

Observational Report

Opioid-Sparing Effect of Intravenous Outpatient Ketamine Infusions Appears Short-Lived in Chronic-Pain Patients with High Opioid Requirements

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Background and Objectives: Ketamine is opioid-sparing. It attenuates the onset of opioid tolerance, and suppresses opioid-induced hyperalgesia. This study evaluated whether or not repeated outpatient infusions of intravenous ketamine reduced the amount of pain and the amount of opioid requirements for patients suffering with chronic, non-cancerous pain.

Study Design: Retrospective study

Setting: Outpatient pain clinic

Methods: We reviewed the records of 18 patients taking high doses of opioids chronically and nonetheless reporting poorly controlled pain. A comparison control group of 18 similar patients with high opioid requirements who were not given ketamine were selected from our clinic population.

Intervention: Intravenous ketamine infusions

Measurement: VAS pain scores and opioid use

Results: Morphometric and demographic characteristics, baseline opioid use, and pain scores were similar in the ketamine and comparison groups. Five patients given ketamine experienced no benefit and discontinued treatment after 1-2 infusions. One patient developed a supraventricular arrhythmia which immediately resolved upon cessation of the infusion. And another, despite pain relief, felt overly-anxious and opted out. Eleven patients thus completed 3-6 weekly ketamine infusions. At 6 months, 5 patients maintained less than 50% of their baseline opioid use, while the remaining patients returned to the baseline opioid use or increased their requirements. There was no significant difference in pain scores at 6 months in patients who received ketamine infusions and control group patients.

Limitations: Retrospective nature of the study

Conclusions: Outpatient intravenous ketamine infusions did not improve long-term pain scores in patients with high opioid requirements and only a few were able to substantially reduce opioid use. Considering infusion risks and cost of such outpatient treatment, ketamine infusions do not appear to be a feasible option for improving pain relief and decreasing opioid use in high-opioid requirement patients.

Key words: Ketamine; anesthesia; chronic pain; opioids; continuous infusion; opioid requirements

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Ketamine is a non-competitive antagonist of NMDA (N-methyl-D-aspartate) receptors that can also act on a variety of receptors (nicotinic, muscarinic, and opioid) and channels (Na⁺ and Ca²⁺) (1). It has been used as an anesthetic for the past 35 years. Ketamine is also an effective analgesic in a variety of clinical settings (1-5), and is opioid-sparing in post-surgical (6) and other (7) settings. Additionally, ketamine attenuates the onset of opioid tolerance (7-10) and suppresses opioid-induced hyperalgesia (11-13). Ketamine-induced analgesia has been successfully achieved when the drug is given intravenously (14-22).

Ideally, ketamine infusions should provide long-term pain relief and decrease opioid use, preferably in outpatient environments to keep costs relatively low. The excessive costs of low-dose ketamine infusion trials conducted over many days in an inpatient setting (22) and/or anesthetic-dose ketamine infusions in intensive care settings (19) would be a major obstacle to making this approach routine. Furthermore, recent studies suggested that the prolonged low-dose ketamine infusion (i.e., 4.2 days) might improve pain scores only over a short period, such as 12 weeks, in patients with CRPS (22). And finally, anesthetic-dose ketamine infusions might be risky (19).

Currently it remains unclear if repeated outpatient ketamine infusions provide long-term pain relief in patients with high opioid requirements. The opioid-sparing effect of ketamine has been extensively studied in post-operative pain patients (21), but not in chronic pain patients. We thus evaluated whether repeated 3-6 weekly infusions of high-dose intravenous ketamine in an outpatient setting reduces long-term pain relief and reduces opioid requirements in patients with chronic non-malignant pain that is poorly controlled despite high-dose opioid use.

METHODS

With approval from the Internal Review Board (IRB), the records of 18 consecutive patients given ketamine infusions were reviewed. Each patient was chronically taking high-dose opioids (Table 1) for nociceptive or neuropathic conditions. The opioids included controlled-release forms of Class II agents such as morphine, oxycodone, or fentanyl; some also took short-acting forms of oral opioids for breakthrough pain.

