ANESTHESIOLOGY

Ketamine and Magnesium for Refractory Neuropathic Pain

A Randomized, Double-blind, Crossover Trial

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ABSTRACT

Background: Ketamine is often used for the management of refractory chronic pain. There is, however, a paucity of trials exploring its analgesic effect several weeks after intravenous administration or in association with magnesium. The authors hypothesized that ketamine in neuropathic pain may provide pain relief and cognitive–emotional benefit *versus* placebo and that a combination with magnesium may have an additive effect for 5 weeks.

Methods: A randomized, double-blind, crossover, placebo-controlled study (NCT02467517) included 20 patients with neuropathic pain. Each ketamine-naïve patient received one infusion every 35 days in a random order: ketamine (0.5 mg/kg)/placebo or ketamine (0.5 mg/kg)/magnesium sulfate (3g) or placebo/placebo.

The primary endpoint was the area under the curve of daily pain intensity for a period of 35 days after infusion. Secondary endpoints included pain (at 7, 15, 21 and 28 days) and health-related, emotional, sleep, and quality of life questionnaires.

Results: Daily pain intensity was not significantly different between the three groups (n = 20) over 35 days (mean area under the curve = 185 ± 100, 196 ± 92, and 187 ± 90 pain score-days for ketamine, ketamine/magnesium, and placebo, respectively, $P = 0.296$). The effect size of the main endpoint was –0.2 (95% CI [–0.6 to 0.3]; $P = 0.425$) for ketamine *versus* placebo, 0.2 (95% CI [–0.3 to 0.6]; $P = 0.445$) for placebo *versus* ketamine/magnesium and -0.4 (95% CI [–0.8 to 0.1]; $P = 0.119$) for ketamine *versus* ketamine/magnesium. There were no significant differences in emotional, sleep, and quality of life measures. During placebo, ketamine, and ketamine/magnesium infusions, 10%, 20%, and 35% of patients respectively reported at least one adverse event.

Conclusions: The results of this trial in neuropathic pain refuted the hypothesis that ketamine provided pain relief at 5 weeks and cognitive–emotional benefit *versus* placebo and that a combination with magnesium had any additional analgesic effect.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The use of low-dose ketamine infusion for the treatment of chronic pain has expanded rapidly despite a paucity of data supporting the practice
- Magnesium ion, like ketamine, is a blocker of *N*-methyl-D-aspartate receptor function that may have analgesic properties in some settings

What This Article Tells Us That Is New

- Using a triple-crossover paradigm, saline, ketamine, and ketamine + magnesium infusions were given to a group of 20 patients with chronic neuropathic pain
- No effect of either the ketamine or ketamine + magnesium in terms of pain relief over the 35 days after infusions was identified
- Additional secondary health-related, emotional, sleep, and quality of life measures were also unchanged by the drug infusions

Neuropathic pain is difficult to treat, and the efficacy of recommended drugs is limited. *N*-methyl-D-aspartate receptor (NMDA) is a pharmacologic target in central sensitization and neuropathic pain. Ketamine, a general anesthetic agent and NMDA receptor antagonist, has been used in recent decades as an analgesic in refractory pain conditions such as complex regional pain syndrome,[1,2] postherpetic neuropathy,[3] trigeminal neuralgia,[4] traumatic pain,[3] cancer-related pain,[5] and other types of chronic pain such as fibromyalgia,[6] postischemic pain, or neuropathic pain of central origin.[7] Recent reviews,[8–10] however, have stressed the poor to moderate level of evidence of ketamine analgesic effect in published randomized, controlled trials. Concerning neuropathic pain of peripheral origin, levels of evidence are particularly weak as only four studies had

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more than 3 weeks' follow-up [11–14]; only one of these used an IV administration route[11] (combined with gabapentin), and had negative results. To reach a consensus on the use of ketamine for refractory pain, more randomized, controlled trials with IV ketamine are needed.

Magnesium sulfate, a physiologic blocker of NMDA receptor, modulates this receptor and has also been shown to be effective in the treatment of neuropathic pain in preclinical[15–17] and clinical studies, including cancer,[18] headache,[19] and postoperative pain.[20]

The combination of ketamine with magnesium in a double-blind, randomized, controlled trial showed beneficial effects on postoperative pain intensity and opioid consumption in patients undergoing scoliosis surgery compared with ketamine alone, with no additional adverse events.[21] However, no randomized, controlled trial of this possibly additive combination has so far been performed in established neuropathic pain.

Considering limited evidence in the literature on the analgesic impact of ketamine alone or combined with magnesium in neuropathic pain for more than 3 weeks, we hypothesized in the present trial with neuropathic pain patients that (1) IV ketamine or (2) IV ketamine and magnesium combination could bring analgesic and cognitive–emotional benefits *versus* placebo for 5 weeks postinfusion and (3) magnesium combined with ketamine could have an additive effect.

Materials and Methods

Study Design

The trial methodology was detailed in a recent article.[22] This randomized, placebo-controlled, crossover, double-blind clinical study was conducted by the Clinical Pharmacology Center/CIC Inserm-1405 and Pain Clinic of University Hospital of Clermont-Ferrand, France. The French Research Ethics Committee gave its approval on April 13, 2015 (review board number: AU 1173). The trial was registered in ClinicalTrials.gov on June 10, 2015 (trial number: NCT02467517). The principal investigator was Gisèle Pickering. The supporting Consolidated Standards of Reporting Trials checklist is available as Supplemental Digital Content (http://links.lww.com/ALN/C377). At inclusion (14 days before first course of treatment) and at each subsequent consultation (randomization, first, second and third treatment periods and end of study), patients filled out questionnaires concerning the pain status, cognitive–emotional domains, quality of life, and patient satisfaction. Any adverse events were collected by phone on the day following each infusion.

