Prospective Study

# Assessment of Three Regimens of Ketamine Infusion in Complex Regional Pain Syndrome: A Randomized Prospective Comparative Study

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**Background:** Ketamine helps in the management of complex regional pain syndrome (CRPS) by blocking N-methyl-D-Aspartate receptors, reducing inflammation, relieving pain, and offering antidepressant effects.

**Objectives:** To investigate how 3 sub-anesthetic doses of ketamine infusions aid pain reduction in CRPS patients.

**Study Design:** A randomized prospective comparative study

**Methods:** This study was carried out on 75 men and women over 21 years of age who were diagnosed with CRPS and categorized as I or II according to the physical status classification system used by the American Society of Anesthesiologists. Patients were divided into 3 groups and given ketamine infusions over a period of 6 hours at doses ranging from 0.1 to 0.35 mg/kg/h, with a maximum dose of 24 mg/h. Three days of treatment were given to Group A, 5 days to Group B, and 7 days to Group C.

**Results:** The scores on the Brief Pain Inventory—Short Form and on the numerical rating scale were significantly lower in groups B and C than in group A ($P < 0.05$) at the first, second, and third months. Nevertheless, no significant differences were observed between group B and group C at the same intervals. Side effects associated with ketamine infusion were significantly lower in group A than groups B and C. Similarly, the side effects were also significantly lower in group B than group C ($P < 0.05$).

**Limitations:** The study had no control group and was performed in a single center with a short period of follow-up.

**Conclusions:** A 5-day regimen of ketamine infusion was associated with the best outcome for pain control and minimal side effects. Meanwhile, the 7-day regimen of ketamine infusion had the greatest number of side effects. The 3-day period of infusion had the lowest number of side effects and offered the least pain control.

**Key words:** Ketamine, receptors, N-methyl-D-aspartate, pain measurement, analgesics, chronic pain, complex regional pain syndrome, anesthetics, infusions, parenteral

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Complex regional pain syndrome (CRPS) is a chronic pain disorder that can develop long after the initial damage and affects the arms or legs. The pain is disproportionate to the initial injury (1).

Fractures, particularly distal radius and Colles' fractures, are frequently associated with the onset of CRPS, occurring in 36.7% of cases. The condition may also follow orthopedic surgeries, various forms of trauma, prolonged immobilization, or a stroke (2).

The treatment plan for chronic CRPS combines medical care, psychological support, physical therapy, and occupational therapy. While immunomodulation and hyperbaric oxygen therapy can be helpful, pharmacological treatments remain the primary mode of treatment (3).

The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine, which is derived from phencyclidine (PCP) or phenylcyclohexyl piperidine, has been studied for its potential to reduce pain, with usual dosages between one and 4.5 mg/kg. The FDA now classifies ketamine as an anesthetic induction drug, although it was initially launched in 1970 as a fast-acting intravenous (IV) anesthetic (4).

Through its noncompetitive blocker action at the PCP-binding site on NMDA receptors in the central nervous system, ketamine lowers neuronal activity. Ketamine does this by blocking NMDA receptors, which are activated by glutamate, the central nervous system's main excitatory neurotransmitter (5).

Beyond its antagonism of NMDA receptors, ketamine influences mood and pain through a variety of mechanisms. In addition to inhibiting potassium and sodium channels, ketamine does the same to muscarinic cholinergic and nicotine receptors. Additionally, it increases GABA-A signaling, voltage-gated calcium channels, D2 dopamine receptors, and descending modulatory pathways (6,7).

Patients with refractory CRPS may benefit from a low sub-anesthetic ketamine infusion, according to the present study's hypothesis. The goal was to assess how well 3different sub-anesthetic ketamine infusion methods reduced the pain levels of CRPS patients.

## Methods

This prospective comparative study was randomized and included 75 patients who were categorized as I or II on the American Society of Anesthesiologists' physical status classification system and were at least 21 years old. The patients were diagnosed with CRPS for having severe debilitating chronic refractory pain (> 3 months) that interfered with daily activities and did not respond to conventional multimodal medical therapy. The Budapest criteria (8) included chronic pain that was excessive compared to any triggering event, at least one symptom from 3 or more categories, and at least one sign from 2 or more categories at the time of assessment.

