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# Safety and Efficacy of Prolonged Outpatient Ketamine Infusions for Neuropathic Pain

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Ketamine has demonstrated usefulness as an analgesic to treat nonresponsive neuropathic pain; however, it is not widely administered to outpatients due to fear of such side effects as hallucinations and other cognitive disturbances. This retrospective chart review is the first research to study the safety and efficacy of prolonged low-dose, continuous intravenous (IV) or subcutaneous ketamine infusions in noncancer outpatients. Thirteen outpatients with neuropathic pain were administered low-dose IV or subcutaneous ketamine infusions for up to 8 weeks under close supervision by home health care personnel. Using the 10-point verbal analog score (VAS), 11 of 13 patients (85%) reported a decrease in pain from the start of infusion treatment to the end. Side effects were minimal and not severe enough to deter treatment. Prolonged analgesic doses of ketamine infusions were safe for the small sample studied. The results demonstrate that ketamine may provide a reasonable alternative treatment for nonresponsive neuropathic pain in ambulatory outpatients.

*Keywords:* ketamine, neuropathic pain, NMDA-receptor antagonists, continuous infusion, complex regional pain syndrome

## INTRODUCTION

Neuropathic pain is frequently resistant to conventional treatments, including opioids. Some patients suffer lifelong disability due to associated pain and physiologic changes. Choices in medications are often limited by a perception of unsafe side effects; medical directors of insurance companies, pharmacists and many researchers share this view. Ketamine, a drug sometimes abused on the streets, falls into this category of perception. However, a growing body of literature attests to the effectiveness of low-dose ketamine as an analgesic and as an alternative treatment for neuropathic pain.[1–11]

Ketamine is an anesthetic not commonly used in analgesic doses and is associated with drowsiness, disorientation, dizziness, and hallucinations. Despite the reported side effects, the literature reports some success with the use of low-dose ketamine as an adjuvant to opioids for advanced cancer pain.[1,2] Other studies show success in relieving nonmalignant nerve pain in a hospital setting using intravenous (IV) ketamine infusions,[3,4] subcutaneous infusions,[6] or singledose IV ketamine,[5,7] although some problems with side effects were reported. In a case study of 1 inpatient, Harbut and Correll[8] reported the complete remission of complex regional pain syndrome (CRPS) accompanied by subanesthetic doses of ketamine.

Ketamine's apparent value in mitigating neuropathic pain is explained by its blocking of the N-methyl-D-aspartate (NMDA) receptor.[12] This receptor mediates neuropathic pain and, when stimulated, leads to central sensitization.[13] A reversal of central sensitization by NMDA antagonists such as ketamine is believed to reduce pain and may also reduce the amount of opioid analgesics needed to control pain.[14]

To date, most studies involving continuous ketamine infusion have been limited to inpatients. Studies involving outpatients have been case reports[15,16] with only 1 prospective study of 5 patients receiving subcutaneous ketamine for more than 7 days.[6] All 5 patients experienced side effects with 1 discontinuing treatment after 2 weeks due to side effects. The current study is the first to undertake to assess the

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- Place PICC line for continuous IV infusions.
- Chest x-ray to evaluate placement of PICC line
- 0.1-0.25 mg/kg bolus at onset of infusion at the discretion of practitioner.
- 0.05-0.25 mg/kg continuous infusion.
- Rate increases authorized by practitioner as needed (Generally, rates are increased by 1-2 mg/hr, e.g., rate increased from 7 mg to 8 mg/hr).
- Patient returns to clinic twice weekly for evaluation.
- Patient must not drive or operate hazardous machinery during ketamine infusion.
- Patient reports adverse events to practitioner immediately.
- Infusion may continue for 14-60 days. May be discontinued earlier at the discretion of practitioner.
- It is not necessary to taper ketamine before discontinuation.

