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Ketamine infusion therapy for chronic pain management in South Korea

A national survey for pain physicians with a narrative review

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Abstract

Although ketamine infusion therapy (KIT) has been used extensively for the treatment of chronic persistent pain, there remains high heterogeneity in the administration protocols. The aim of this study was to assess the current clinical use and the infusion protocols of KIT in South Korea and to compare the protocol details with previous relevant studies.

In the first phase, an online survey about KIT, including protocol information, was distributed to pain physicians managing chronic pain patients at 47 teaching hospitals registered in the Korean Pain Society. In the second phase, a review of the KIT protocols in previous clinical studies was conducted and compared with the survey results.

Among 47 institutions, 35 replied; among them, 25 institutions performed KIT on an outpatient basis. The administration protocol for KIT varied greatly among institutions: the total infusion dose of ketamine ranged from 3.5 to 140 mg/70 kg, with a mode of 70 mg [interquartile range (IQR): 62.0; 8.0–70.0 mg] administered in 1 to 3 hours. In 10 previous studies of outpatient KIT, the total dose of ketamine ranged from 12.6 to 98 mg/70 kg, with a mode of 35 mg [IQR: 40 mg; 23–63 mg] given in 1 to 4 hours, which was significantly lower than in our results ($P = .01$). In the survey, physicians listed hallucination as the most frequent side effect.

Although KIT is used in Korean pain centers, there is wide variation regarding the specific infusion protocols. The total dose of ketamine used in South Korea is significantly higher than the general recommendations for outpatient management and may compromise patient safety. The results of this survey reinforce the need for specific guidelines for KIT in managing chronic pain that counterbalance its risks and benefits.

Abbreviations: CRPS = complex regional pain syndrome, IQR = interquartile range, KIT = ketamine infusion therapy, LD = loading dose, MD = maintenance dose, NMDAR = *N*-methyl-D-aspartate receptor, PHN = postherpetic neuralgia, RCT = randomized controlled trials, SRQR = Standards for Reporting Qualitative Research.

Keywords: chronic pain, ketamine infusion therapy, protocol, survey

1. Introduction

The treatment of chronic persistent pain remains challenging due to its uncertain pathophysiology and unpredictable clinical course, despite decades of basic and clinical research.[1,2] Among a plethora of treatments, ketamine ([2R]-2-[2-chlorophenyl]-2-[methylamino]cyclohexanone) has been considered for the management of chronic refractory pain, most often as the last in a long line of therapies. Ketamine is an *N*-methyl-D-aspartate receptor (NMDAR) antagonist that, at high doses, has monoamine, muscarinic, μ2 opioid, and voltage-gated calcium channel effects.[3] The analgesic properties of ketamine may enhance descending inhibition, anti-inflammatory, and immune function effects.[4–7] It was first introduced in the 1960s for analgesia and has been used to treat chronic pain, despite possible psychomimetic side effects.[8]

The first clinical report of ketamine use for pain was in 1989.[9] Since then, randomized controlled trials (RCTs), prospective uncontrolled trials, and retrospective studies on chronic pain syndromes such as postherpetic neuralgia (PHN),[10] fibromyalgia,[11,12] neuropathies,[13–16] spinal cord injury,[17,18] complex regional pain syndrome (CRPS),[19–22] cancer pain,[23] and phantom limb pain[24,25] have been reported. In general, ketamine infusion therapy (KIT) may offer short-term efficacy, lasting from a few to 11 weeks. However, previous studies are limited by their small sample sizes and lack of effective blinding. Furthermore, a wide range of ketamine dosages and heterogeneous administration protocols used in previous studies cause ambiguous results and dose-related side effects that vary from hallucinations to ketamine comas, which may limit the application of KIT for chronic pain management.

Despite the limited evidence and unpleasant side effects, KIT has been extensively used to treat persistent chronic pain. In the present study, we conducted a national survey of pain physicians

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to assess the current clinical use of KIT in South Korea and to evaluate its protocol details in comparison with previous studies of KIT for chronic pain.

2. Methods

The Institutional Review Board at the Seoul National University Hospital approved this study (E-1712-032-904) and waived the requirement to obtain informed consent for all subjects. All methods and results have been reported according to the SRQR recommendations.[26]

2.1. First phase: ketamine infusion therapy survey

A prospective, observational survey regarding KIT was conducted through an online questionnaire distributed by e-mail to a representative pain physician in the anesthesiology and pain medicine departments of all secondary or tertiary teaching hospitals registered in the Korean Pain Society. The questionnaire was available for 2 months, from July to August 2016. The survey (Appendix 1) assessed the KIT protocols of the correspondent hospital with questions that included use, dose, duration of infusion, number of infusions per treatment series, the interval of administration between infusions and series, adjuvant medication to prevent ketamine's side effects, number of KITs performed at each institution per year, and the side effects and safety measures associated with KIT such as anxiety, agitation, hallucinations, nightmares, etc. In addition, the survey requested the physicians' opinion regarding the clinical effectiveness of KIT using a 5-point Likert scale, from 1 (very effective) to 5 (worsened symptoms). If the institution did not perform KIT, the reason for not using it was asked.

