Observational Study

Long-Term Effectiveness of Repeated, Single-Day Intravenous Ketamine Infusions for Severe Arthritis: A Retrospective Cohort Study

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Disclaimer: There was no external funding in the preparation of this article.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Article received: 09-06-2025
Revised article received: 01-27-2026
Accepted for publication: 03-03-2026

Free full article: www.painphysicianjournal.com

Background: Ketamine, either adminstered as an infusion or orally as an analgesic, was considered only to be a drug for neuropathic pain. More recently it has been speculated to be efficacious for other types of pain, including nociceptive pain.

Objectives: We aimed to examine the long-term effects of single-day ketamine infusions for treating diffuse chronic pain caused by rheumatoid arthritis, osteoarthritis, or psoriatic arthritis.

Study Design: Our study analyzed the records of a cohort of 38 consecutive patients treated with repeated single-day intravenous ketamine infusions for chronic arthritis pain.

Setting: Outpatient private practice.

Methods: Outcome data on patients treated from January 2019 through December of 2024 in our clinic were collected from our electronic medical records and analyzed. It included numeric pain scores and opioid usage. All procedures were completed under conscious sedation using a vitals monitoring protocol. Ketamine was administered at about 1–1.5 mg/kg/h during a 3 hour session. The sessions were repeated as needed at approximately every 3–12 months (median 6 months). Dosing was decided based on a patient's comorbidities. Patients with advanced cardiovascular issues, sleep apnea, or a history of substance abuse were not considered for an infusion.

Results: A total of 38 patients—35 women and 3 men, aged from 21–73 years (median 58) with a median body mass index (BMI [kg/m^2]) of 33 received repeated ketamine infusions (300–500 mg per session) for control of their chronic arthritis pain. They averaged 3 sources of chronic pain in their body. Of the 38 study patients, 18 were on opioids with a median morphine milligram equivalent of 45. Their baseline pain score was 8 and decreased at 3 months follow-up to 4 which was maintained at 4 at 24 months. Nineteen patients had more than 50% pain relief at 3 months and 20 patients at 24 months. Pain relief was maintained through 24 months after the initial infusion. Eight patients received minimal or no benefit from infusions. The number of patients on opioids decreased from 18 to 10 at 24 months with a median morphine milligram equivalent of 30.

Limitations: This was a retrospective study.

Conclusions: Ketamine infusion provided substantial and lasting pain relief in the majority of patients with arthritis. Repeated ketamine infusions provided consistent pain relief throughout 24 months. Opioid usage somewhat decreased in those patients on opioid medications.

Key words: Ketamine, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ketamine infusion.

Pain Physician 2026: 29:363-368

Arthritis, a leading health care problem in the United States, affects nearly 21.2% of the population, or about 50 million Americans (1). Osteoarthritis, the most common type, affected 11.6% of the population in 2017—an increase from 9.6% in 2013—and is likely to become a leading cause of disability (2). Rheumatoid arthritis, another common type, affected 1.3 million Americans or 0.6%-1% of the population, resulting in significant annual health care costs of $20 billion (3).

Intravenous (IV) ketamine, an effective analgesic, has been used to treat chronic pain for 20 years. Ketamine acts as a noncompetitive antagonist on N-methyl-D-aspartate (NMDA) receptors, which play a crucial role in nociceptive hypersensitivity in the spinal dorsal horn (4-6). NMDA receptors are glutamate receptors with excitatory neurotransmitters located in the central nervous system and periphery (5). While ketamine may modulate peripheral and central neural plasticity, thereby decreasing pain hypersensitivity, it also potentiates dopamine signaling and reduces substance P receptor-mediated pain. Consequently, modifying these pathways reduces chronic pain (4-6). In addition, IV ketamine is an effective therapy to treat severe and treatment-resistant major depressive disorder, which is commonly associated with chronic pain (7,8).