**FIGURE 1.** Ketamine infusion protocol.

safety and efficacy of prolonged, continuous ketamine infusions when administered to outpatients with neuropathic pain. Based on the authors' experience, a recommended protocol for administering IV ketamine to outpatients is described (Fig. 1).

# MATERIALS AND METHODS

### Study design

The study design involved all patients treated for severe neuropathic pain in which prolonged IV ketamine was prescribed in the author's pain clinic from October 2002 to April 2004. Deidentified data were collected by retrospective chart review. Pretreatment pain was compared with posttreatment pain in this single-patient series without a control group. The pain assessments were standard patient charting practice in the authors' clinic.

### Study subjects

The study consisted of 13 outpatients (8 males, 5 females), ranging in age from 15 to 65, treated in the authors' pain clinic for severe neuropathic pain (Table 1). Eight patients (62%) were diagnosed with CRPS, 1 with migraine (8%), 3 with neuropathy (23%), and 1 with phantom limb pain (8%). All patients reported experiencing ongoing pain recalcitrant to previous treatments. At the start of ketamine infusions, all 13 patients were receiving opioids, 12 were receiving anticonvulsants, and 5 were receiving antidepressants.

### Ketamine treatment

Prior to initiating therapy, patients were informed that prolonged IV ketamine in an outpatient setting had not been reported as safe or effective and was an off-label application of the medication. Patients were advised of potential risks and complications. The authors based the decision to administer ketamine infusions to outpatients on many years of success treating inpatients using ketamine infusions with minimal side effects.

**Table 1.** Patient characteristics (N = 13).

| | |
|---|---|
| Age, y, mean ± SD | 38.8 ± 12.8 |
| Min, max | 15, 65 |
| Sex, n (%) | |
| Male | 8 (62) |
| Female | 5 (38) |
| ICD-9 Dx, n (%) | |
| CRPS | 8 (62) |
| Migraine | 1 (8) |
| Neuropathy | 3 (23) |
| Phantom limb | 1 (8) |

Each patient was assessed for severity of pain during the clinic visit where the decision to administer ketamine was made. Patients were assessed using the 10-point verbal analog score (VAS) (1 = no pain; 10 = worst pain) and the global pain relief scale (0 = poor; 1 = fair; 2 = good; 3 = very good; 4 = excellent).

Within 24 hours of the initial assessments, each patient received a continuous ketamine infusion by a peripherally inserted central catheter (PICC) line or, in 5 patients, a secure subcutaneous needle. All 5 patients receiving subcutaneous infusions developed irritation or sterile abscesses at the infusion site. After this, ketamine infusions were administered only through a PICC line. After placement of the PICC line, a chest x-ray was performed to evaluate the placement.

Ketamine concentration was 100 mg/mL delivered through a programmable pump, equipped with security locks to prevent any alteration in the infusion rate by the patient. Patients were required to have a family member or friend with them for the first 24 hours after the initial infusion and were left alone only briefly thereafter. Patients were advised not to drive or operate heavy machinery. Home health care personnel, who provided daily medical observation for the length of the treatment period, delivered subsequent infusions to the patient and were available 24 hours per day to the patient and family.

The doses and durations of infusions are shown in Table 2. The mean duration of infusion treatment was 16.4 days, with a minimum of 5 days and a maximum

**Table 2.** Dose and duration of ketamine infusion (N = 13).

| | | *P* |
|---|---|---|
| Start dose, mg/kg/h, mean ± SD | 0.12 ± 0.06 | |
| Min, max | 0.03, 0.25 | |
| End dose, mg/kg/h, mean ± SD | 0.12 ± 0.06 | |
| Min, max | 0.01, 0.25 | |
| Change in dose, n (%) | | |
| Decrease | 2 (15) | |
| Same | 4 (31) | |
| Increase | 7 (54) | |
| Change in dose, mg/kg/h, mean ± SD | −0.002 ± 0.09 | 0.240* |
| Min, max | −0.24, 0.14 | |
| Duration of infusion, d, mean ± SD | 16.4 ± 12.9 | |
| Min, max | 5, 55 | |
| Duration of infusion (excluding 1 patient with a 55-d infusion duration), d | | |
| Mean ± SD | 13.2 ± 5.8 | |
| Min, max | 5, 28 | |