2.2. Second phase: review of previous studies with similar KIT protocols

In the second phase, to compare the current clinical use of KIT in South Korea with previous studies, an electronic literature search using the National Library of Medicine's MEDLINE and PubMed, Embase, and Cochrane databases with the keywords "ketamine infusion" and "chronic pain" was conducted to identify articles relevant to the present study. Clinical trials, observational studies, and retrospective studies were all considered. The search was limited to human subjects, written in the English language, studying adults (aged 18 years and older), and dated from 1990 to 2017. The reference sections of prime articles were then searched to obtain additional references. The most recent search was performed in December 2017. The emphasis of the extracted data was the KIT protocol (duration of infusion, dose, multiple or single infusion, adjuvant medication), pain intensity decrease (proportion and duration of the pain relief, pain scores measured), and occurrence of side effects (frequency and severity).

Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY). The continuous variables are expressed as mode or median values (75% interquartile range [IQR]), and frequency (%) is reported for categorical variables. Wilcoxon's signed-rank test was used to compare total dosage of ketamine between our survey results and previous studies. A p-value $< .05$ was considered to indicate statistical significance.

3. Results

3.1. First phase: ketamine infusion therapy survey

A total of 47 institutions were enrolled and received the survey. Among them, 35 institutions replied (Fig. 1). A total of 25 institutions (71%) used KIT for the management of chronic pain patients, while 10 (29%) did not. The 10 institutions that did not conduct KIT based their decision on the doubtful effectiveness (n=3), complex administration protocol (n=2), limited resources of the pain department (n=5), cumbersome side effects and the risk of drug dependency (n=3), and insurance restrictions

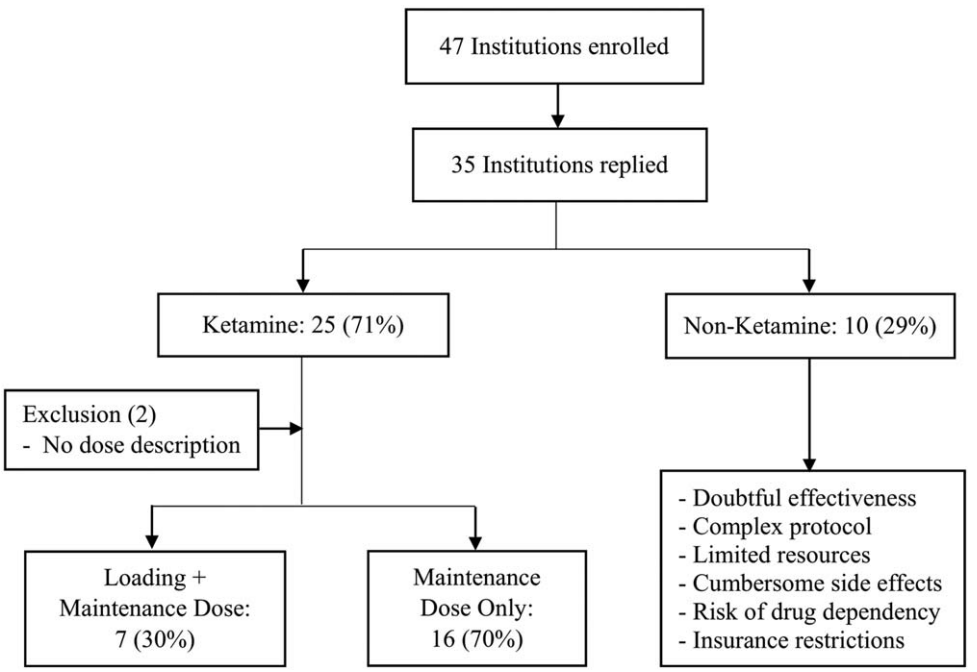

Figure 1. Flowchart of institutions surveyed.

(n = 1). Two institutions were excluded from the analysis because they did not describe their KIT protocol in detail. Therefore, 23 institutions were included in the analysis.