Oral or IV ketamine has historically been considered a primarily neuropathic pain drug (9-12). However, evidence suggests that ketamine, like some other analgesics, may also be efficacious for other types of pain (13-18). Although most preclinical evidence supporting an antinociceptive pain effect for ketamine has been conducted using peripheral neuropathic and central pain models (9-12), several studies have demonstrated an analgesic benefit in both inflammatory and other nonneuropathic animal models (13,14). For example, Lu, et al (14) showed that when rabbits with osteoarthritis were injected with intra-articular ketamine, their inflammation significantly decreased.

Methods

We analyzed the records of a cohort of 38 consecutive patients treated with repeated single-day IV ketamine infusions for their chronic arthritis-related pain. These patients had an established diagnosis of either rheumatoid arthritis (28 patients), psoriatic arthritis (2 patients), or osteoarthritis (8 patients). There were no patients diagnosed with or being treated for depression.treated by psychiatrist for depression. Long-term clinical outcomes were assessed for these patients who were treated from January 2019 through December of 2024 in our clinic.

Following the Forsyth Medical Center Institutional Review Board's study approval, data were collected from our electronic medical records. The data included a patient's identifier, date of birth/age, gender, body mass index (BMI [kg/m^2]), number of other chronic pain sources, baseline numeric pain score, baseline opioid usage (in morphine milligram equivalents), and IV ketamine infusions (number of ketamine infusions, time interval between ketamine infusions, average dose given). Numeric pain scores and opioid usage were recorded at 3, 6, 12, and 24 months post the first ketamine infusion. Patient identifiers (including name, medical record number) were removed immediately after a complete set of data for each patient was collected and the identifiers then permanently discarded.

Procedure

Patients with advanced cardiovascular issues, sleep apnea or a history of substance abuse were not considered for infusion. Study patients received an initial 1–3 ketamine infusions every 3–7 days, followed by a single ketamine infusion at intervals of approximately 6 months or earlier as needed for pain control. Overall, they received anywhere from 1–ketamine infusions within the time intervals of 3 to 12 months (median 5 months). All procedures were completed under sedation with direct monitoring of vitals. Midazolam (3–6 mg) was administered for sedation and prevention of hallucinations. A single-day ketamine infusion dose was 5 mg/kg (or 300–500 mg) during a single 3–5-hour session (about 1.5 mg/kg per hour).

We used 4 mg IV ondansetron just before initiation of an infusion and placed 300–500 mg of ketamine and 25 mg promethazine in a 500 mL saline infusion bag, slowly infusing as described above. Patients were monitored using automated blood pressure, pulse oximetry, and observation by an attending anesthesiologist. Patients were accompanied by one close relative or friend who stayed with patient for the entire duration of infusion and was able to take patient home following recovery. Patients were discharged home responsive and oriented.

Statistical Methods

Data were summarized using descriptive statistics for continuous variables. We used Student t-tests and

the Mann-Whitney Rank Sum Test as appropriate to determine whether there was a statistically significant difference in pain scores and opioid usage after initiation of ketamine infusions compared to baseline. We calculated the percentage of patients who maintained pain relief following initiation of ketamine infusions. All analyses were completed using the Sigma Plot for Windows Version 14 (SYSTAT Software).

Results

The patient's body mass index (BMI [kg/m^2]) scores ranged from 16.8 to 47.7 (median 33) and they had a mean of 2.5 other sources of chronic pain (range from 0–6), which persisted for a mean of 11.5 years. Their baseline mean (SD) pain score on the Visual Analog Scale (VAS) was 7.87 (1.54) cm and and median daily opioid usage was 45 mg in morphine milligram equivalents (MME). The patients received 300–500 mg infusions of ketamine over approximately 3 hours (1–1.5 mg/kg/h). Baseline characteristics of all patients who received therapy are shown in Table 1.

Patients then received 1 to 9 therapeutic ketamine infusions and were followed for more than 24 months. There were 3 initial loading ketamine infusions followed by a repeated single infusion. Seven patients only received a single infusion; 5 of them reported no significant improvement in their chronic arthritic pain. The rest of the patients received repeated periodic ketamine infusions at various time intervals (between 3 and 12 months (median of 5 months). All treated patients were included in the analysis. Mean (SD) baseline VAS pain scores for the 38 patients decreased from 7.87 (1.54) to 4.15 (2.7) at 3 months post the initial infusion, 4.8 (2.3) at 6 months, 4.34 (2.5) at 12 months, with maintained improvement at 3.76 (2.4) at 24 months (Fig. 1). At 3 months postinfusion, 19 out of 38 patients received over 50% of pain relief and at 24 months, 20 out of 38 patients. Eight patients received minimal or no benefit from the ketamine infusions. By the 24 months follow-up, the number of patients using opioids decreased from 18 to 10; their median MME was 30 mg/d (Fig. 2).