*Wilcoxon matched-pairs signed-ranks test.

of 55 days. Doses were carefully titrated to minimal effective levels to avoid side effects. Although more than half of patients had some upward titration in dose, the mean start dose and the mean end dose were the same (0.12 mg/kg/h). Increases in infusion rates were by increments of 1–2 mg/h and were not increased more often than every 48 hours. By the end of the treatment period, the minimum dose was 0.01 mg/kg/h and the maximum dose was 0.25 mg/kg/h.

On the last day of treatment, patients were readministered the VAS and global pain relief assessments as measures of pain severity. Patients were evaluated again as to pain relief 1 month after infusion treatments were discontinued.

### Statistical methods

Dichotomous variables measured at one time point were tested for significance using the binomial test, comparing the observed proportion to 0.5 (50:50 chance of occurring). This single-sample test was appropriate for pain assessments made only at the end of treatment, having the possible values of improved or not improved. If the response was due to random variation, then improvement would be equally likely as nonimprovement, and thus the comparison to the proportion of 0.50 was the correct comparison to test the treatment effect. Ordered categorical variables measured at 2 time points were tested for significant change using the Wilcoxon matched-pairs signed-ranks test. The VAS was treated as an ordered categorical variable for significance testing. Continuous variables measured at 2 time points were tested for significant change using the paired sampled *t* test if the change scores were symmetrically distributed and the Wilcoxon matched-paired signed-ranks test if the distribution was skewed. Given the small sample size, a multivariate analysis was not performed. All reported *P* values are for a 2-sided comparison.

## RESULTS

Pain-relief outcomes are shown in Table 3. Using the VAS, 11 of 13 patients (85%) reported a decrease in pain from the start of infusion treatment to the time treatment was discontinued. Overall, pain severity dropped from a mean VAS of 7.7 at the start of infusion treatment to 4.8 at treatment end, representing a drop of 2.9 points ($P = 0.003$).

Similar improvement was seen in global pain relief data. At the start of treatment, 10 patients rated their pain relief poor or fair, while 3 rated their pain relief good or very good. At the conclusion of treatment, those numbers were reversed with 10 patients rating their pain relief good or very good and 3 rating their pain relief poor or fair. At the conclusion of treatment, 8 patients (62%) reported good pain relief compared with 2 patients (15%) who had done so when treatment commenced. Eight patients (62%) claimed improvement using the global pain relief scale, while 3 (23%) said their pain relief remained the same and 2 (15%) reported a decrease in pain relief ($P = 0.041$).

Perception of pain improvement data were gathered in verbal interviews with the patients. Of 13 patients, 12 (92%) perceived an improvement in pain, while 1 patient (8%) did not ($P = 0.003$). Seven or 54% of patients still perceived improvement 1 month after infusion treatment ended ($P = 1.000$).

Adverse events are reported in Table 4. The most frequently reported problem was irritation associated with subcutaneous delivery (5 patients or 38%), a method that was discontinued as previously mentioned. Next was fatigue (4 patients or 31%), dizziness (3 patients or 23%), confusion (2 patients or 15%), and spinal pain (2 patients or 15%). No patients reported hallucinations (0%).

