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# Efficacy of Outpatient Ketamine Infusions in Refractory Chronic Pain Syndromes: A 5-Year Retrospective Analysis

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## Abstract

**Objective. We evaluated whether outpatient intravenous ketamine infusions were satisfactory for pain relief in patients suffering from various chronic intractable pain syndromes.**

**Design. Retrospective chart review.**

**Setting and Patients. Following Institutional Review Board approval, we retrospectively analyzed our database for all ketamine infusions administered over 5 years from 2004 to 2009.**

**Outcome Measures. Data reviewed included doses of intravenous ketamine, infusion duration, pain scores on visual analog scale (VAS) pre- and post-procedure, long-term pain relief, previous interventions, and side effects. All patients were pretreated with midazolam and ondansetron.**

**Results. We identified 49 patients undergoing 369 outpatient ketamine infusions through retrospective analysis. We excluded 36 infusions because of missing data. Among our patients, 18 (37%) had a diagnosis of complex regional pain syndrome (CRPS). Of the remaining 31 (63%) patients, eight had refractory headaches and seven had severe back pain. All patients reported significant reduction in VAS score of 5.9 (standard error [SE] 0.35). For patients with CRPS, reduction in VAS score was 7.2 (SE 0.51, $P < 0.001$); for the others, the reduction was 5.1 (SE 0.40, $P < 0.001$). The difference of 2.1 between groups was statistically significant (SE 0.64, $P = 0.002$). In 29 patients, we recorded the duration of pain relief. Using the Bernoulli model, we found (90% confidence interval) that the probability of lasting pain relief in patients with refractory pain states was 59–85% (23–51% relief over 3 weeks).**

**Conclusions. We conclude that in patients with severe refractory pain of multiple etiologies, subanesthetic ketamine infusions may improve VAS scores. In half of our patients, relief lasted for up to 3 weeks with minimal side effects.**

**Key Words. Ketamine; CRPS; Chronic Pain; Pain Management**

## Introduction

Chronic pain affects over 76 million people in the United States. Long-standing intractable pain can be particularly challenging to treat and resistant to multiple treatment modalities. Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to be effective in patients with complex regional pain syndrome (CRPS) and has also been studied for its effectiveness with pain syndromes in an intraoperative setting [1,2]. There is still some reluctance, however, to use ketamine in the management of chronic pain. As an anesthetic, ketamine has been associated with drowsiness, dizziness, disorientation, and hallucinations. These psychotomimetic side effects have likely limited the use of ketamine for management of pain in outpatients.

NMDA receptors are activated by the excitatory neurotransmitter glutamate and have a known involvement in various forms of neural plasticity, both short and long term. By this mechanism, the NMDA receptors and their antagonist, ketamine, may be crucially involved in chronic pain pathways.

The first evidence of clinical relief of neuropathic pain by ketamine was found in clinical case reports from patients with cancer pain from nerve injury [3]. Since then, several controlled studies have been performed with intravenous ketamine for post-herpetic neuralgia, diabetic neuropathy, and CRPS [1,4,5]. Ketamine has also been used in low doses to relieve fibromyalgia-related pain symptoms [6,7].

Because of the analgesic efficacy of intravenous subanesthetic doses of ketamine, we routinely administer it to outpatients with severe intractable pain syndromes, for whom conventional treatments are unsuccessful. We hypothesized that intravenous infusions of ketamine in outpatients would offer satisfactory pain relief from chronic intractable pain syndromes of many etiologies.

## Materials and Methods

Following IRB approval, a database from a university pain clinic was retrospectively analyzed for the period from 2004 to 2009. All patients had refractory pain for at least 6 months and received low-dose outpatient ketamine infusion treatments after being informed of its risks and giving consent. Patient records were reviewed for demographics, doses of intravenous ketamine, infusion duration, pain scores on a visual analog scale (VAS) pre- and post-treatment, previous pain clinic interventions, and side effects. Infusions were administered by a physician. Standard monitors were applied throughout treatment, including electrocardiography, pulse oximetry, blood pressure every 5 minutes, and oxygen therapy as needed. Patients were monitored for 30–60 minutes after infusions and before discharge home. No changes were made in their medications on the day of infusion, and no changes had been made to their medications in the previous month.