Study Population

Participants were recruited in the study from the Clinical Research Center database of patients with neuropathic pain; patients were known to be ketamine-naïve with long-standing refractory pain. Before giving informed consent, patients were informed that participation was voluntary and that they could withdraw at any time. A medical investigator evaluated eligibility, obtained informed consent, and enrolled the participants during a selection visit that took place in the Clinical Research Center of University Hospital of Clermont-Ferrand. Patients were enrolled in the study if they met the inclusion criteria. The general aims, questionnaires, and pharmacologic treatment involved in the study were explained to each participant by the study investigators. Patients were required not to change their concomitant treatment during the study. In case of additional treatment, patients had to report it in their daily diary.

Eligibility criteria comprised the following: at least 18 yr of age, chronic pain for more than 3 months, peripheral or central pain requiring IV ketamine infusion, and no previous ketamine treatment (naïve patients). Exclusion criteria comprised the following: previous IV ketamine treatment; contraindication (1) to ketamine (hypersensitivity, uncontrolled high blood pressure, severe heart failure), (2) to magnesium (severe kidney failure), or (3) to sodium chloride (water inflation, fluid retention); medical/surgical history or drug treatment judged by the investigator to be incompatible with the trial; women of childbearing age without effective contraceptive method; pregnancy or lactation; involvement in another clinical trial; and inability to comply with protocol requirements.

Neuropathic pain was assessed by the investigator at inclusion with the four-item Neuropathic Pain Questionnaire.[23] This questionnaire is composed of 10 items. An affirmative answer is worth one point, a negative answer 0 point. For the diagnosis of neuropathic pain the threshold value has to be at least 4 of 10. Moreover, the following parameters were assessed by the investigator before inclusion: history of illness compatible with an injury or disease of the somatosensory system, localized pain in a neuroanatomical territory, and sensory abnormalities shown during neurologic examination.

Study Treatment

After inclusion, each patient received, in random order, by IV route: IV placebo/placebo (placebo), IV ketamine/placebo (ketamine), and IV ketamine/magnesium (ketamine/magnesium), every 35 days, this period refers to the elapsed time from each infusion. After the first period (35 days), patients came back to the Center for the second randomization. They were reevaluated and randomized if their pain intensity on the day of randomization was similar to pain intensity at inclusion. The same assessment was done before the third period.

Placebo was injectable physiologic saline (0.9% NaCl). Ketamine was administered at 0.5 mg/kg diluted in 45 ml physiologic saline (0.9% NaCl) for 2 h; magnesium infusion comprised two 0.15 g/ml ampoules (1.5 g per 10 ml)

diluted in 250 ml 0.9% NaCl for a total 3,000 mg magnesium administered over 30 min, or 100 mg/min.

Concerning ketamine doses, no national specific recommendations have been published for refractory chronic pain in France or in Europe. Recent works (NCT01602185) showed that the dosages administered and the duration and frequency of administration of ketamine vary greatly from one clinical team to another. The ketamine dose of 0.5 mg/kg was chosen according to the usual procedures of most pain clinics in France. Moreover, several studies of good methodologic quality used a dose ranging from 0.07 to 0.42 $mg \cdot kg^{-1} \cdot h^{-1}$.[1,2] According to these data, we chose a dose of 0.5 mg/kg for this randomized, controlled trial to provide an analgesic effect without serious adverse events.

Concerning magnesium effectiveness, several studies have been published in postoperative pain, but very few studies in neuropathic pain. One randomized, controlled trial used a IV dose of 500 mg (corresponding to 1 ml of 50%) over 5 min and 1,000 mg (corresponding to 2 ml of 50%) over 10 min (100 mg/min). They observed no serious adverse events and improvement in pain.[18]

Randomization and Blinding

Blocked randomization was performed by a clinical research associate completely independent of the study. The randomization ratio was 1:1:1. The randomization number was obtained from the hospital pharmacy by a clinical nurse who was independent of the trial, and patients were randomized according to the predetermined randomization list. Treatment packagings were identical to maintain blinding. To respect double-blinding, nurses were trained to the following procedure: A clinical nurse of the clinical research center independent from the protocol was isolated in a room dedicated to drug preparation and prepared the material and infusion. She then placed and strapped a sheet around the infusion support. A second nurse, belonging to the pain clinic, administered blindly the treatment as ketamine, magnesium, and placebo were all colorless liquids. The person who attended the patient with the questionnaires was not involved in other steps of the study. All patients were ketamine-naïve to avoid detection of the treatment by the patient, taking into account possible adverse events, such as a dysphoric effect that may accompany ketamine infusion.