All patients had drastically increased their opioid requirements over the previous 12 months but still had an average daily pain score exceeding 5 cm on a 0-10-cm verbal response scale (0 cm indicating no pain and

10 cm being the worst imaginable pain). Patients with a history of ischemic heart disease, tachyarrhythmia, uncontrolled hypertension or a history of psychological issues were not considered for the ketamine infusion treatment.

Patients were counseled on the side effects of ketamine infusion, including light-headedness, dizziness, headache, feeling tired, sedation, dream-like state, vivid dreams, increased distractibility, and disorientation. Physiological side effects such as tachycardia, increased blood pressure, nystagmus, hypersalivation, increased urinary output, decreased sensitivity to pain, amnesia, slurred speech, and lack of coordination were also disclosed.

Patients were given 2-4 mg of midazolam just before initiation of each ketamine infusion, and an additional 2-4 mg if needed during infusions. Generally, the ketamine infusions were initiated at the rate of 10 mg/hour. The rate was increased as tolerated until patients reported no pain or until the infusion rate reached 100 mg/hour. Once an effective infusion rate was identified, it was continued for 3 hours or as long as tolerated. When unacceptable side effects were noted, the rate was decreased or the infusion was completely/temporarily discontinued. Patients were expected to receive between 3 and 6 weekly infusions.

A comparison group of 18 patients with the same sex distribution (10 men and 8 women) was retrospectively assembled from the physician-assistant opioid-refill schedule of chronic-pain patients. Patients who were receiving >80 mg per day of MSO4 equivalent and had pain for >1 year were selected (also see the first paragraph in Results and Table 1). Patients in both groups experienced a comparable duration of chronic pain and their baseline pain scores ($P = 0.62$) and baseline opioid daily requirements ($P = 0.173$) mg were comparable (Table 1).

Demographic characteristics, pain intensity and duration, and opioid use were obtained for patients in the ketamine infusion and comparison groups. Pain was evaluated using a 0-10-point verbal response score with 0 indicating no pain and 10 being the worst imaginable pain. In the ketamine treatment patients, pain scores and opioid use (in morphine sulfate equivalents) were recorded before beginning the first infusion, after completing the series of infusions, and 6 months later. In the comparison group, pain scores were compared at 8-month intervals to approximate the follow-up interval of the group who received ketamine infusion.

Table 1. Characteristics of the patients who underwent a series of ketamine intravenous infusions.

Patient Number	Age	Sex	Diagnosis	Chronic pain (years)	Ketamine infusions (number)	Highest ketamine infusion rate (mg/h)	VRS pain before infusion	VRS pain score 6 months later	Opioid use (mg MSO4 equivalents) before infusion	Opioid use (mg MSO4 equivalents) 6 months later
1	28	M	Neuralgia	4	3	100	8	8	100	100
2	46	M	CRPS 1	5	1	80	4	6	396	396
3	46	M	CLBP	7	6	100	7	7	540	510
4	25	F	CLBP	3	1	75	8	8	220	220
5	42	M	CAP	3	2	50	7	7	270	300
6	24	F	Neuropathy	3	6	40	10	7	150	25
7	50	M	CLBP	10	3	50	4	4	80	80
8	61	F	Neuropathy	30	1	50	8	8	120	200
9	45	M	PLS	4	3	50	7	7	150	150
10	36	F	CAP	2	6	100	10	5	160	120
11	53	M	Neuropathy	3	3	100	10	9	250	250
12	30	F	PLS	9	3	100	10	3	80	0
13	52	F	CAP	20	3	90	4	2	80	0
14	69	F	PLS	11	1	35	10	7	82	52
15	31	F	CLBP	8	1	100	8	9	174	70
16	38	M	CLBP	6	2	100	8	9	118	45
17	42	M	CLBP	20	6	60	7	8	190	150
18	48	M	CRPS 1	7	4	50	4	4	247	150

CRPS 1 – Complex Regional Pain Syndrome type 1; CAP- Chronic Abdominal Pain; CLBP-Chronic Lower Back Pain; PLS- Post-laminectomy syndrome. VRS is verbal response pain score on a 0-10 scale (0 = no pain; 10 = worst imaginable pain).