All patients were pretreated with midazolam and ondansetron. The initial dose of ketamine was 0.5 mg/kg given over 30–45 minutes. If this dose was effective, it was continued in subsequent infusions. If tolerated, the dose was increased at subsequent infusion to the highest tolerated dose producing analgesia without unacceptable side effects. Ketamine infusions were discontinued when pain relief was not adequate.

The efficacy of the treatment was measured with pain scores recorded pre- and post-infusion on a VAS of 0–10. A score of 0 indicated no pain, and 10 corresponded to the worst pain imaginable. The reduction in pain score was tabulated, and adverse effects were recorded at each infusion.

The change in VAS (data given as mean with standard deviation [SD] or median with ranges) was computed using a mixed effects model with autoregressive (AR) correlation for the repeated measures. Incidence was defined as the number of events and the number of patients experiencing at least one treatment-related adverse event during the treatment period. Data on safety were tabulated separately for the patients with and without CRPS. All of the analyses were conducted using Statistical Productive analytic software (PASW Statistics 18.0, Chicago, IL, USA). The level of significance was set at $P < 0.05$.

The ketamine infusions were scheduled routinely every 3–4 weeks per pain clinic protocol. For evaluating the long-term pain relief with the intravenous ketamine infusion, we contacted the patients on the roster and asked directly about the duration of pain relief following treatment. We asked the patients about their pain score at the conclusion of the ketamine infusion. We then asked how long this score was maintained. A few patients responding to the infusions were also prescribed memantine. They were followed up for the efficacy of the treatment.

## Results

We identified 49 patients who had a total number of 369 outpatient ketamine infusions. Three infusions were excluded from analysis because of missing data. Based on our review of patient's charts, outpatient ketamine infusion was considered as a potential, last-line adjuvant therapy in cases with refractory pain, only partially responsive to conventional treatments. As a consequence, only approximately 10 patients per year were offered and underwent outpatient ketamine infusions. Demographics and patient characteristics are described in Table 1. Overall, the median patient age was 45 (range, 18–68 years). The majority (63.3%) of the patients were female. The average weight was 83.8 kg (±23.9 kg). The median number of infusions per patient was 4 (range 1–36).

Figure 1 shows that CRPS was diagnosed in 18 patients (37%). Of the remaining 31 patients (63%) with intractable pain syndromes, eight had refractory headaches and seven had severe back pain. Figure 1 illustrates the distribution of diagnoses. All patients had chronic unrelenting pain for at least 6 months, with a mean duration of pain symptoms of 5.62 years. They underwent extensive diagnostic and treatment modalities including, but not limited to, somatic (neuraxial or peripheral) and/or sympathetic

**Table 1** Demographics and patient characteristics

| | Patient Subgroup | | |
|---|---|---|---|
| | CRPS (N = 18) | Non-CRPS (N = 31) | Total (N = 49) |
| Age (years) | | | |
| Median | 46 | 42 | 45 |
| Range | 21–55 | 18–68 | 18–68 |
| Gender, n (%) | | | |
| Female | 11 (61.1) | 20 (64.5) | 31 (63.3) |
| Male | 7 (38.9) | 11 (35.5) | 18 (36.7) |
| Weight (kg) | | | |
| Mean | 79.9 | 86.1 | 83.8 |
| SD | 21.3 | 25.3 | 23.9 |
| Number of infusions | | | |
| Median | 5.5 | 3 | 4 |
| Range | 1–36 | 1–34 | 1–36 |
| Total | 153 | 210 | 363 |
| VAS at baseline | | | |
| Mean (SD) | 8.2 (1.7) | 6.7 (1.9) | 7.2 (2.0) |
| 95% CI | 7.4, 9.1 | 6.0, 7.4 | 6.7, 7.8 |