All institutions included in the present study (n = 23) conducted KIT on an outpatient basis with 1–3 hours infusion durations. Among the 23 institutions, 7 (30%) used a loading dose (LD) and a maintenance dose (MD), while 16 (70%) used an MD only. The KIT doses varied widely between institutions, as shown in Table 1. The LD+MD protocol administered an LD ranging from 0.1 to 1 mg/kg (mode = 0.2 mg/kg) and an MD from 0.5 to 1 mg/kg/h (mode = 1 mg/kg/h) with an infusion duration of 1 to 3 hours (mode = 2 hours). Conversely, the MD-only protocol used a dose ranging from 0.05 to 0.1 to 0.5 to 2 mg/kg/h (mode = 0.5–1 mg/kg/h) with an infusion lasting 2 hours or less (mode = 1 hours). The total infusion dosage of ketamine varied greatly, from 3.5 to 140 mg with a mode of 70.0 mg [IQR: 62.0 mg; 8.0–70.0 mg] normalized to a 70-kg patient given over 1–3 hours. If we assumed a subanesthetic dose of ketamine as a total of < 1 mg/kg,[8] an anesthetic dose of ketamine as a total of ≥ 1 mg/kg infusion was administered in 2 institutions.

Most responders used adjuvant medications to prevent ketamine's side effects or to improve its effectiveness. Midazolam was the most commonly used adjuvant, as a total of 18 institutions (78%) used it alone or in combination with other drugs. The doses of midazolam varied from 1 to 17 mg, and it was used as an exclusive adjuvant in 8 institutions (35%). Other adjuvants were lidocaine, used in 6 institutions at a dose from 30 to 300 mg; thiopental, used in 5 institutions at a dose from 2 to 2.5 mg/kg; lorazepam, precedex, and nefopam, used in 2 institutions; and morphine, mepivacaine, and fentanyl, used in one institution.

Information regarding the infusion's frequency per KIT series varied significantly among responders (Table 2). The most common answer was from 1 to 3 infusions per series (61%), each infusion with an interval of 1 to 2 weeks (75%), and each series with an interval of 1 to 3 months (59%).

Patients were prescribed KIT to manage chronic persistent pain for neuropathic conditions such as CRPS, spinal cord injury, and postherpetic neuralgia, or for functional pain syndromes such as fibromyalgia that was unresponsive to other therapeutic approaches including invasive pain interventions. The number of KITs per year also varied between institutions, from 20 to 1000 per year with a median of 180 per year per institution. In terms of the most common adverse events associated with KIT, physicians reported hallucinations (n = 11 responders, 44%), anxiety/agitation (n = 8, 32%), and depression (n = 3, 12%). Three institutions (12%) reported other side effects of KIT, such as hangover, tachycardia, and psychosis.

The clinical effectiveness of KIT was reported to be somewhat effective (moderate efficacy) by 21 institutions (92%); one declared that it was very effective (good efficacy). One institution reported that the efficacy was doubtful, and no institutions reported KIT to be ineffective or to worsen the patients' symptoms.

3.2. Second phase: review of previous studies with similar KIT protocols

The search of keywords generated a total of 98 articles in PubMed, 76 in Embase, and 56 in Cochrane. After applying the search limitations, a total of 34 articles were selected, including 19 prospective randomized placebo-controlled trials, 9 prospective observational nonrandomized trials, one prospective randomized noncontrolled trial, and 5 retrospective chart review studies (Fig. 2). The heterogeneity of the protocols does not allow for direct comparisons; therefore, they were divided into the use of a single infusion for 2 hours or less (n = 18), the use of single infusion for 2–5 hours (n = 4), and the use of continuous infusion for $\geq$ 24 hours (n = 12). Additionally, these studies were classified into KIT conducted on outpatient basis (n = 17), inpatient basis (n = 14), or unreported (n = 3). All institutions in South Korea reported the use of KIT on an outpatient basis and none used continuous infusions; thus, 10 studies of KIT with the required characteristics (Table 3) were selected to compare their protocols with the survey responses. Among them, 2 studies were performed for the management of fibromyalgia,[11,12] one for

Table 1

Ketamine dosages reported in the survey.

		Units	Dose	Total (70 kg)	Number of responders	Total per dose type
LD + MD (7)	LD	mg/kg	0.1–0.2	7.0–14.0	1	7
			0.2	14.0	4	
			0.25	17.5	1	
			0.8–1	56–70	1	
	MD	mg/kg/h	0.5	35	2	7
			0.8–1	56–70	1	
			1	70	1	
		mg/kg (no h)	1	70	3	
MD only (16)		mg/kg/h	0.05–0.1	3.5–7.0	1	8
			0.1–0.2	7.0–14.0	2	
			0.5–1.0	35–70	3	
			2.0	140	2	
		mg/kg (no h)	0.6–1	42–70	1	4
			1	70	1	
			$\leq$ 2	$\leq$ 140	2	
		mg/h (no kg)	4–5	4–5	1	4
			8.3–63	8.3–63	1	
			50	50	2	
Total Responders						23

LD = loading dose, MD = maintenance dose.