Discussion

Here we report the clinical outcomes of therapeutic ketamine infusions in patients with either rheumatoid arthritis, osteoarthritis, or psoriatic arthritis who received repeated single-day high-dose infusions (3–5 mg/kg over 3–5 hours) for control of their diffuse joint pain. An analysis of this cohort showed that a large percent of the patients benefited greatly from repeated IV ketamine infusion. Twenty-two out of 38 patients (58%) had more than 50% pain relief and 81% had 30% pain relief throughout the 24 months of follow-up.. A clinically significant improvement of 2 points on the VAS pain scale was achieved in 84% of the patients, showing that the vast majority of the patients with severe arthritis pain benefited from this therapy.

The opioid sparing effect of lower doses of ketamine has been well documented in literature. Ketamine infusions after total knee arthroplasty decreased postoperative morphine consumption by up to 35% (19). Years after the initial data on ketamine infusions for chronic pain were reported, there is still no established consensus on dosing, conscious sedation level, or appropriate time interval between infusions to provide maximal benefit and minimal side effects from the therapy (19–24). A published consensus between major chronic pain management societies took a step forward toward a more critical and detailed discussion (24).

A review by Maher and colleagues (21) concluded that higher total infused dosages of ketamine and longer infusions were associated with longer durations of pain relief. Similarly, data collected from 2 large cohorts of patients with chronic fibromyalgia and arthritis, recently presented at a national meeting, suggest that higher doses indeed may provide longer pain relief (23,24). A total of 300–500 mg of ketamine were used in both studies. A meta-analysis of sedated and awake pediatric and adult patients (19) estimated the number-needed-to-harm for hallucinations to be high—21—when ketamine is used without coadministration of a benzodiazepine; when patients are given a benzodiazepine prior to ketamine administration, the number increases to 35, suggesting premedication may lessen but not eliminate psychomimetic events. Optimization of a short-acting benzodiazepine, primarily midazolam, given at higher than 4–5 mg just before initiating ketamine infusion (23,24) seems to eliminate or minimize the frequency of hallucinations and allows quiet sleep under conscious sedation and careful monitoring. The larger problem in treated patients was postinfusion nausea. Prophylactically, patients received both ondansetron before and promethazine during infusion to reduce the number of patients with post-procedure nausea to only a few (23,24).

Limitations

Weaknesses of our study include the retrospective nature of data collection which can introduce bias, the

Table 1. *Baseline characteristics of consecutive patients receiving ketamine infusions for control of their chronic arthritic pain.*