CRPS = complex regional pain syndrome; VAS = visual analog scale; SD = standard deviation; CI = confidence interval.

| Diagnosis | Number of patients |
|---|---|
| CRPS | 18 |
| Intractable headache | 8 |
| Chronic back pain | 7 |
| Somatic pain | 5 |
| Fibromyalgia/myalgias | 4 |
| Central neuropathic pain | 4 |
| Postherpetic neuralgia | 2 |
| Cervical radiculopathy | 1 |

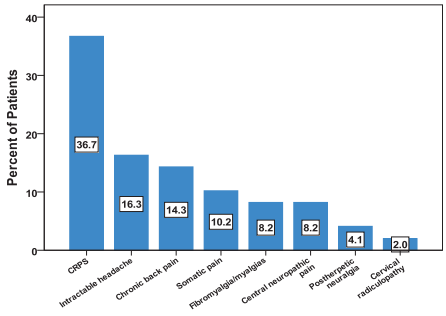


**Figure 1** Patient subgroups by diagnosis. CRPS = complex regional pain syndrome.

nerve blocks, spinal cord or peripheral nerve stimulation, various surgical decompressions or interventions, various injections (trigger points, scar infiltrations, field blocks, joint injections) physical therapy, psychotherapy, and medical management. Upon offering the outpatient ketamine infusion as a treatment option, all the treatments mentioned above failed to provide satisfactory pain relief. In addition, all patients exhibited signs of central sensitization as evidenced by presence of an increased area of perceived pain in the absence of a specific, identifiable nociceptor as well as worsening pain with minimal stimuli.

The infusion data are described in Table 2. Ketamine infusions were administered for a median of 38.3 minutes (range, 30 minutes to 8 hours). Mean (SD) total ketamine dose per infusion was 0.9 (±0.4) mg/kg. Median duration between infusions was 233.7 days (range 12–680 days). Before infusion, mean VAS was 7.6 (±1.9) for all patients. For patients with CRPS, mean score was 8.5 (±1.1), and for the others it was 7.0 (±2.0). After infusion, the median VAS overall was reduced to 0.9. The change in VAS was computed using a mixed effects model that took into account the repeated measures per patient. All patients reported a significant reduction in VAS score of 5.9 (standard error [SE] 0.35) or 77% pain relief. For patients with CRPS, reduction in VAS score was 7.2 (SE 0.51, $P < 0.001$); for the others, the reduction was 5.1 (SE 0.40, $P < 0.001$). The difference of 2.1 between the two groups was statistically significant (SE 0.64, $P = 0.002$).

A total of 35 nonserious adverse events were reported by 23 (46.9%) patients (Table 3), 9 (50.0%) patients with CRPS, and 14 (45.2%) others. Hypertension and sedation were among the most common adverse events in both groups. Comparatively, there was a higher incidence of hallucination and confusion in patients without CRPS. In all cases, the side effects were minimal.

Unfortunately, we did not have data for long-term relief for all the patients. However, we attempted telephone interviews for all the patients on the roster. We were able to contact only the patients for whom current contact information was available. We identified 29 (59%) patients from our 49 patients included in the study. When contacted, the patients were asked about pre- and post-infusion pain scores as well as how long the post-infusion scores were maintained. Duration of pain relief after ketamine infusions was defined as time period until the low pain score

**Table 2** Infusion data by patient subgroup

| | Patient Subgroup | | |
|---|---|---|---|
| | CRPS (N = 18) | Non-CRPS (N = 31) | Total (N = 49) |
| Infusion dose (mg/kg) | | | |
| Mean | 1.0 | 0.9 | 0.9 |
| SD | 0.5 | 0.4 | 0.4 |
| Infusion duration (minute) | | | |
| Median | 43.8 | 34.7 | 38.3 |
| Range | 30–60 | 30–165 | 30–165 |
| Days between infusion | | | |
| Median | 30.8 | 34 | 33.7 |
| Range | 18–680 | 12–95 | 12–680 |
| VAS before infusion | | | |
| Mean | 8.5 | 7.0 | 7.6 |
| SD | 1.1 | 2.0 | 1.9 |
| VAS after infusion | | | |
| Median | 0.8 | 1.0 | 0.9 |
| Range | 0–6 | 0–9 | 0–9 |

CRPS = complex regional pain syndrome; SD = standard deviation; VAS = visual analog scale.