From April 2023 to October 2023, the institutional ethical committee gave the study its approval (approval code: 36264MS44/1/23) and registered at Clinicaltrials.gov (ID: NCT05997134). All patients provided informed written consent.

### Randomization

With the use of computer-generated numbers, patients were divided randomly into 3 groups and given ketamine infusions over a period of 6 hours at doses ranging from 0.1 to 0.35 mg/kg/h, with a maximum dose of 24 mg/h. Three days of treatment were given to Group A, 5 days to Group B, and 7 days to Group C.

Patients with unstable psychological or psychiatric conditions that could interfere with the treatment or evaluation process were excluded from the study. Additionally, individuals who had recently undergone significant pain-related procedures were not included, since those interventions could have affected the study's results. Those with a history of drug dependence, particularly involving ketamine or psychostimulants, were also excluded due to the potential for misuse or adverse interactions. Lastly, patients with severe allergic reactions to ketamine or existing cardiovascular, hepatic, or renal impairments were excluded, because those conditions could have led to complications or adverse effects during treatment.

Patients received a complete history, clinical examination, laboratory tests (CBC, renal, hepatic functions), and an ECG before the infusion. All patients fasted from solid and heavy meals for at least 8 hours, from light meals for 6 hours, and from clear fluid (water) 2 hours before the infusion. On arrival, 2 IV lines were inserted (20 G), ringer lactate or acetate was maintained in one of the lines at an infusion rate of 100 mL/h, and a ketamine infusion was maintained in the other line at an infusion rate of 24 mg/h for about 6 hours. The infusion was prepared as follows: 3 mL of ketamine plus 47 mL of normal saline at a total volume of 50 mL was applied at a rate of 3 mg/mL, so the infusion rate through the infusion pump was 8mL/h.

Patients were monitored during the time of infusion for noninvasive blood pressure, ECG, and peripheral oxygen saturation. All patients were on nasal cannula with a flow rate of 2 L/m and were observed for at least 60 minutes after the infusion for possible side effects (headache, hallucinations, desaturation, nausea, and vomiting). The level of sedation was assessed during the period of infusion. All patients continued the previous medications during the follow-up period.

For every patient, demographic information, such

as age, gender, and BMI, was documented. Pain and psychological effects were assessed at the baseline and each month during a 3-month time span, using the Brief Pain Inventory Short—Form (BPI-SF) questionnaire and numeric rating scale (NRS). Continuous hemodynamic monitoring (heart rate and mean arterial blood pressure) was done, and any adverse events were noted and managed. Sedation levels during infusion were evaluated using the Richmond Agitation Sedation Scale (RASS), a 10-point scale from -5 (unarousable) to +4 (combative), with a score of 0 indicating alert and calm (9).

### Sample Size Calculation

The Epi Info™ program (version 2002) was used to calculate sample size and power analysis. With a 95% confidence interval, a 10% margin of error, the estimated success rate for sub-anesthetic ketamine infusions in lowering the chronic refractory pain felt by CRPS patients was 35% (ranging from 25% to 45%) (10). The initial calculation of the necessary number of patients per group was 22 but was later modified to 25 to account for possible dropouts.

### Statistical Analysis

SPSS Statistics 27 (IBM Corp.) was used for statistical analysis. Histograms and the Shapiro-Wilks test were used to determine whether the data were normal. Mean ± SD was used to present the parametric data, the median (interquartile range) was used to present the non-parametric data, and frequency (%) was used to present the qualitative data. The ANOVA and a Tukey post hoc test were used to analyze the parametric data, the Kruskal-Wallis and Mann-Whitney tests were used to assess the non-parametric data, and the chi-square test was used to assess the qualitative data. Statistical significance was defined as a *P*-value of less than 0.05.

## Results

Ninety-three patients were evaluated for eligibility in this study, and 18 patients were eliminated; 11 of those patients did not fit the inclusion requirements, and 7 of them refused to participate. Three equal groups of 25 patients each were randomly selected from the remaining patients. Every one of the patients was followed up on, and statistical analysis was done on their data (Fig. 1).