Study Objectives and Endpoints

The primary objective was to assess the analgesic clinical effect of IV ketamine *versus* placebo in neuropathic pain patients. The primary endpoint was the area under the curve of average pain intensity assessed on a 0 to 10 numeric pain rating scale 35 days after infusions. Pain intensity during the day was assessed once a day during 35 days in a diary and these values were used to calculate the area under the curve. Secondary endpoints were assessed after each treatment period (ketamine; ketamine/magnesium and placebo) to study (1) the time-course of pain intensity: area under the curve of pain intensity on numeric pain rating scale at Day 7, 15, 21, and 28 after infusions (and Day 35 for ketamine/magnesium); maximum pain and night pain intensity on numeric pain rating scale in a daily pain diary; Brief Pain Inventory,[24] McGill pain questionnaire,[25] Neuropathic Pain Symptom Inventory,[26] and Patient Global Impression of Change; (2) concomitant analgesics on daily pain diary and the impact of the three treatments on (3) anxiety and depression, with the Hospital Anxiety and Depression scale,[27] (4) quality of life, with Short Form 36 Health Survey,[28,29] and (5) quality of sleep, with the Pittsburgh Sleep Quality Index.[30]

Sample Size

As previously reported,[22] to highlight the analgesic clinical effect of IV ketamine in patients with intractable neuropathic pain, the requisite sample size was estimated from a pilot study in the pain clinic of the University Hospital of Clermont-Ferrand (IV ketamine in a similar open-label population); 28-day area under the curve of pain intensity was 164 ± 38 (unpublished data). Furthermore, in a study comparing similar treatments (ketamine *vs.* placebo) in a different chronic pain setting (complex regional pain syndrome), area under the curve analysis suggested a 35% reduction in area under the curve at 28 days and that 18 patients were needed to detect an absolute difference of 57 for the primary outcome, with two-sided type I error of 2%, statistical power of 90%, and intraindividual correlation coefficient of 0.5 (owing to the crossover design, assuming no carry-over effect). Enrollment was stopped when the planned 20 patients had finished the trial and the target sample size was obtained.

Statistical Analysis

Statistical analysis was performed on an intention-to-treat basis using Stata software (version 13, StataCorp, USA) for two-sided type I error of 5%. Continuous data were reported as mean ± SD or median [interquartile range] according to the statistical distribution, with normality assessed on Shapiro-Wilk test. Areas under the curve were calculated using the trapezoidal rule. The primary endpoint was compared between groups by random-effects models for crossover designs, taking account of the following effects: treatment group, sequence, subject (as random effect), and carry-over. The normality of residuals and the sequence × treatment interaction were assessed. Analysis of continuous secondary endpoints was performed similarly to primary endpoint analysis. In case of nonnormal distribution, a logarithmic transformation was implemented. For categorical parameters, generalized linear mixed models (using the software logit link function) were used, taking the above effects into account. Random-effects models were

implemented to take account of between- and within-subject variability with the aforementioned effects, to compare the additive analgesic effect of associating magnesium sulfate *versus* placebo to ketamine, and to study the progression of pain and analgesia during treatment waning. When omnibus *P* values were less than 0.05, *post hoc* analysis for multiple comparison was applied using Sidak's type I error correction. Intraclass correlation coefficient was estimated.

Sensitivity analyses were applied to determine the statistical nature of the missing data. When the patient had not reported pain in the diary, this was considered as missing data. Missing data concerning average pain intensity are reported in Supplemental Digital Content, table 1 (http://links.lww.com/ALN/C378), table 2 (http://links.lww.com/ALN/C379), and table 3 (http://links.lww.com/ALN/C380). First, the last observation carry-forward approach was implemented for the primary and secondary endpoints: area under the curve of average pain intensity 35 days after infusion, area under the curve of maximum pain, and night pain intensity on a numerical pain rating scale in the daily pain diary. All the areas under the curve (for these outcomes) were calculated for 20 patients (data shown). Second, to support our conclusions, the method developed by Verbeke and Molenberghs[31] was also applied (data not shown). For the exploratory endpoints such as area under the curve of pain intensity on numerical pain rating scale at Day 7, 15, 21 and 28 after infusions, the statistical analyses were initially carried out without applying an imputation data approach. Furthermore, no missing data were observed for questionnaires (*i.e.*, Brief Pain Inventory, McGill pain questionnaire, Patient Global Impression of Change, Hospital Anxiety and Depression scale, Short Form 36 Health Survey, and Pittsburgh Sleep Quality Index).

Results

Patient Characteristics

Twenty-three patients were screened; two refused to participate in the study, one did not meet the inclusion criteria; finally, 20 gave written informed consent. They were randomized to ketamine/placebo, ketamine/magnesium, or placebo/placebo (fig. 1). All patients received the allocated treatment; none discontinued the study and all 20 patients were analyzed. Recruitment was carried out from November 10, 2015 to January 31, 2018, and the study finished in May 2018.

Demographics and clinical characteristics are summarized in table 1: age, weight, height, body mass index, pain