**Table 3** Adverse events

| | Patient Group: N (%) of Patients | | |
|---|---|---|---|
| | CRPS (N = 18) | Non-CRPS (N = 31) | Total (N = 49) |
| Any event | 9 (50.0%) | 14 (45.2%) | 23 (46.9) |
| Agitation | 1 (5.7%) | 1 (3.2%) | 2 (4.1%) |
| Confused state | 1 (5.7%) | 2 (6.5%) | 3 (6.1%) |
| Disorientation | 0 (0.0%) | 1 (3.2%) | 1 (2.0%) |
| Dissociation | 0 (0.0%) | 1 (3.2%) | 1 (2.0%) |
| Feeling cold | 0 (0.0%) | 1 (3.2%) | 1 (2.0%) |
| Hallucination | 1 (5.7%) | 4 (13.2%) | 5 (10.2%) |
| Hypertension | 4 (22.2%) | 2 (6.5%) | 6 (12.2%) |
| Nausea | 1 (5.7%) | 1 (3.2%) | 2 (4.1%) |
| Nystagmus | 0 (0.0%) | 1 (3.2%) | 1 (2.0%) |
| Paresthesia | 0 (0.0%) | 1 (3.2%) | 1 (2.0%) |
| Pharyngolaryngeal pain | 0 (0.0%) | 1 (3.2%) | 1 (2.0%) |
| Restlessness | 1 (5.7%) | 0 (0.0%) | 1 (2.0%) |
| Sedation | 2 (11.1%) | 2 (6.5%) | 4 (8.0%) |
| Somnolence | 0 (0.0%) | 1 (3.2%) | 1 (2.0%) |
| Tachycardia | 1 (5.7%) | 0 (0.0%) | 1 (2.0%) |
| Vertigo | 0 (0.0%) | 1 (3.2%) | 1 (2.0%) |
| Vomiting | 2 (11.1)% | 1 (3.2%) | 3 (6.1%) |

CRPS = complex regional pain syndrome.
One patient may have experienced more than one adverse event.

obtained at the conclusion of their treatment started to increase. In all the cases, the analgesic regimen was not altered. When asked about functional status, patients reported subjective improvements in quality of life after ketamine infusion such as improved exercise tolerance and increased energy.

Eight (27%) of the 29 patients contacted reported pain relief lasting several hours after the ketamine infusion. Twenty-one patients (73%), considered responders to the treatment, reported pain relief for more than 1–2 days; for 11 (38%) of them, relief lasted more than 3 weeks.

Using a Bernoulli statistical model, we stated the hypothesis that ketamine infusion is effective in intractable pain states and calculated the probability that a random patient suffering from severe chronic pain would respond to this treatment. This probability is the $p$ parameter of the Bernoulli trial. To carry out the confidence interval calculations, we used the standard approximation of the outcomes in a repeated Bernoulli trial to a normal distribution. The second assumption we made was that the patients were statistically independent. This was considered appropriate as upon review of all patients' demographic data, there were no obvious common patterns. We proceeded on calculating the 90% confidence interval using the mathematical formulae associated with the chosen statistical model.