Table 2

Frequencies of ketamine infusion therapy at institutions surveyed.

Number of infusions per one treatment session	N (%)
1–3	8 (61%)
5–10	3 (23%)
No limit	1 (8%)
No protocol	1 (8%)
Intervals between each ketamine infusion therapy	
1 d	3 (13%)
1 week	10 (42%)
1–2 weeks	6 (25%)
2 weeks	2 (8%)
1 month	2 (8%)
No interval	1 (4%)
Intervals between infusions for each treatment session	
1 week	1 (8%)
1–2 months	3 (25%)
3 months	4 (34%)
3–6 months	2 (17%)
No interval	1 (8%)
No protocol	1 (8%)

CRPS,[19] one for cancer pain,[23] one for phantom limb pain,[24] 4 for mixed neuropathic pain,[13–16] and 1 for various neuropathic pain including CRPS.[21]

Of the 10 studies, 2 (20%) used LD+MD, while 8 (80%s) used MD only. Intravenous infusion dosages of ketamine ranged from 0.25 to 0.75 mg/kg/h (mode = 0.3–0.5 mg/kg/h). A total infusion dose of ketamine widely varied, from 12.6 to 70 mg with a mode of 35 mg [IQR: 40 mg; 23–63 mg] normalized to a 70-kg patient given over 1 2 hours, or 98 mg given over 4 hours. The total doses of ketamine in the previous studies were significantly lower than the results of this survey, which found a total infusion dose of ketamine ranged from 0.05 to 2 mg/kg/h with a mode of 70 mg [IQR: 62.0 mg; 8.0–70.0 mg] administered in 1 to 3 hours ($P = .01$). Of the 10 selected studies, 5 used a single infusion and 5 conducted several sessions of infusions with intervals that varied from 1 day to 4 weeks, except a study on CRPS for 10 consecutive days.[19]

Regarding the efficacy of KIT, 3 studies showed superiority to placebo,[11,19,23] while one study demonstrated similar efficacy to a single midazolam infusion.[15] However, these studies reported no benefits beyond the first few hours after the infusion, except Schwartzman's study,[19] which used 98 mg of ketamine (normalized to a 70-kg patient) over 4 hours for 10 consecutive days to manage CRPS and demonstrated pain reduction lasting up to 12 weeks. In other studies, KIT showed superior effectiveness to calcitonin[24] or magnesium[14] infusion, but a similar effectiveness to alfentanil[15,16] for mixed neuropathic pain, with a short duration of pain relief.

Nausea, headache, tiredness, visual hallucination, hypertension, mild sedation, and dissociative reactions were reported as side effects associated with KIT.[11–16,19,21,23,24]

4. Discussion

This survey revealed that KIT is widely used by pain physicians at secondary and tertiary hospitals in South Korea. In this study, only 1 private practice performed KIT; therefore, the results are largely based on the protocols of the secondary and tertiary teaching hospitals in South Korea and are expected to reflect the current clinical practice of KIT throughout the nation. The results revealed no consensus regarding KIT protocols and the clinical practices of KIT varied greatly among institutions in terms of dosages, adjuvant medications, intervals between infusions, and duration of administration.

One notable finding of this survey was that the total dose of infused ketamine reported in South Korea was significantly higher than those used in previous clinical studies in outpatient settings. The total infusion dose of ketamine ranged from 3.5 to 140 mg/70 kg with a mode of 70 mg [IQR: 62.0 mg; 8.0–70.0 mg] administered in 1–3 hours contrasted with a total dose of ketamine in previous studies ranged from 12.6 to 98 mg/70 kg with a mode of 35 mg [IQR: 40.0 mg; 23.0–63.0 mg] given in 1–4 hours, ($P = .01$). Moreover, 2 responders reported anesthetic doses of 1 and 2 mg/kg, respectively, and the median infused dose was more than twice that of previous studies.[20,22] In addition, our survey showed a generalized tendency of short period infusions (mode 1 hour), even when administering high doses of ketamine. According to a recent systematic review,[8] increases in the total dose of ketamine administered result in a higher degree of pain relief and possibly greater duration of pain reduction. Nonetheless, the available data in the outpatient setting are contradictory and studies with a higher total dose administered during a short period[14,21,23] resulted in similar clinical effectiveness to those with lower doses.[11,16,24] Currently, to avoid excessive sedation and undesirable effects, a subanesthetic dose of ketamine between 0.1 and 0.5 mg/kg/h is recommended for monitored outpatients to manage chronic persistent pain.[8,19,20] Therefore, evidence from comparative effectiveness trials analyzing different infusion protocols is needed to establish the efficacy and safety of KIT in the management of chronic persistent pain.