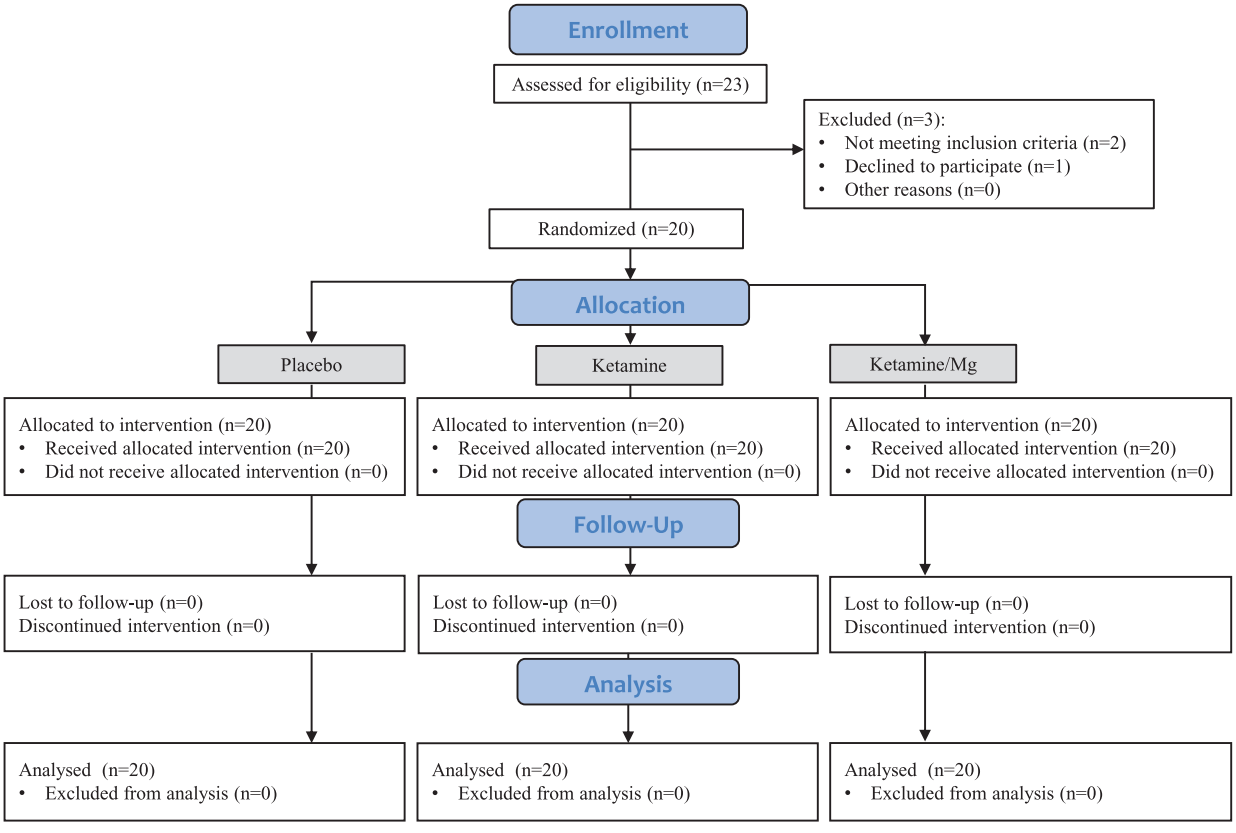

Fig. 1. Flowchart.

type, pain status, and concomitant treatment before first infusion. All patients were ketamine-naïve, experienced peripheral neuropathic pain for 5 [3; 12] years, owing to surgery (45%), radiculopathy (35%), trauma (10%), diabetes (5%), or chemotherapy (5%), with a mean four-item Neuropathic Pain Questionnaire score of 6 ± 2. At baseline, most patients were taking at least one of the following: antidepressants (65%), antiepileptics (45%), paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs; 40%), anxiolytics (40%), nefopam (5%), tramadol (20%), fentanyl (10%), or adjuvants (20%). Pain level of the 20 patients was similar before each treatment period (mean pain score: 7 ± 2; 6 ± 3 and 6 ± 2 for placebo, ketamine, and ketamine/magnesium period, respectively; $P = 0.174$).

Primary Endpoint

Daily pain intensity was not statistically significantly different between the three groups (n = 20) over the 35-day study period (mean area under the curve after the last observation carry forward imputation method: 185 ± 100, 196 ± 92, and 187 ± 90 pain score-days for ketamine, ketamine/magnesium, and placebo, respectively; $P = 0.296$; fig. 2 and table 2). The effect size for the main endpoint was −0.2 (95% CI [−0.6 to 0.3]; $P = 0.425$) for ketamine *versus* placebo, 0.2 (95% CI [−0.3 to 0.6]; $P = 0.445$) for placebo *versus* ketamine/magnesium, and -0.4 (95% CI [−0.8 to 0.1]; $P = 0.119$) for ketamine *versus* ketamine/magnesium. Intraclass correlation coefficient was equal to 0.89 for the primary endpoint (area under the curve at Day 35 after imputation data approach).

Secondary Endpoints

There was no difference between ketamine and placebo in the area under the curve of average daily pain at 15, 21, or 28 days, although there was a statistically smaller area for ketamine than placebo after 7 days (omnibus P value = 0.048 and 35 ± 25 *vs.* 41 ± 21 pain score-days, without imputation, $P = 0.042$; fig. 3 and table 2). Intraclass correlation coefficient was equal to 0.86 for area under the curve at Day 7. For this result at Day 7, very few missing data were observed, with similar trends and no impact on results.

There was no difference at any time point with ketamine/magnesium *versus* placebo. A number of patients nevertheless improved (decreased area under the curve) with ketamine and/or ketamine/magnesium at Day 7 (n = 10 of 20, fig. 4A) and at Day 35 (n = 5 of 20, fig. 4B).