To evaluate differences between the various values, Mann-Whitney Rank Sum Test was used. Statistical tests and graphs were produced using Sigma Plot software (Systat Software Inc., Chicago, IL). Results are presented as means \pm SDs unless otherwise specified.

RESULTS

The mean age of the comparison group was 46 ± 10 (median 46) years vs. the ketamine group mean age of 45 ± 12 (median 44) years. There were 10 men and 8 women in each of the groups. Patients in each group experienced a comparable duration of chronic pain: 10 ± 9 years vs. 9 ± 8 years for the group who received ketamine infusion. Their pain scores (7 ± 2 vs. 7 ± 2) and opioid daily requirements (153 ± 158 (median 93) mg morphine sulfate equivalents vs. 190 ± 121 (median 155) mg were comparable (Table 1).

Five of the 18 patients treated with ketamine infusions experienced no beneficial effect after one or 2 infusions and therefore opted not to receive additional infusions. One patient developed a supraventricular ar-

rhythmia, which reversed upon immediate cessation of the infusion. One other patient, despite good analgesia, felt overly anxious and experienced unpleasant dreams, and thus opted not to have another infusion. Eleven patients thus completed 3-6 weekly ketamine infusions. A total of 55 infusion cycles were given among all 18 patients. The peak infusion rate given varied from 35 to 100 mg/hour (Table 1). There were a few side effects such as dizziness and sleepiness. All of the patients were released without difficulties from our outpatient pain management center.

Baseline pain scores in the 11 patients given 3-6 ketamine infusions were 8 ± 2 . Immediately after the last ketamine infusion, pain was 0, but at 6 months returned to 7 ± 2 which did not differ significantly from baseline scores ($P = 0.13$) (Fig. 1).

In the 11 patients who received 3-6 ketamine infusions, opioid use decreased following the last infusion visit (1-1.5 months follow-up) (Fig. 2) from 184 ± 133 mg morphine sulfate equivalents (150 mg median) to 92 ± 100 mg (60 mg median), and the decrease was

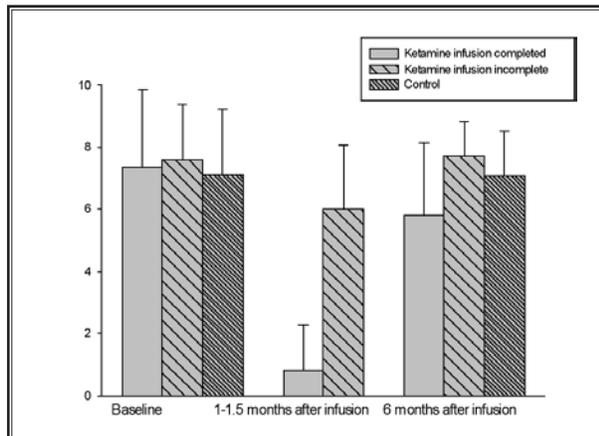


Fig. 1. Changes in the verbal pain scores (on a 0-to-10 scale) just before, immediately after, and 6 months after completion of a series of ketamine infusions in 11 patients who completed a series of 3-6 infusions, 5 who started but never completed, and the control group ($n = 18$). There was no significant difference between the mean baseline pain scores of those who did and did not receive ketamine infusions ($P = 0.181$). There was a significant decrease in the verbal pain scores after completion of the ketamine infusion series ($P < 0.001$), but it was not sustained at 6 months ($P = 0.17$).