Regarding the duration of the ketamine infusion, the longest infusion duration, using multiple consecutive outpatient clinic visits, has been suggested to provide longer-duration pain relief.[8,19] A previous randomized, controlled trial in CRPS patients by Schwartzman et al,[19] in which they performed 4 hours of outpatient ketamine infusion (maximum rate of 0.35 mg/kg/h or 25 mg/h, whichever was lower) on 10 consecutive weekdays, demonstrated pain reduction for a relatively long duration—up to 12 weeks. In South Korea, however, there have been limitations on performing KIT on an outpatient basis, such as a restriction in the number of KIT sessions covered by public insurance (> 3 KIT sessions cannot be reimbursed)[27] and limited resources available within pain departments. Therefore, a specific guideline for KIT, using up-to-date available data, is imperative in South Korea to avoid dangerous high doses in the outpatient setting, in order to balance the benefits of this therapy over its inherent risks.

Another finding of this survey was the use of various co-administered medications, with no consensus among the hospitals that participated. Compared to the protocols in previous outpatient studies,[11–16,19,21,23,24] various combinations of medications, such as midazolam, lidocaine, lorazepam, precedex, nefopam, morphine, mepivacaine, and fentanyl, were used as single or combined adjuncts for KIT in South Korea. Among them, the use of midazolam was most popular in 8 of the 25 institutions to decrease hallucinations, which was the most common adverse event reported by physicians in our study. One study suggested that midazolam's muscle relaxation properties may have contributed to the analgesic effects of KIT.[12] However, midazolam did not seem to correlate with the duration of pain relief in their study. Similarly, other co-administered medications, such as clonidine,[19] calcitonin,[24] or alfentanil,[15,16] and their combinations were rarely