Table 1. Demographics and Clinical Characteristics of Neuropathic Pain Patients at Baseline

	General Population n = 20	Male n = 10	Female n = 10
Clinical characteristics			
Age, yr	55 ± 12	52 ± 16	53 ± 15
Weight, kg	78 ± 17	77 ± 20	70 ± 23
Height, m	1.7 ± 0.4	1.7 ± 0.4	1.6 ± 0.4
Body mass index, kg/m²	27 ± 7	24 ± 6	26 ± 9
Peripheral neuropathic pain type			
Postsurgery	9 (45)	4 (40)	5 (50)
Radiculopathy	7 (35)	4 (40)	3 (30)
Posttraumatic	2 (10)	1 (10)	1 (10)
Postdiabetic	1 (5)	0 (0)	1 (10)
Postchemotherapy	1 (5)	1 (10)	0 (0)
Pain status			
Duration of pain, yr	5 [3–12]	6 [4–22]	4 [3–6]
Douleur Neuropathique 4 mean score	6 ± 2	5 ± 1	6 ± 2
Average pain	6 ± 3	6 ± 3	6 ± 3
Concomitant treatment			
Paracetamol/NSAIDs	8 (40)	4 (40)	4 (20)
Nefopam	1 (5)	1 (10)	—
Opiates			
Tramadol	4 (20)	3 (30)	1 (10)
Fentanyl	2 (10)	—	2 (20)
Antidepressants	13 (65)	6 (60)	7 (70)
Antiepileptics	9 (45)	4 (40)	5 (50)
Adjuvants	4 (20)	1 (10)	3 (30)
Hypnotics/Sedatives	2 (10)	—	2 (20)
Anxiolytics	8 (40)	4 (40)	4 (40)
Antipsychotics	1 (5)	—	1 (10)

Data expressed as mean ± SD, as median [interquartile range], and as percentages. NSAID, nonsteroidal anti-inflammatory drug.

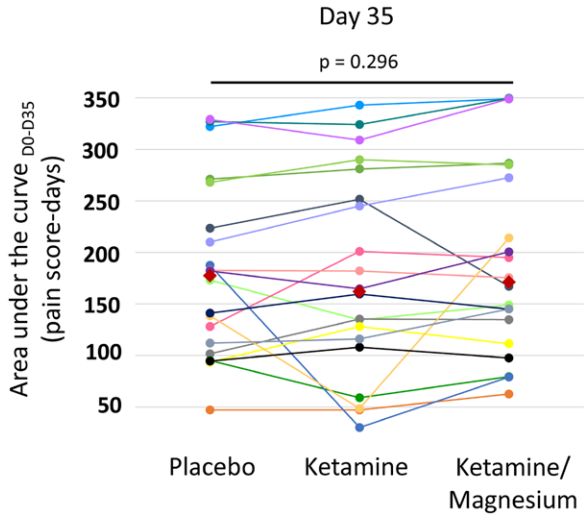

Fig. 2. Pain status per treatment group at Day 35 (primary outcome). Median area under the curve (pain score-days) of average daily pain at Day 35 after placebo, ketamine, and ketamine/magnesium infusion. The *red diamond* represents the median, and each *color point/line* represents individual patient area under the curve per treatment group. Statistical analyses were carried out using random-effects models taking into account treatment group, sequence, and subject (as random effect). The carry-over effect was specified but dropped from the model because of lack of effect (for carry-over; *i.e.* the result was obtained with models excluding this parameter).

Table 2. Pain Status after Each Treatment Period

Area Under the Curve (Pain Score-Days)	Placebo n = 20	Ketamine n = 20	Ketamine/Magnesium n = 20	*P* Value
Average daily pain				
Day 7	41 ± 21	35 ± 25	40 ± 25	0.048
Day 15	80 ± 39	74 ± 47	84 ± 48	0.156
Day 21	112 ± 54	107 ± 64	118 ± 65	0.312
Day 28	144 ± 71	138 ± 80	152 ± 79	0.288
Day 35	**187 ± 90**	**185 ± 100**	**196 ± 92**	**0.296**
Maximal pain (Day 35)	191 ± 89	205 ± 98	207 ± 97	0.291
Night pain (Day 35)	148 ± 113	146 ± 114	161 ± 107	0.261

Data are expressed as mean area under the curve (pain score-days) ± SD. Bold text indicates the primary outcome.

A few patients however improved with the placebo (n = 4 of 20 at 7 days and n = 3 of 20 at 35 days; fig 4, A and B).

There was no significant difference at Day 35 for area under the curve of maximal pain or night pain (table 2). Moreover, there was no significant difference in average pain between patients with two consecutive ketamine treatment periods (ketamine and ketamine/magnesium or ketamine/magnesium and ketamine) and those receiving placebo in between these two periods (area under the curve = 378 ± 212 pain score-days, for consecutive *vs.* 343 ± 151 pain score-days, for nonconsecutive ketamine treatment periods, $P = 0.883$).

Pain, health-related, emotional, sleep, and quality of life questionnaires scores are presented in table 3. Each questionnaire was administered at baseline and every 35 days, before randomization of the treatment of the following period. There were no statistically significant differences between the three groups regarding pain (McGill global score, Neuropathic Pain Symptom Inventory global score, and Brief Pain Inventory subscores), emotional status (Hospital Anxiety and Depression scale anxiety and depression), sleep (Pittsburgh Sleep Quality Index global score), quality of life (Short Form 36 Health Survey physical and mental health score), or patient satisfaction (Patient Global Impression of Change global score).

Safety

No serious adverse events occurred during the study. During placebo, ketamine, and ketamine/magnesium infusions, 2 of 20 (10%), 4 of 20 (20%) and 7 of 20 (35%) patients, respectively, had at least one adverse event deemed possibly, probably, or certainly treatment-related; 7 of 20 (35%) had no adverse events during the trial.

With placebo, 15% of patients experienced fatigue and 5% had nausea. With ketamine, 20% had fatigue, 15% nausea, 10% a feeling of drunkenness, 5% insomnia, 5% hypertension, 5% headache, and 5% hot flushes. With ketamine/magnesium, 15% of patients had fatigue, 15% nausea, 10% vomiting, 10% dizziness, 10% high blood pressure, 5% a feeling of drunkenness, 5% headache, 5% hot flushes, and 5% breathing difficulty.