**Table 3.** Outcomes (N = 13).

| | | *P* |
|---|---|---|
| Start VAS,* mean ± SD | 7.7 ± 1.8 | |
| Min, max | 5.5,10.0 | |
| End VAS, mean ± SD | 4.8 ± 2.3 | |
| Min,max | 2, 10.0 | |
| Change in VAS, n (%) | | |
| Decrease | 11 (85) | |
| Same | 1(8) | |
| Increase | 1(8) | |
| Change in VAS, mean ± SD | 22.9 ± 2.2 | 0.003† |
| Min, max | −7.0 ± 1.0 | |
| Start global pain relief scale, n (%) | | |
| Poor | 4 (31) | |
| Fair | 6 (46) | |
| Good | 2 (15) | |
| Very good | 1 (8) | |
| Excellent | — | |
| End global pain relief scale, n (%) | | |
| Poor | 1 (8) | |
| Fair | 2 (15) | |
| Good | 8 (62) | |
| Very good | 2 (15) | |
| Excellent | — | |
| Change in global relief scale, n (%) | | 0.041† |
| Decrease | 2 (15) | |
| Same | 3 (23) | |
| Increase | 8 (62) | |
| Patient report of perceived improvement, n (%) | | 0.003‡ |
| Improved | 12 (92) | |
| Not improved | 1 (8) | |
| Patient report of perceived improvement 1 after infusion ended, n (%) | | 1.000‡ |
| Improved | 7 (54) | |
| Not improved | 6 (46) | |

*Verbal analog score (1–10 scale, 10 = worst pain).
†Wilcoxon matched-pairs signed-ranks test.
‡Binomial test comparing observed proportion to 0.5.

Table 5 shows the conversion of administered opioids to morphine equivalents and the change in opioid doses as ketamine treatment progressed. The mean start dose of morphine equivalents was 494.8 mg. The mean end dose was 409.4 mg, showing a slight decrease of −85.4 mg ($P = 0.347$).

## DISCUSSION

This report is the first to study prolonged, continuous IV ketamine infusions in noncancer outpatients. For the sample studied, infusions in analgesic doses were safe for up to 8 weeks. The research raises several important points. First, ketamine has not been commonly used in outpatient nonmalignant pain populations primarily due to concerns about serious side effects. Although all but 1 of the patients reported side effects, the side effects were not considered severe enough to impair activities of daily living. Close to a third of patients experienced fatigue, one fourth complained of dizziness or lightheadedness, and 2 patients reported confusion. One patient suffered a nonserious IV complication. In this case, the patient's pump was inadvertently programmed to deliver 1500 mg over 1 hour. The patient became

**Table 4.** Adverse events (N = 13).

| | |
|---|---|
| AE combinations in same patient, n (%)* | |
| None | 1 (8) |
| Confusion | 2 (15) |
| Dizziness, lightheadedness | 3 (23) |
| Fatigue, sleepiness | 4 (31) |
| Subcutaneous erythema, irritation | 5 (38) |
| Thirst | 1 (8) |
| IV complications (infiltration or inflammation) | 1 (8) |
| Flushing | 1 (8) |
| Spinal pain | 2 (15) |
| Hallucination | — |
| Fever | — |

*Multiple AEs were possible, so counts total more than 13.

**Table 5.** Dose and duration of treatment in morphine equivalent dose (N = 13).

| | | *P* |
|---|---|---|
| Start dose, mean ± SD, mg/d | 494.8 ± 555.7 | |
| Median | 180.0 | |
| Min, max | 22.5, 1755.0 | |
| End dose, mean ± SD, mg/d | 409.4 ± 503.7 | |
| Median | 102.2 | |
| Min, max | 0.0, 1665.0 | |
| Change in dose, n (%) | | |
| Decrease | 5 (38) | |
| Same | 5 (38) | |
| Increase | 3 (23) | |
| Change in dose, mean ± SD, mg/d | −85.4 ± 243.3 | 0.347* |
| Min, max | −627.0 ± 262.5 | |
| Duration of treatment, d, mean ± SD | 16.8 ± 13.5 | |
| Min, max | 5, 55 | |
| Duration of infusion (excluding 1 patient with a 55-d infusion duration), d | | |
| Mean ± SD | 13.7 ± 7.5 | |
| Min, max | 5, 29 | |

*Wilcoxon matched-pairs signed-ranks test.

disoriented and confused but otherwise suffered no ill effects. Hallucinations and dissociative cognition are the most worrisome side effects associated with ketamine. No patients in this study reported hallucinations, and dissociative thought processes were also absent. The lack of significant side effects was probably due to the low starting dose and slow upward titration. In any case, side effects did not present a reason to avoid the therapy.