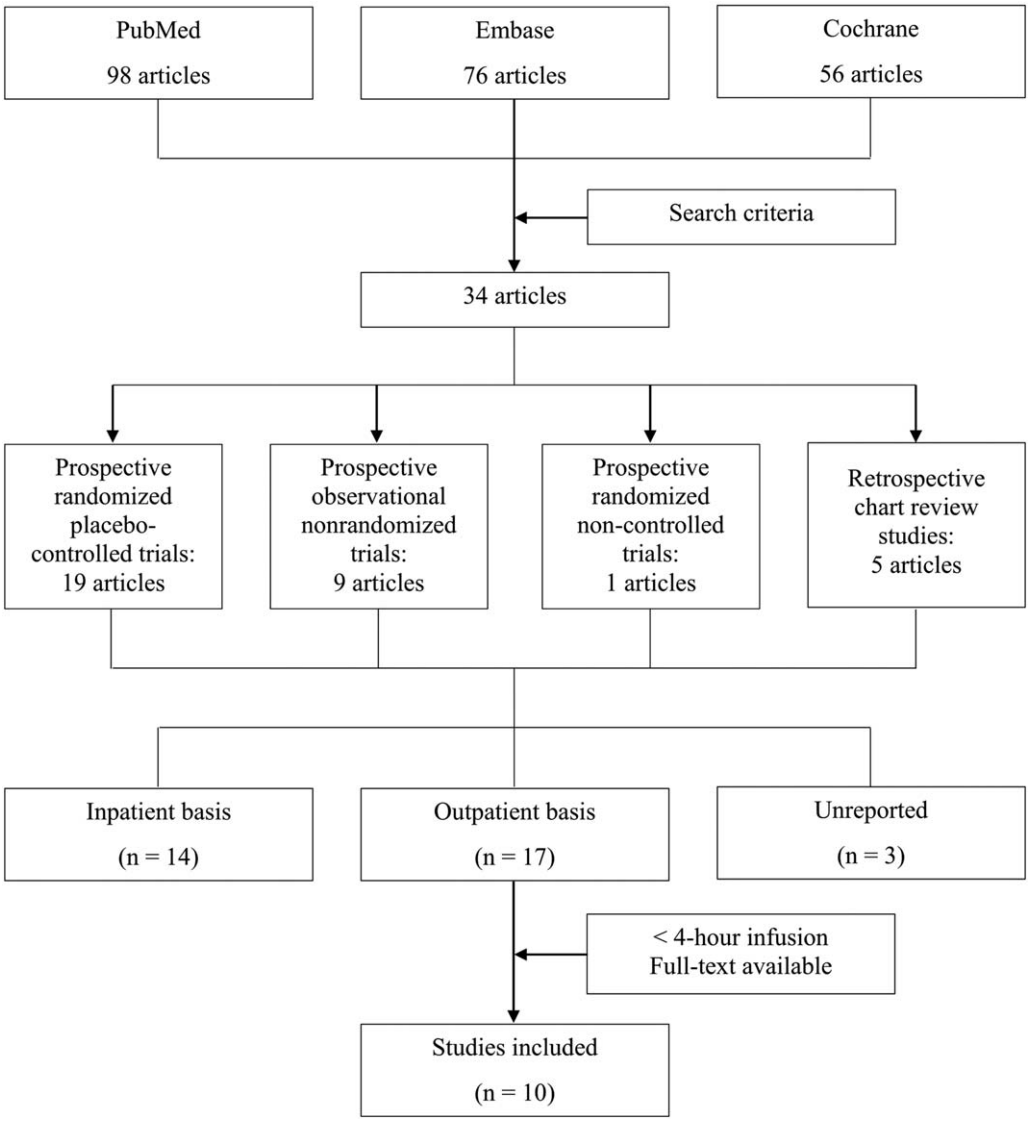

Figure 2. PRISMA flow diagram.

suggested as superior analgesic medications to ketamine alone. Therefore, despite a lack of strong clinical evidence, KIT should be regarded as a therapeutic measurement to manage some cases of chronic pain in clinical practice.

KIT was used in South Korea to manage chronic persistent pain of neuropathic (CRPS, spinal cord injury, and postherpetic neuralgia) or fibromyalgia etiology. Similarly, previous studies used KIT in the treatment of neuropathic pain conditions[10,13–25] and fibromyalgia.[11,12] Although the use of ketamine in the management of chronic pain conditions have been justified by the drug's particular pharmacology including direct analgesic activity and action on opiate tolerance and hyperalgesia,[28] the evidence in the current literature remains insufficient and inconclusive. Regarding the variations in the responses to KIT for specific pain conditions, out of 8 studies in neuropathic pain, 6 found ketamine to be superior and 2 equal to placebo, and out of 2 studies in fibromyalgia, 1 found it superior and another equal to placebo. Nonetheless, the response of the different pain conditions to KIT may be dependable of inter-study's variations regarding sample size, dosage administered, route and duration of administration, and lack of effective blinding. Further high-quality homogeneous studies that investigate the responses to specific chronic pain conditions to ketamine are needed.

According to previous articles[11–16,19,21,23,24] and the results of our survey, the side effects of KIT may not be severe and typically subside once the infusion is discontinued. However, the side effects limit ketamine's safety profile and practicality in an outpatient setting. Additionally, these side effects depend on the dosage and duration of the infusion, as well as on interindividual variability.[29] Moreover, the satisfaction of both patients and physicians with KIT for acute postoperative pain has been recognized in previous studies,[30] but is not well known and understudied in chronic pain. Although it is well understood that the administration of ketamine diminishes the attention span while the drug is active, there has been controversy regarding its long-term effects on the attention span.[31] Another worrisome aspect of ketamine's use is the risk of drug dependence and abuse. In higher doses exceeding 1.5 mg/kg, ketamine induces a state commonly referred to as a "K-hole," in which the user experiences an intense detachment from reality.[32] "K-hole" states were not reported in this survey;

Table 3

Previous studies of ketamine infusion therapy for chronic pain on an outpatient basis.