The main statistical estimator was the outcome mean, $M = \frac{1}{N}\sum_{i=1}^{N} R_i$, where $R_i$ denotes the random variable for the outcome of the treatment on a given patient, and assumes a value of 1 in case of success and 0 otherwise, and $N$ is the number of trials. Based on the normal approximation, the $1 - \alpha$ two-sided confidence interval for the unknown parameter $p$ can be computed as

$$\left[ M - z\left(1-\frac{\alpha}{2}\right)\sqrt{\frac{M(1-M)}{N}}, M + z\left(1-\frac{\alpha}{2}\right)\sqrt{\frac{M(1-M)}{N}} \right]$$

Here, $z(r)$ is the $r$-quantile of the standard normal distribution. In particular, for $\alpha = 0.1$, we obtain that $z(0.95) \approx 1.65$.

For 90% confidence interval, when taking into consideration only the patients contacted regarding the duration of pain relief (29), our calculations showed 59–85% probability that a patient with severe pain would respond favorably (either short or long term) to the ketamine infusion with 23–51% probability that this pain relief in this random patient would last more than 3 weeks. If assumed that all the patients not contacted did not have long-standing pain relief, for the total number of patients (49), the calculations showed 31–53% chance that a random patient would respond to the ketamine infusion with lasting pain relief, but only 13–31% probability that this relief will last more than 3 weeks. The results of this analysis (Table 4) were statistically significant showing a favorable effect when compared with the alternative.

Nine (18%) of the 49 patients evaluated were given memantine, an oral NMDA-receptor antagonist at the current Food and Drug Administration approved dose of 10 mg po bid, after they had at least one successful outpatient ketamine infusion. The oral regimen with memantine was started with the purpose of gradually transitioning patients from intravenous therapy to an oral

**Table 4** Results of the mathematical calculations based on the statistical Bernoulli model showing favorable outcome (long-term pain relief) after ketamine infusion (90% confidence interval)

| | Nt | Nc | Rt | Rl |
|---|---|---|---|---|
| Numbers of patients | 49 | 29 | 21 | 11 |
| $p$ (Nc) | N/A | 100% | 59–85% | 23–51% |
| $p$ (Nt) | 100% | N/A | 31–53% | 13–31% |

Nt = total number of patients (N total); Nc = number of patients contacted (N contacted); Rt = number of patients reporting more than 1–2 days pain relief in response to ketamine infusion (responders total); Rl = number of patients reporting more than 3 weeks pain relief in response to ketamine infusion (responders long); $p$ (Nc) = chance of a random patient to respond to ketamine infusion based on the number of patients contacted; $p$ (Nt) = chance of a random patient to respond to ketamine infusion based on the total number of patients; N/A = not applicable.

regimen. Table 5 summarizes those results. The mean dose of ketamine per infusion for these patients was 0.65 mg/kg (range 0.3–1.2 mg/kg). Mean reduction of pain from ketamine infusions was 65% (range 0–100%), and mean pain reduction after starting memantine was 22% (range 0–60). Three of the patients had CRPS, and the other six patients had chemo-induced neuropathy, neurofibromatosis, Brown–Sequard syndrome, visceral pain, headache, or spinal stenosis. Three patients experienced side effects from memantine. Six (66%) patients reported improved quality of life with memantine (either improved sleep quality or enhanced pain relief from subsequent ketamine infusions).

## Discussion

Ketamine acts both centrally and peripherally. Its action is mediated by multiple receptor subtypes including opioid, NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate, kainite, and gamma-amino butyric acid A receptors [8]. In chronic pain, ketamine appears to interact with the NMDA receptor. When stimulated, primarily by the excitatory neurotransmitter glutamate, the NMDA receptor leads to central sensitization via an upregulating feedback mechanism, a potential pathway for chronic pain. Reversal of central sensitization by NMDA-receptor antagonists such as ketamine is believed to reduce pain and may reduce the amount of opioid analgesics patients need as well [9,10]. Ketamine also has been shown to decrease opioid tolerance through an interaction between NMDA receptors, the nitric oxide pathway, and μ-opioid receptors [11].

Psychomimetic actions of ketamine and its perceived unfavorable clinical risk–benefit ratio preclude its wide use as a pain management agent. However, a growing body of literature supports the use of ketamine in low doses as an analgesic [8]. It has been used in the treatment of various neuropathic pain syndromes and CRPS in subanesthetic intravenous doses [4,12–15].