Differences in the patients' characteristics among the 3 groups studied were insignificant (Table 1). BPI-SF scores in the areas of pain intensity and effects on daily activity, sleep, mood, and enjoyment were significantly lower in groups B and C than group A ($P < 0.05$) at the first, second, and third months, but there was no significant difference between groups B and C at the same follow-up intervals (Fig. 2). NRS scores were significantly lower in groups B and C than group A ($P < 0.05$) at the first, second, and third month, but no significant differences were observed between groups B and C (Fig. 3). Adverse events associated with ketamine infusion were significantly lower in group A than groups B and C and were also significantly lower in group B than in group C ($P < 0.05$). (Fig. 4). Adverse hemodynamic events and level of sedation were insignificantly different between the studied groups (Table 2).

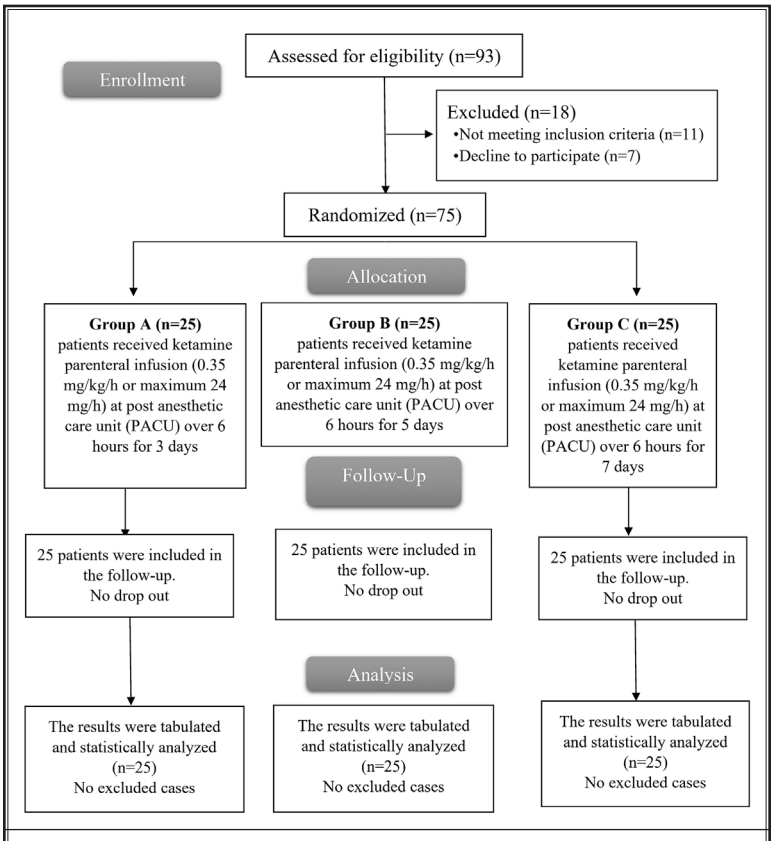


Fig. 1. *CONSORT flowchart of the enrolled patient.*

## Discussion

CRPS is a long-term pain disorder that affects extremities, often occurring after an injury. The symptoms include severe pain, edema, and changes in skin tone or temperature (11). The condition affects sensory, motor, and autonomic functions, and its exact cause remains unclear, though it is thought to involve abnormal nervous system responses. Treating CRPS is difficult and requires a multidisciplinary approach (12).

The current study assessed pain using the BPI-SF questionnaire, including the pain intensity and pain interference areas. The questionnaire showed that the ratings in

Table 1. *Comparisons among the 3 studied groups according to patient characteristics.*

| | | Group A (n = 25) | Group B (n = 25) | Group C (n = 25) | Test of Sig. | *P* |
|---|---|---|---|---|---|---|
| Age (years) | | 56.40 ± 11.43 | 55.24 ± 13.28 | 54.84 ± 12.39 | F = 0.107 | 0.899 |
| Gender | Male | 12(48.0%) | 13(52.0%) | 12(48.0%) | $X^2$ = 0.107 | 0.948 |
| | Female | 13(52.0%) | 12(48.0%) | 13(52.0%) | | |
| BMI (kg/m$^2$) | | 25.60 ± 3.79 | 25.12 ± 3.64 | 25.24 ± 3.43 | F = 0.119 | 0.888 |

Data are presented as mean ± SD or frequency (%). F: one-way ANOVA test, $X^2$: chi-square test, BMI: body mass index.