Chronic pain condition	Authors	n	Disease duration	Dosage of IV infusion and ratio (placebo: KIT)	Total dosage of ketamine (70 kg)	Infusions and interval*	Study design and methodology	Results (pain relief)	Comments
Fibromyalgia	Graven–Nielsen et al (Part 1),[11] 2000	29	3.2 y	KIT 0.3 mg/kg or placebo for 30 min	21 mg	Single infusion to determine KIT responders	DB, PC Crossover	KIT > Placebo (NS)	KIT: 17 patients (59%) reported at least a 50% reduction in VAS. Placebo (NS): 5 patients (17%) reported at least a 50% reduction in VAS.
	Graven-Nielsen et al (Part 2),[11] 2000	15	3.7 y	KIT 0.3 mg/kg or placebo for 30 min	21 mg	Single infusion, 1 week after Part 1	DB, PC Crossover	KIT > Placebo (NS)	Referred pain, temporal summation, muscular hyperalgesia, and muscle pain at rest were attenuated by KIT in FMS patients.
	Noppers et al,[12] 2011	24	1–192 months (median 1.3 y)	Randomized 12:12 KIT 0.5 mg/kg or MDZ 5 mg for 30 min	35 mg	Single infusion 8 weeks f/u	DB, APC with open-label after 8 weeks Parallel	KIT = MDZ	No differences in VAS or FIQ between groups at 2.5 hours after infusion or at week 8 f/u. No significant effect of KIT on spontaneous and experimental pain parameters. No differences in SE. Mild to moderate SE in both groups.
CRPS	Schwartzman et al,[19] 2009	19	0.8–20 y	Randomized 10:9 KIT 100 mg over 4 h Max. 0.35 mg/kg/h or placebo for 4 h. Both groups received Clonidine and MDZ	Max. 98 mg	Daily infusions for 10 days 12 weeks f/u	DB, PC Parallel	KIT > Placebo (NS)	KIT reduced MPQ up to 12 weeks, $P < .05$. KIT group improved pressure-evoked pain, brush allodynia, monofilament stimulation, cold and heat-evoked pain, and finger tap. More SE in ketamine. No psychomimetic SE.
Cancer pain	Mercadante et al,[23] 2000	10	ND	KIT 0.25, or 0.5 mg/kg, or placebo for 30 min. On 3 separate days, at least 2 days apart	17.5 mg or 35 mg	Three sessions with 2 days of interval	DB, PC Crossover	KIT > Placebo (NS)	All participants reported decrease in pain scores after ketamine when compared with pretreatment pain scores (0.5 mg/kg dose $P < .01$, 0.25 mg/kg dose $P < .05$). No decreased pain scores after NS administration. Pain relief lasted up to 12 hours. Hallucinations in 4 patients, and unpleasant sensation in 2 patients. Significant increases in drowsiness in ketamine group.
Phantom limb pain	Eichenberger et al,[24] 2008	20	0.9–32.3 y	Randomized in 4 groups: KIT 0.4 mg/kg, Calcitonin 200 IU, KIT/ Calcitonin, and placebo infusions for 1 h The minimum time between infusions was 48 h	28 mg	Single infusion	DB, PC Crossover	KIT = KIT/Calcitonin > Calcitonin > Placebo (NS)	KIT but not calcitonin, reduced phantom limb pain. Six of 10 patients in KIT reported a 50% reduction in VAS. The combination group was not superior to ketamine alone.
Mixed neuropathic pain	Max et al,[13] 1995	8	ND	0.75 mg/kg/h, doubled at 60 and 90 min if no analgesic benefit, Alfentanil 1.5 μg/kg/mL, and placebo over 2 h	58 ± 5 mg	Single infusion	DB, PC Crossover	KIT > Alfentanil > placebo	Pain relief: KIT = 65%, alfentanil = 46%, and placebo = 22% ($P < .01$ for ketamine and P= .08 for alfentanil, each compared to placebo). Relief of allodynia: KIT = 71%, alfentanil = 57%, and placebo = 21% ($P < .01$ for both ketamine and alfentanil). After the infusion was stopped, pain relief disappeared before the side effects resolved. Dissociative reactions in 3 patients.
	Felsby et al,[14] 1996	10	ND	KIT 0.2 mg/kg over 10 min → 0.3 mg/ kg/h infusion or Magnesium 0.16 mmol/ kg over 10 min → 0.16 mmol/kg/h, up to 1 h	35 mg	Single infusion	DB, APC Crossover	KIT > Magnesium	KIT reduced spontaneous pain (VAS) 57% and area of allodynia 33%. Magnesium chloride reduces VAS 29% and allodynia 18%. Pain thresholds to mechanical and thermal stimuli were not significantly changed. Psychotomimetic effects common after KIT.
	Leung et al,[15] 2001	12	30–240 months	KIT TCI of 50, 100, and 150 ng/mL or Alfentanil TCI of 25, 50, 75 ng/ mL or diphenhydramine over 20 min	ND	Three sessions with 1 week of interval	DB, APC Crossover	KIT = Alfentanil	Dose-dependent increases in cold and cold pain thresholds and reductions in stroking pain scores were noted in both the alfentanil and the KIT. A third of patients in KIT group developed lightheadedness.

(*continued*)

Table 3
(continued).