Concomitant Treatment

Analgesic consumption was overall stable during the trial, with only a few patients taking additional drugs (table 4) for dental or respiratory issues, joint or severe pain.

Discussion

The present trial explored the analgesic effect of a single IV administration of 0.5 mg/kg ketamine and ketamine/magnesium compared with placebo, over a period of 5 weeks

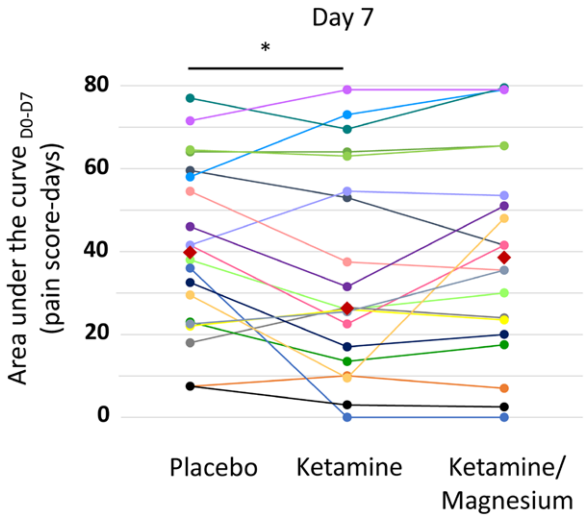

Fig. 3. Pain status per treatment group at Day 7 (secondary outcome). Median area under the curve (pain score-days) of average daily pain at Day 7 after placebo, ketamine, and ketamine/magnesium infusion. The *red diamond* represents the median, and each *color point/line* represents individual patient area under the curve per treatment group. Statistical analyses were carried out using random-effects models taking into account treatment group, sequence, and subject (as random effect). The carry-over effect was specified but dropped from the model because of lack of effect (for carry-over; *i.e.*, the result was obtained with models excluding this parameter).

in neuropathic pain patients. The main results show that the analgesic effect of (1) ketamine and (2) ketamine combined with magnesium were not significantly different *versus* placebo at 5 weeks, with no serious adverse events, and that (3) magnesium provided no additional analgesia to the effect of ketamine.

The use of ketamine as an analgesic drug for neuropathic pain has been reviewed in the literature.[8–10,32,33] Although a few guidelines have been published in chronic pain,[8] the overall evidence for an analgesic effect is weak.[8–10] The effect of ketamine in chronic pain has been mainly studied with less than 2 to 3 weeks follow-up. Concerning the IV route, only one study[11] explored ketamine in neuropathic pain for more than 3 weeks, with negative findings.

As often suggested in the literature, magnesium may have an additive effect with ketamine[34] because both molecules share the NMDA receptor as a target of action. Magnesium alone has often been shown, with conflicting results, to have an impact on pain in animals[15–17] and on quality of life and stress in humans.[20,35] In neuropathic pain, magnesium is reported to be used alone[18] or in combination with morphine.[15,17] In our trial, magnesium did not add any additive effect to ketamine analgesic effect.

Our trial followed patients up for 5 weeks and suggests an improvement in pain for one week only with ketamine. However, the clinical significance of the isolated and small difference in pain over time at 7 days between the ketamine and placebo groups is unknown. This duration is shorter than in complex regional pain syndrome studies (4 and 12 weeks),[1,2] where much higher doses of ketamine have been used. It is interesting to note that Schwartzman *et al.*[1] used clonidine before and after every ketamine infusion to optimize the neuropathic pain-relieving action of NDMA receptor blockers like ketamine and midazolam and diminish anxiety. Moreover, the concomitant use of midazolam and clonidine may have controlled the hallucinogenic and dysphoric effects of ketamine.[36]

It is also informative to observe that patients who received two consecutive doses of ketamine (alone or with magnesium; n = 12 of 20) at a 35-day interval did not improve more than those receiving placebo in between, suggesting that blood and brain ketamine concentrations may be too weak to trigger a "reset in the central nervous system"[8] that could explain ketamine's pain relief mechanism of action in reversing or halting central sensitization in neuropathic pain. Repeat infusions may have a larger effect size than a single infusion as shown with only moderate evidence in depression.[8,37] In clinical settings, it is still difficult to optimize ketamine administration because of the diversity of infusion protocols and the lack of face to face comparisons between protocols.[8,9] In this context, an observational study (NCT03319238) in 585 patients with refractory chronic pain is currently ongoing in French pain clinics, aiming to identify a satisfactory risk/benefit ratio for the dose, duration and frequency of ketamine administration.

We observed that a few patients maintained their improvement between 7 and 35 days with ketamine or ketamine/magnesium *versus* placebo. A larger-scale future study might help to identify ketamine responders beyond one week. It is important to note that some patients also improved with the placebo. Our study included only