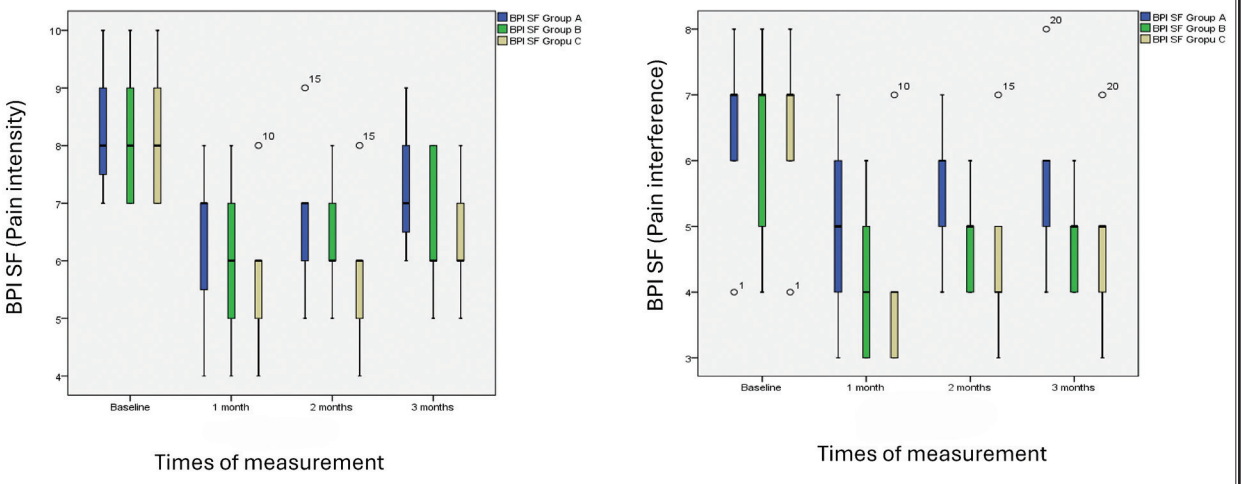


Fig. 2. *Changes in the scores on the Brief Pain Inventory—Short Form in the 3 studied groups. A: pain intensity, B: pain interference.*

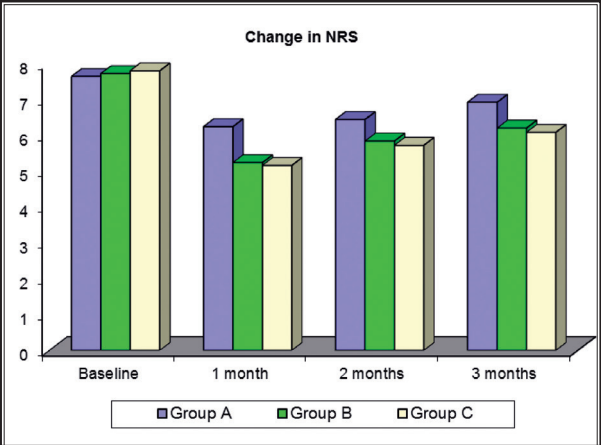


Fig. 3. *Changes in the scores on the numerical rating scale (NRS) in the studied groups.*

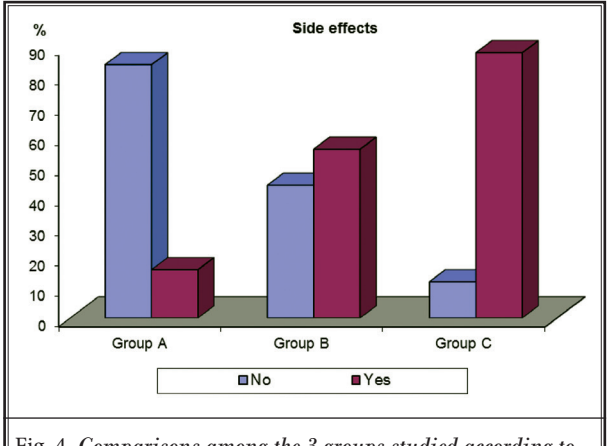


Fig. 4. *Comparisons among the 3 groups studied according to occurrence of any side effects (e.g., headache, desaturation, nausea, and vomiting).*