Chronic pain condition	Authors	n	Disease duration	Dosage of IV infusion and ratio (placebo: KIT)	Total dosage of ketamine (70 kg)	Infusions and interval*	Study design and methodology	Results (pain relief)	Comments
	Jørum et al,[16] 2003	12	1–19 y	KIT 60 μg/kg over 5 min → 6 μg/kg/min infusion, or alfentanil 7 μg/kg bolus → 0.6 μg/kg/min infusion, or placebo for 20 min	12.6 mg	Two sessions with 2 hours interval	DB, APC Crossover	KIT = alfentanil > placebo (NS)	Decreased VAS for spontaneous pain and hyperalgesia to cold pain in both ketamine and alfentanil groups. Dizziness was more common in the KIT group.
CRPS (18), chronic headache (8), LBP (7), mixed neuropathic pain (16)	Patil and Anitescu[21] 2012	49	> 6 months (mean 5.62 y)	KIT started at 0.5 mg/kg over 30–45 min every 3–4 weeks Average CRPS dose 1.0 mg/kg, non-CRPS dose 0.9 mg/kg All received MDZ and ondansetron	70 mg for CRPS 63 mg for non-CRPS	Four sessions with 3–4 weeks of interval	Retrospective chart review studies	High Efficacy	All patients reported significant VAS reduction of 5.9, and 4 CRPS patients a reduction of 7.2 ($P < .001$). 27% report relief lasting several hours, 73% report relief lasting > 1–2 days, 38% report relief lasting > 3 weeks. Minimal SE reported. Hypertension and sedation were the most common SE. Higher incidence of hallucination and confusion in patients without CRPS.

* Number of infusions administered and time interval between them.

APC = active placebo controlled, BP = blood pressure, BPI = brief pain inventory, CRPS = complex regional pain syndrome, DB = double-blind, ESAS = Edmonton Symptom Assessment Scale, f/u = follow-up, FIQ = fibromyalgia impact questionnaire, FMS = fibromyalgia syndrome, HP = habitual pain, IM = intramuscular, IU = international units, IV = intravenous, KIT = ketamine infusion therapy, MDZ = midazolam, MPQ = Short-form McGill Pain Questionnaire, ND = not described, NMDA = *N*-methyl-D-aspartate, NPIS = Numeric Pain Intensity Scale, NRS = 11-point numerical rating scale, NS = normal saline, PBO = placebo, PC = placebo-controlled, PHN = postherpetic neuralgia, RMF = remifentanil, SCI = spinal cord injury, SE = side effects, TCI = target controlled intravenous infusion, tid = 3 times a day, VAS = visual analog scale, WAD = Whiplash associated pain.

however, the frequent short-term side effects, possible long-term effects, and risk of abuse at higher doses call for stricter restrictions and cautious prescribing for chronic pain patients, at least until stronger evidence arises.

Based on the results obtained in our survey, the most prevalent protocol for KIT in Korea is an infusion of ketamine 0.5 to 1 mg/kg/h, combined with administration of midazolam 4–7 mg as an adjuvant, for 2 hours. The infusions can be administered 3 times per series (covered by South Korean national insurance), and patients should be properly monitored during and after the KIT. Nonetheless, formal guidelines for KIT should be based on well-designed clinical trials with effective blinding, a range of dosages, the inclusion of the disease duration, and various routes of administration, in order to determine its role (benefits, toxicity, and side effects) in the management of chronic pain conditions.

There are limitations in the present study. First, the results of this study are dependent on physicians' declarative information, based on their empirical experience in real clinical practice; therefore, there might be biases of available information, such as reporting, recall, and observer biases. Second, the specific and detailed information regarding the administration of ketamine at each institution, such as disease duration, patient characteristics, and prospective determinants of KIT outcomes, were not in the scope of the study and therefore are not available. Finally, although we have reported the most popular administration protocol of KIT used by hospitals that participated in the survey, this should not be utilized as a formal guideline and must be reviewed after controlled clinical trials have been conducted to evaluate the effectiveness of different KIT protocols in patients with chronic pain.

In conclusion, the practical clinical application of KIT is present in anesthesiology and pain medicine departments across South Korea. However, there is no consensus protocol for KIT; the current practice consists of heterogeneous randomized controlled trials with limited evidence strength due to small sample sizes, lack of generalizability, ineffective blinding, and discouraging pain relief outcomes. Moreover, this study is a call for attention to the institutions that practice KIT in South Korea with high doses of ketamine in outpatient settings, urging them to review their protocols and safety assessments. The results of the present survey reinforce the need for specific guidelines for KIT administration that counterbalance the side effects, risks, and possible benefits of this therapy for managing chronic pain arising from a variety of etiologies.

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