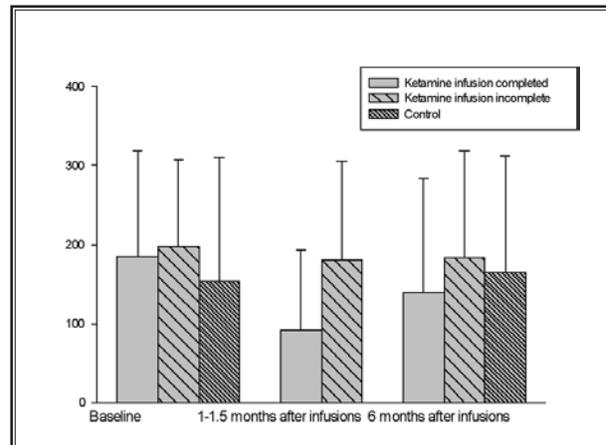


Fig. 2. Opioid requirement (in mg of morphine sulfate equivalents) just before, immediately following, and 6 months after the completion of a series of ketamine infusions in 11 patients who completed series of 3-6 infusions compared with those who did not and the control. There was no significant difference in mean opioid use before and 6 months after the ketamine infusions ($P = 0.274$).

statistically significant ($P = 0.015$). Six months after the final ketamine infusion, the difference was no longer statistically significant with opioid use returning to 140 ± 144 mg morphine sulfate equivalents (120 mg median) ($P = 0.274$; Fig. 2). Six months after completing the ketamine infusion cycles, 5 patients maintained less than 50% of their baseline opioid use. Two among these 5 patients also reported a $>50\%$ improvement in their verbal pain scores. However, the remainder of the patients returned to the baseline dose or even increased their opioid use.

DISCUSSION

Several recent studies report successful short-term treatment of chronic pain from complex regional pain syndromes with ketamine infusions (19,20,22-24). Unfortunately, improvements were only reported over 2-12 weeks, and the studies failed to document long-term benefit. Furthermore, ketamine was given to inpatients as a subanesthetic, low-dose infusion with a gradual titration (20,22). Such lengthy infusions are expensive and are seldom reimbursed by third-party payers. We thus tried relatively short outpatient infusions which do not require hospitalization.

In general, we could not demonstrate significant improvement in pain scores or opioid consumption in most treated patients (Fig. 1). Furthermore, 7 of 18 patients who received an initial ketamine infusion never even completed the planned series of 3-6 infusions — either because of the side effects or, more commonly, because they perceived no apparent benefit. Consequently, only 5 of 11 patients who received the entire series of ketamine infusions maintained significantly decreased opioid use 6 months after completing treatment. It seems unlikely that this modest response in a small fraction of the 18 initial patients justifies the approach we tested.

High-dose desensitization with ketamine infusions of 5–7 mg/kg/hour for 5–7 days have been used in patients with complex regional pain syndrome (19). However, this anesthetic-dose approach requires patients to be admitted to an intensive-care unit. Considering the costs of inpatient infusions, especially in an intensive care unit, this approach cannot be considered feasible unless considerable long-term benefit is demonstrated and proven safe.

We included patients with poorly controlled pain, despite taking high doses of opioids. Most had several opioid rotations prior to ketamine treatment, but still had relatively high opioid intake (from 80 to 540 mg of morphine sulfate equivalents). These were patients

who were generally doing poorly under conventional therapy for the chronic pain, and were the population most likely to benefit from ketamine infusions and justify the concomitant expense. The comparison group was similar in important respects, especially with regard to pain experience and opioid consumption. Regarding the variability of the patient group studied and the control group, such diversity of the causes of the chronic pain in either group should not be an issue considering the ketamine mechanism of action. Ketamine is a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors and can also act on a variety of other receptors (nicotinic, muscarinic, and opioid) and ion channels (Na⁺ and Ca²⁺).

The major weakness of this retrospective study is lack of randomization. However, the intention behind reviewing our data was to determine whether a randomized study was likely to be worthwhile. That does not appear to be the case. We also cannot comment on the mechanism of action of the ketamine opioid-spar-

ing effect in the 5 patients who maintained improved analgesia 6 months after the completion of this series of infusions. However, it might be the result of long-term suppression of opioid-induced hyperalgesia. It is equally likely, though, that some patients worsen over time and some improve. Focusing on the 5 patients who ultimately improved thus ignores the 13 who either didn't complete the infusions or didn't improve. Our results should thus be considered negative, rather than effective, in the population as a whole

In conclusion, repeated ambulatory intravenous ketamine infusions did not consistently produce long-term reductions in pain or opioid use in patients with severe chronic pain.

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