Table 2. *Hemodynamic changes and level of sedation of the studied groups.*

| | | Group A (n = 25) | Group B (n = 25) | Group C (n = 25) | $X^2$ | *P* |
|---|---|---|---|---|---|---|
| Hemodynamic Changes | Hypertension | 2(8.0%) | 2(8.0%) | 3(12.0%) | 0.324 | 0.854 |
| | Hypotension | 1(4.0%) | 1(4.0%) | 1(4.0%) | 0.0 | 1.0 |
| | Tachycardia | 2(8.0%) | 2(8.0%) | 3(12.0%) | 0.324 | 0.854 |
| | Bradycardia | 1(4.0%) | 2(8.0%) | 1(4.0%) | 0.528 | 0.768 |
| | Arrhythmia | 1(4.0%) | 1(4.0%) | 2(8.0%) | 0.528 | 0.768 |
| Level of Sedation | Restless | 2(8.0%) | 1(4.0%) | 1(4.0%) | 0.528 | 0.768 |
| | Drowsy | 2(8.0%) | 1(4.0%) | 2(8.0%) | 0.431 | 0.807 |
| | Light sedation | 3(12.0%) | 3(12.0%) | 4(16.0%) | 0.233 | 0.891 |

Data is presented as frequency (%). $X^2$: chi-square test.

those categories in groups B and C were significantly lower than those in group A at the first, second, and third months. However, the scores on the BPI-SF showed no significant difference between groups B and C at the same follow-up interval.

Similarly, according to the 3 groups' responses to the pain-assessment component of the NRS, groups B and C experienced significantly less pain than did group A in the first, second, and third months. By contrast, the NRS scores showed no significant difference between groups B and C at the same interval of follow-up. Supporting our results, Marzoughi et al (13) observed a notable decrease in the ratings of pain intensity at the follow-up compared with the baseline. As for the pain assessments on the BPI-SF, patients' follow-up scores on the standardized measures of pain, pain interference, anxiety, and depression significantly decreased from their baseline counterparts. A study by Chebini et al (14) also reported significant pain reduction at the follow-up in comparison to the baseline. In an additional instance of agreement with our study, Mangnus et al (15) showed a significant reduction in pain from the baseline to the follow-up.

By contrast, the pain-assessment portion of the BPI-SF revealed that there was no significant improvement in mood, walking ability, or daily activities in the ketamine group. This result may be attributable to the different duration and the change in sample size. In agreement with our study, Schwartzman et al (16) showed that the administration of IV ketamine in an outpatient setting was associated with significant reductions in many pain parameters. Also, Kiefer et al (17) found that for most patients, the scores at the first, third, and sixth months of follow-up indicated significant pain relief as well as considerable improvements in quality of life, movement disorders, and work capacity. Goldberg et al (18) observed minimal pain relief on the first day, with more marked improvements by day 3. Dahan et al (19) similarly reported a decrease in NRS scores that persisted beyond the treatment but eventually reverted to baseline levels. These variations could be due to differences in the dose and length of the treatment

In the current study, side effects were comparable among the 3 groups; Group A had the fewest side effects, followed by Group B, while Group C had the most. As for hemodynamic changes, including heart rate, MAP, and the level of sedation as measured by the RASS score, no statistically significant difference was observed among the 3 studied groups. Supporting our study, Marzoughi et al (13) demonstrated that no serious side effects were reported during the course of infusion. All reported side effects were mild, such as headache, nausea, flushing, and dizziness, and tolerable to the patients. In another example of confirming the findings of our study, Tay et al (10) demonstrated the occurrence of transient minor side effects in the central nervous system that most patients tolerated and required no treatment. Once the ketamine infusion was stopped, these temporary side effects usually disappeared. In contrast to our study, tachycardia and hypertension were noted by Tay et al, but these side effects were transient and also dissipated following the infusion. Sigtermans et al (20) observed noninvasive blood pressure 3 times a day throughout the infusion and discovered that ketamine had no discernible effect on blood pressure, which was consistent with our findings. In a similar vein, Schwartzman et al (16) noted that while some patients experienced headaches, nausea, and fatigue, none of them experienced agitation, blurred vision, or psychomimetic symptoms like hallucinations or delusions.

This study's limitations included its small sample size, single-center design, and brief follow-up period. Also, the research did not have a control group to better assess the outcome of ketamine infusion on drug requirements and psychological health of the patients.

## Conclusions

The 5-day period of ketamine infusion had the best outcome for pain control and minimal side effects. By comparison, the 7-day ketamine-infusion regimen was associated with the greatest number of side effects. The 3-day infusion was associated with the least number of side effects and least amount of pain control.

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