Next, it is important to note that several patients in the current study reported a delay in benefit. Time to onset of pain reduction was not recorded, but several patients reported no pain reduction during the first 24–72 hours of infusion. The reason for the delayed response is unknown but could be explained by the low infusion rate requiring several days to achieve an effective blood level of ketamine. There are several subunits of the NMDA receptor. Low infusion rates of ketamine may block a different subunit than do higher infusion rates, delaying the analgesic response normally seen at higher infusion rates.[17] Alternatively, duration of infusions may be more important than blood levels in the cellular reversal of central sensitization, meaning a minimum duration may be required to effect reversal regardless of which NMDA receptor subunits are antagonized. In the authors' opinion, the magnitude of sustained pain reduction is most likely a product of both time and dose with time being the critical factor. This is supported by the case report of Harbut and Correll[8] of a complete reversal of CRPS type I in which ketamine was infused over 6 days in the hospital, and an actual decrease in the patient's pain level was first noted 48 hours after beginning infusion therapy.

The maximum dose of ketamine given in the current study was 0.25 mg/kg, and the mean dose 0.12 mg/kg. This is similar to the doses seen in other studies of lowdose IV ketamine.[1,3,5] Although more than half of patients had some upward titration, the mean change in dose was not statistically significant ($P = 0.240$).

It was not a goal of ketamine-infusion therapy to taper or eliminate other medications, although a reduction in medications sometimes occurred. The mean morphine equivalent dose of opioids administered had dropped slightly by the end of ketamine infusions (−85.4 mg), although that number was not statistically significant ($P = 0.347$) (Table 5).

Another important message from this study is that no patient experienced the complete reversal of signs or symptoms of CRPS reported by Harbut and Correll, although CRPS represented a majority (62%) of the sample. Although ketamine infusions may be helpful in reversing some neuropathic pain states, it should not be considered a universally successful treatment. However, most patients (92%) reported significant perception of pain relief at the end of treatment compared with when treatment began. The perception of benefit continued 1 month after treatment among 54% of patients, although that number was not statistically significant. These data suggest that a patient may benefit even though complete reversal of a neuropathic pain disorder is not accomplished. A larger sample size drawn from a variety of settings in a double-blind, placebo-controlled study is needed to demonstrate long-term safety and efficacy.

The final important observation is that tachyphylaxis was not observed even in the 1 patient receiving an infusion for 8 weeks. Tachyphylaxis, a rapid development of tolerance, is a phenomenon known to occur with repeated doses of ketamine. The mechanism of tolerance to ketamine is unknown, but this study suggests that it may be related more to the amount of ketamine administered than the duration of administration. In a previous report, it was suggested that low doses of ketamine might interact with peripheral NMDA receptors more than with central receptors, sparing some of the central side effects.[18] Tolerance to ketamine may require interaction with primarily central receptor subunits and thus require higher doses of ketamine.

In summary, prolonged analgesic doses of IV ketamine were safe for the small sample studied. In this study, noncancer outpatients received infusions for up to 8 weeks without serious complications or injury, and tolerance was not observed. Additional studies should follow to determine optimal dose and duration for specific pain disorders and to minimize side effects. Further research should also investigate the possibility that a subset of neuropathic pain disorders may even be reversed using ketamine infusions. Question regarding which patients would be most susceptible to this type of therapy and when treatment should be instituted remain unanswered. Yet if the observation of minimal risk of serious side effects can be further substantiated, ketamine infusions may offer clinicians an opportunity for the treatment of selective neuropathic pain conditions recalcitrant to all other therapies.

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