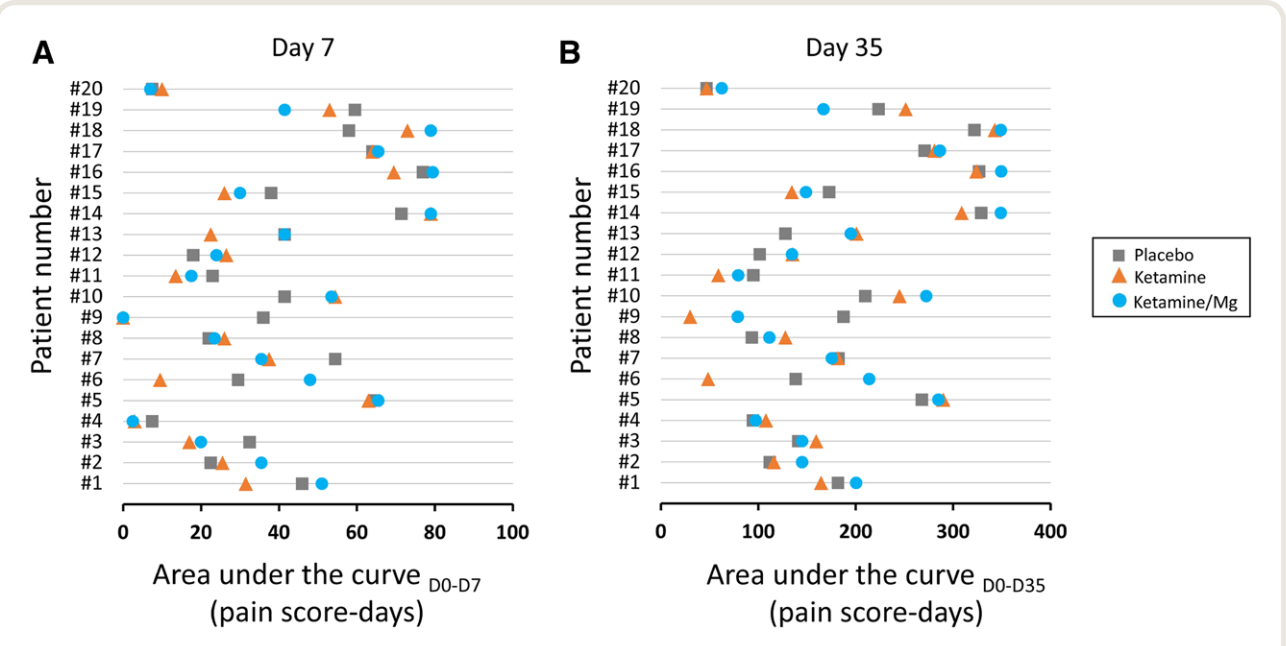

Fig. 4. Pain status per patient. Area under the curve (pain score-days) of average daily pain at Day 7 (*A*) and at Day 35 (B) after placebo, ketamine, and ketamine/magnesium for patients number 1 to 20. Data are expressed as area under the curve per patient.

Table 3. Psychologic Parameters and Quality of Life of Neuropathic Pain Patients at Baseline and after Placebo, Ketamine, and Ketamine/Magnesium Infusions

	Baseline n = 20	Placebo n = 20	Ketamine n = 20	Ketamine/Magnesium n = 20	*P* Value
McGill global score	99 ± 41	82 ± 51	90 ± 51	83 ± 44	0.408
Sensory subclass	53 ± 27	43 ± 28	48 ± 29	44 ± 29	0.477
Affective subclass	47 ± 19	39 ± 26	42 ± 24	39 ± 20	0.527
Neuropathic Pain Symptom Inventory global score	43 ± 18	39 ± 23	41 ± 24	37 ± 23	0.638
Burning spontaneous pain	5 ± 3	5 ± 4	5 ± 4	4 ± 4	0.142
Pressing spontaneous pain	4 ± 3	3 ± 4	4 ± 3	3 ± 4	0.482
Paroxysmal pain	5 ± 3	3 ± 4	4 ± 3	4 ± 3	0.563
Evoked pain	4 ± 3	4 ± 3	4 ± 3	4 ± 3	0.962
Paresthesia/dysesthesia	5 ± 3	4 ± 3	4 ± 3	4 ± 3	0.703
Brief Pain Inventory					
Average pain severity	6 ± 2	6 ± 2	6 ± 3	6 ± 2	0.527
Patient's pain experience	6 ± 2	5 ± 2	5 ± 2	6 ± 2	0.784
Improvement percent with treatment	Not applicable	27 ± 33	22 ± 33	16 ± 26	0.285
Interference of pain with affect	4 ± 3	4 ± 3	4 ± 3	4 ± 2	0.767
Interference of pain with activity	6 ± 2	6 ± 2	6 ± 2	6 ± 2	0.728
Hospital Anxiety and Depression scale – Anxiety score	9 ± 5	7 ± 4	8 ± 4	7 ± 4	0.155
Hospital Anxiety and Depression scale – Depression score	9 ± 5	7 ± 5	8 ± 5	7 ± 4	0.484
Short Form 36 Health Survey physical health	30 ± 10	32 ± 8	32 ± 9	32 ± 10	0.804
Short Form 36 Health Survey mental health	42 ± 13	43 ± 13	44 ± 14	44 ± 13	0.892
Physical Function	37 ± 31	43 ± 33	43 ± 28	41 ± 28	0.851
Role-Physical	30 ± 38	28 ± 31	30 ± 31	34 ± 37	0.733
Body Pain	23 ± 14	31 ± 18	34 ± 19	30 ± 18	0.434
General Health	47 ± 12	49 ± 12	47 ± 12	47 ± 10	0.717
Vitality	33± 17	39 ± 18	35 ± 19	36 ± 16	0.635
Social Functioning	53 ± 28	62 ± 31	59 ± 30	62 ± 32	0.926
Role Emotional	47 ± 42	40 ± 43	57 ± 42	55 ± 41	0.270
Mental Health	52 ± 24	57 ± 17	56 ± 19	57 ± 20	0.857
Patient Global Impression of Change global score	Not applicable	4 ± 1	4 ± 1	4 ± 1	0.886
Pittsburgh Sleep Quality Index global score	12 ± 5	11 ± 6	10 ± 6	10 ± 5	0.295
Subjective sleep quality	2 ± 1	2 ± 1	2 ± 1	2 ± 1	0.349
Sleep latency	1 ± 1	2 ± 1	1 ± 1	1 ± 1	0.119
Sleep duration	2 ± 1	2 ± 1	2 ± 1	2 ± 1	0.599
Habitual sleep efficiency	2 ± 1	2 ± 1	2 ± 1	2 ± 1	0.734
Sleep disturbances	1 ± 1	1 ± 1	1 ± 1	1 ± 1	0.021
Use of sleep medication	1 ± 1	1 ± 2	1 ± 2	1 ± 1	0.066
Daytime dysfunction	2 ± 1	2 ± 1	2 ± 1	2 ± 1	0.842