	Diagnosis	AGE	BMI	Other Pains	Baseline VAS	Baseline opioid (mg)	Ketamine dose (mg)
Patient 1	RA	50	33.25	4	6	0	500
Patient 2	RA	45	25.23	4	9	100	500
Patient 3	RA	59	26.6	4	9	50	500
Patient 4	RA	40	35.63	0	6	0	400
Patient 5	RA	54	43.05	2	8	40	500
Patient 6	RA	71	17.2	4	10	0	300
Patient 7	RA	55	41.3	6	10	90	500
Patient 8	RA	51	24.03	0	9	40	500
Patient 9	OA	53	33.38	0	6	0	450
Patient 10	RA	37	29.69	0	6	0	300
Patient 11	RA	55	35.71	0	10	150	325
Patient 12	RA	44	16.8	6	7	10	500
Patient 13	RA	60	32.1	4	8	0	500
Patient 14	RA	51	29.02	5	7	40	300
Patient 15	RA	73	32.8	1	6	180	450
Patient 16	RA	61	32.96	3	9	60	300
Patient 17	RA	59	34	3	8	0	500
Patient 18	RA	60	33.69	6	7	20	400
Patient 19	RA	35	45.35	4	8	0	300
Patient 20	RA	37	35.43	1	8	0	400
Patient 21	OA	63	43.53	4	7	0	350
Patient 22	OA	72	27.2	3	6	0	300
Patient 23	OA	66	28.57	1	4	0	450
Patient 24	RA	52	30.5	0	9	0	350
Patient 25	RA	49	25.24	4	9	0	400
Patient 26	PA	46	31.57	1	6	20	300
Patient 27	OA	53	36.34	0	10	0	400
Patient 28	RA	56	33.83	1	7	20	400
Patient 29	OA	53	33.38	3	6	0	400
Patient 30	RA	48	21.6	2	9	0	300
Patient 31	OA	54	36.64	3	10	60	300
Patient 32	PA	51	34.8	4	8	45	300
Patient 33	RA	48	27.28	0	8	0	450
Patient 34	OA	50	47.72	1	8	20	450
Patient 35	RA	68	32.87	2	10	0	300
Patient 36	PA	48	37.9	3	8	96	450
Patient 37	RA	21	29.69	0	7	0	500
Patient 38	RA	61	23.42	1	10	80	400

RA, rheumatoid arthritis; OA, osteoarthritis; PA, psoriatic arthritis; VAS, Visual Analog Scale; BMI, body mass index (kg/m^2)

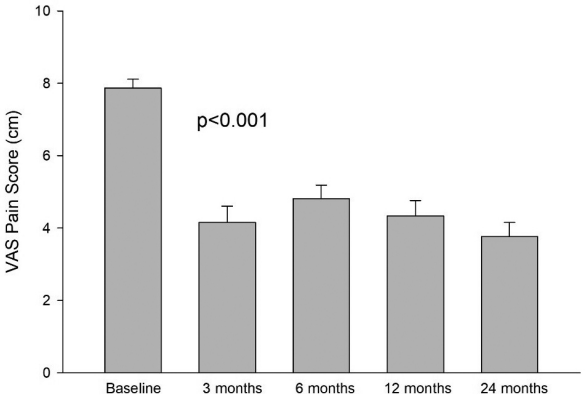


Fig. 1. *Change of the visual analog scale pain scores from baseline to 24 months after an initial ketamine infusion. Please note a significant improvement in pain scores spanning throughout 24 months ($P < 0.001$). Time interval of pain relief, and consequently number of infusions, varied.*

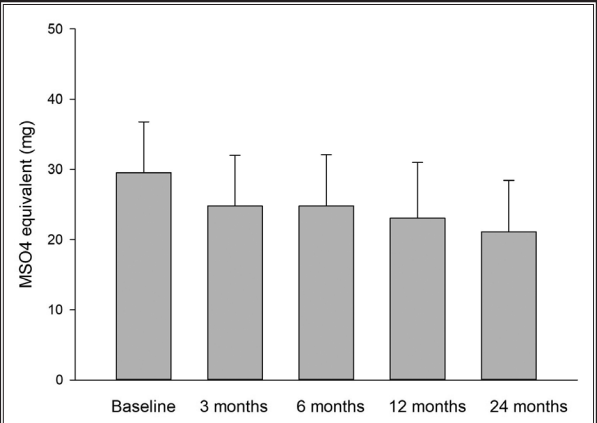


Fig. 2. *Decrease of opioid usage in 18 patients receiving opioids at baseline. Note that the majority of the patients decreased their opioid usage, while 6 eliminated opioid usage completely. Seven patients maintained the same baseline opioid dosage through 24 months while one patient who did not use opioids at baseline went from no opioid usage to 40 mg morphine equivalent.*

various dosing of ketamine with 300–500 mg given over one infusion session, and the occasional presence of other sources of chronic pain in addition to chronic arthritis. Although patients in this cohort reported an average of 2 additional sources of chronic pain, their predominant clinical indication for chronic pain was arthritis-related.

Conclusions

Ketamine infusions gave substanial and lasting pain relief to patients with severe arthritis. Repeated infusions provided consistent improvements throughout 24 months. Opioiod usage decreased in those patients taking opioids.

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