Early evidence suggestive of clinical relief of neuropathic pain in patients with cancer pain involving nerve injury was followed by several controlled studies using low-dose ketamine for a few other conditions (post-herpetic neuralgia, diabetic neuropathy, CRPS, and fibromyalgia) [1,3–7]. Much of the research has been focused on neuropathic pain and far less studies investigates effects of intravenous ketamine on other chronic pain states. Twenty-five milligrams of intranasal ketamine was demonstrated to be an effective treatment for severe disabling aura in patients with severe familial hemiplegic migraine [16]. However, only two of the 11 patients studied demonstrated reduction in their headache quality.

Our results are supported by those of several other studies. Krusz [17] had a high success rate with ketamine for patients with multiple refractory pain syndromes.

This retrospective review found good efficacy for ketamine infusions in a variety of clinical situations with a safe

**Table 5** Patients transitioned to oral memantine

| | | Ketamine Infusions | | Memantine Treatment | | | |
|---|---|---|---|---|---|---|---|
| Diagnosis | Age/ Gender | Pain Reduction (%) | Duration of Pain Reduction | Pain Reduction (%) | Side Effects | Subjective Improvement in Quality of Life | Continued Ketamine Infusions After Memantine |
| CRPS | 40/F | 8 | 2 weeks | 60 | Sedation | Yes | No |
| CRPS | 45/F | 40 | 1.5 weeks | 40 | Headache | Yes | Yes* |
| CRPS | 39/F | 95 | 4 weeks | 0 | No | Yes | Yes |
| Chemo-induced neuropathy | 49/M | 65 | 5 weeks | 0 | No | Yes | Yes* |
| Neurofibromatosis | 58/F | 100 | 4 days | 60 | No | Yes | No |
| Brown–Sequard syndrome | 26/F | 50 | 3.5 weeks | 10 | Sedation | Yes | No |
| Visceral pain | 41/M | 100 | 3 weeks | 10 | No | No | No |
| Headache | 50/M | 70 | 2 weeks | 20 | No | No | No |
| Spinal stenosis | 58/F | 60 | 1 week | 0 | No | No | No |

* Enhanced pain relief with infusions after memantine.
CRPS = complex regional pain syndrome.

margin of tolerability evidenced by the low degree of severity for the documented side effects.

One of the limitations of our study is the lack of data on long-term pain relief. However, our results from documented records, phone calls, and statistical analysis suggest that there is a significant chance (more than 30%) that a patient with refractory pain will have lasting pain relief after a 30-minute infusion with subanesthetic doses of ketamine. Our study design was retrospective, which is another limitation. To date, there have been no large randomized controlled trials with ketamine. Whether patients responding to ketamine infusions can be transitioned to an oral medication regimen remains to be seen. Thus far, no oral medication has proven to elicit a great analgesic response. Recently approved in the United States as a neuroprotective drug for Alzheimer patients, memantine, an oral NMDA-receptor antagonist, has shown some results in the treatment of phantom limb and neuropathic pain conditions [18]. Ketamine provides a more potent decrease in pain than memantine, possibly related to a lower equipotent dose of memantine po when compared with intravenous ketamine. Despite this difference, memantine improved quality of life in two-thirds of patients with minimal side effects. While limited by possible risks involved with higher doses of memantine (such as apoptosis, controlled neuronal cell death reported in animal models), additional studies are needed to investigate the optimal dose of memantine when used as an oral adjunct in refractory chronic pain patients responding to ketamine infusions [19].

For patients suffering from intractable chronic pain syndromes, alternative pain regimens may prove valuable. Our retrospective study demonstrates that for some patients with severe refractory pain of multiple etiologies, outpatient intravenous infusions of ketamine for 30 minutes at subanesthetic doses may significantly improve VAS scores with minimal side effects. These infusions are particularly useful when other interventions have failed.

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