Data are expressed as mean ± SD.

ketamine-naïve patients who had never experienced the effect of ketamine, and this may explain the strong placebo effect we observed. The contextual effect may have also influenced the patient's feelings, a phenomenon previously reported in knee osteoarthritis[38] and fibromyalgia.[39] It has been suggested that high levels of empathy are linked to positive patient outcomes, particularly in the context of chronic pain.[40]

The study also followed up a number of domains over 5 weeks: depression, anxiety, quality of life, sleep, and patient satisfaction. No significant differences between groups emerged.

In depression, ketamine has in recent years been considered as a possible treatment, especially when suicidal ideation is present. Many studies reported that ketamine provides a rapid antidepressant effect with an onset 40 min after a single IV infusion in major depressive disorder and bipolar depression, and peak effect at 24 h postinfusion.[41,42] This effect on depression is however transient and disappears 1 to 2 weeks postinfusion. Although in our study patients had depressive symptoms, the lack of effect may be due to variations of modulation according to depression severity[43] or cause.[44]

Concerning sleep, only the Patient Global Impression of Change sleep disturbance subscore showed an improvement ($P = 0.021$). In patients with major depressive disorder or bipolar depression, sleep homeostatic and circadian components have been shown to both modulate and mediate the antidepressant and antisuicidal effects of ketamine through its capacity to increase neurotrophic activity and synaptic strength, normalize sleep, and reinforce the circadian system.[45] Pain patients would benefit from sleep improvement, because lack of sleep impacts dramatically the burden of pain.[46]

Table 4. Concomitant Analgesics Drugs of Neuropathic Pain Patients Taken Punctually during the Study Period in Addition to Their Baseline Treatment

	Placebo n = 20	Ketamine n = 20	Ketamine/Magnesium n = 20
Paracetamol/NSAIDs	2 (10)	1 (5)	—
Nefopam	1 (5)	1 (5)	1 (5)
Tramadol	1 (5)	—	—
Paracetamol/opium	1 (5)	—	1 (5)
Antidepressants	—	—	—
Antiepileptics	—	—	—
Adjuvants	—	1 (5)	1 (5)
Hypnotics/sedatives	—	—	1 (5)
Anxiolytics	1 (5)	—	—
Antipsychotics	—	—	—

Data are expressed as effective (percentage). NSAID, nonsteroidal anti-inflammatory drug.

This study has several limitations. The absence of an analgesic effect at 5 weeks may be linked to too low a dose of ketamine, although some patients had some pain relief. Some studies reported that larger doses of ketamine may decrease pain to a greater extent.[33] However, a recent meta-analysis showed that ketamine administration at higher doses (cumulative dose more than 400 mg) *versus* low doses did not result in a better improvement in pain.[8,47] On the other hand, it has been suggested that the analgesic effect of ketamine could be optimized with a longer duration of infusion but also by combining with other molecules such as midazolam or cloninide.[1]

In our study, patients were all ketamine-naïve to avoid early recognition of the treatment and maintain double-blinding. Nurses were trained to a specific procedure when the treatment was administered. In addition, at the end of the protocol, patients were questioned informally to identify whether they had guessed the order of treatments they received, and their answer was "No" in 50 to 75% of them. Blinding is, however, difficult to achieve satisfactorily with ketamine. In both complex regional pain syndrome studies, 90% of patients (28 of 30) in the Sigtermans study knew which treatment they received,[2] and Schwartzman *et al.*[1] used positive placebos (midazolam and clonidine) to effect blinding. Although it could be relevant to assess blinding in such a study, there has been a debate concerning the importance of testing the blinding. The Consolidated Standards of Reporting Trials 2010 statement[48] removed this blinding assessment because the authors suggested that blinding on the basis of patient's guess could be influenced by whether or not they observed an improvement with treatment. The authors of the review explained that if the patient guessed the treatment allocation, failed blinding could be a marker of an effective treatment.[48]

Conclusion

Taken together, the present data did not show an analgesic effect of ketamine or ketamine combined with magnesium 5 weeks postinfusion in ketamine-naïve neuropathic pain patients. No major immediate or late improvement in psychologic or health-related components were observed. This limited effect may result from too low a dose, drug competition, small number of patients, or from a strong placebo effect related to naivety. Some patients, however, did show an improvement with ketamine, suggesting different responder profiles that need to be studied further to identify predictive factors for an analgesic effect and to reach a consensus on the use of ketamine in refractory neuropathic pain.

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Competing Interests

Dr. Delage declares conflicts of interest with Grunenthal laboratories, Nanterre, France (regional board membership) with no links with this article. The remaining authors declare no competing interests.

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Full protocol available at: gisele.pickering@uca.fr. Raw data available at: gisele.pickering@uca.fr.

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