0.008
Stabbing pain	17 (17)	9 (9)	0.008
Electric pain	16 (16)	10 (10)	0.031
Sharp pain	12 (12)	9 (9)	0.25
Shooting pain	9 (9)	5 (5)	0.125
Numbness	8 (8)	6 (6)	0.5
Tearing pain	7 (7)	4 (4)	0.25
Freezing pain	7 (7)	3 (3)	0.125
Itching pain	3 (3)	1 (1)	0.5
Grinding pain	2 (2)	1 (1)	1.0
Throbbing pain	1 (1)	0	NA
Cramping pain	1 (1)	1 (1)	NA
Pinching pain	1 (1)	1 (1)	NA
Soreness	0	–	NA

NA = not applicable.

*Eighteen sensory items according to the preliminary item set for a neuropathic pain assessment instrument by Krause and Backonja.[23]

† Multiple pain descriptors were possible in a patient, so counts total >103.

‡ We defined the descriptor as improved if a patient reporting "Yes" for satisfaction reported the improved status for that descriptor at the 2-week follow-up. The rest of the descriptors were considered as unimproved.

§ The susceptibility of the descriptor to the ketamine infusion therapy at 2-week follow-up compared with before therapy using a McNemar test.

a prolonged (≤8 weeks) continuous intravenous administration of ketamine in their study, where mean duration of ketamine infusion (range) was 16.4 (5–55) days in 13 outpatients. However, a continuous infusion of ketamine outside the hospital is not practical.

Previously, there has been no consensus on a single, uniform ketamine protocol or dose. The ketamine infusion regimen in this study used the upper marginal doses of ketamine from ranges mentioned in other studies.[24,31,34] A search of MEDLINE in English (inception–2009) using terms such as *ketamine, NMDA antagonist, pain,* and

neuropathic pain, found few studies regarding the effect of the diagnosis of pain, age, sex, and duration of pain on the effect of KIT. The duration of pain did not influence the outcome of the present study.

In a previous report, the analgesic benefit appeared to be more pronounced in younger patients with a shorter history of pain (<5 years).[35] In this open-label, uncontrolled study only 7 women (aged 47–79 years) with chronic orofacial pain were enrolled. The 3 youngest patients (aged 43–53 years) in this study with pain <3 years showed prolonged pain relief, while 3 of the 4 oldest patients (aged 57–79 years) with pain >5 years did not, with response to one or several injections lasting only 3 days. To the best of our knowledge, the present study is the first to report on the relationship between the analgesic effect of KIT and the relation to pain, age, and sex. And, although the total number of patients was not large, those variables appeared to have no influence on the outcome.

Ketamine is known to act as an antihyperalgesic and antiallodynic compound in pain management.[25] Based on the concept of mechanism-based analysis[20,36] we analyzed the change of pain descriptors to find out the mechanisms or the descriptors that were influenced by ketamine. In this study, 7 descriptors were determined to be significantly more susceptible to KIT. Among them, "overly sensitive to touch" has been associated with mechanical dynamic allodynia or mechanical punctuate hyperalgesia.[36] "Burning pain" has been associated with spontaneous pain.[20] Both pain descriptors are thought to be involved with NMDA receptors[36] and had a significant response to KIT in this study. The mechanism of "electric pain" is thought to be peripheral nociceptor hyperexcitability through sodium channels,[20,36] and this descriptor also had a significant response to KIT. This finding is in accordance with a previous report that suggests that ketamine acts as a pain modulator, targeting sodium channels as well as NMDA receptors.[37] On the other hand, these results might indicate that NMDA receptors have a partial role in evoking "electric pain." The mechanisms of other susceptible pain descriptors have not been uncovered, but our findings suggest that NMDA receptors or sodium channels are involved in evoking those descriptors. KIT may be considered as a treatment option for neuropathic pain with susceptible pain descriptors that affect NMDA receptors.

One risk of using ketamine for neuropathic pain is the occurrence of CNS AEs such as dizziness, dysphoria, and hallucinations.[12] Benzodiazepines have been demonstrated to attenuate CNS AEs associated with ketamine.[21] In the present study, midazolam was administered in a bolus dose followed by a continuous infusion until the end of the ketamine infusion to help with these AEs. This might explain why none of the patients in the present study complained of unacceptable AEs such as hallucinations or dysphoria. On the other hand, midazolam might have caused other AEs during administration.[38]

LIMITATIONS

There was no placebo or control group and, therefore, the changes in VAS and pain descriptors might have been due to other factors not related to KIT. Subjects were recruited at a single university hospital, which poses problems in terms of the generalizability of our findings. Patients were followed up for only 2 weeks. Only the VAS

and a yes-or-no question of satisfaction were used to evaluate the effect. These measurements are not sufficient to evaluate the treatment effectiveness objectively. The existing medications for neuropathic pain that patients had before and during the study may have affected the results; however, the medication was unchanged for 1 week before inclusion and during the entire study period. Finally, there might have been a change of language nuance in translating Korean pain descriptors into English terminologies. Randomized, controlled studies are needed to evaluate the efficacy and safety profile of KIT and to explore the role of KIT in a mechanism-based analysis of neuropathic pain.

CONCLUSIONS

Ketamine infusion therapy was associated with reduced severity of neuropathic pain and generally well tolerated for up to 2 weeks in these patients with neuropathic pain refractory to standard treatment. Variables such as sex, age, and the diagnosis and duration of pain had no association with the analgesic effect of this treatment.

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