

RESEARCH ARTICLE

Effect of intravenous low-dose S-ketamine on pain in patients with Complex Regional Pain Syndrome: A retrospective cohort study

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Abstract

Objective: The objective of this study was to assess the effectiveness of a low-dose intravenous S-ketamine treatment on refractory pain in patients with Complex Regional Pain Syndrome (CRPS).

Methods: In this retrospective study, patients with CRPS who received intravenous S-ketamine from March 2010 to April 2019 were included. According to our inpatient protocol, S-ketamine dose was increased until pain reduction was achieved or side effects were observed. Maximum dose was 14 mg/h and treatment duration was 7 days. Primary outcome parameters were pain scores (Numeric Rating Scale) at baseline (T0), end of infusion (T1), and approximately 4 weeks postinfusion (T2). Patients were categorized as responder/nonresponder at T1 and T2. Patients were considered a responder in case there was pain score reduction of greater than or equal to 2 points or if treatment was reported as successful.

Results: Forty-eight patients were included. Mean disease duration was 5 years (interquartile range [IQR] = 6 years). Median pain score significantly decreased from 8 (IQR = 2) at T0 to 6 (IQR = 4) at T1 ($p < 0.001$). At T1, 62% of the patients were responders. At T2, 48% of the patients remained a responder. A significant proportion of the responders at T1 turned into nonresponders at T2 ($p = 0.03$).

Conclusion: In a group of patients with CRPS with refractory pain, low-dose intravenous S-ketamine treatment resulted in effective pain relief during infusion. Although a significant proportion of initial responders became nonresponders at follow-up, half of the patients were still a responder at ~ 4 weeks postinfusion. Further research is needed to investigate mechanisms responsible for pain relief by S-ketamine infusions and to ascertain possible predictors of response to the treatment.

KEYWORDS

Complex Regional Pain Syndrome (CRPS), dose, intravenous, pain, S-ketamine

INTRODUCTION

Complex Regional Pain Syndrome (CRPS) type 1 is a syndrome characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of pain after trauma or other lesion.¹ The pain is regional, not in a specific nerve territory or dermatome, and usually has a distal predominance.^{1,2} In addition, CRPS is characterized by a variable progression over time.² The estimated incidence of CRPS varies between 5.5 and 26.2 per 100,000 person years^{3,4} and women are affected at least 3 times more often than men.⁴ CRPS is diagnosed using a set of clinical criteria: the International Association for the Study of Pain (IASP) clinical diagnostic criteria.⁵ In sum, the diagnosis is based on continuous pain in the affected limb, which is disproportionate to the inciting event and which is accompanied by (a minimum set of) sensory, sudomotor, vasomotor, motor, and trophic abnormalities.^{5,6}

The Dutch CRPS guidelines (last updated in 2014) for the treatment of CRPS define our daily practice.⁷ Nociceptive pain in CRPS is treated in a step-by-step manner, with weak opioids being the maximum step as strong opioids are not recommended in CRPS. Neuropathic pain is treated with co-analgesics. These guidelines also recommend treatment with intravenous S-ketamine for patients with CRPS type I with therapy-resistant pain. This therapy is therefore regularly prescribed and administered to patients with CRPS with therapy-resistant pain in our department.

Ketamine, a derivative of phencyclidine (“Angel dust”), was introduced in the 1960s as an anesthetic.⁸ Its large margin of safety quickly led to widespread use during the Vietnam war.⁸ Ketamine has been coined a “dissociative anesthetic”⁸; however, its unique methods of action are still incompletely understood. It is thought, that this state of dissociative anesthesia is achieved via a disruption of cortico-cortical communication.⁹

When S-ketamine is administered in a low dose, it can be used as an analgesic in various acute and chronic pain settings.¹⁰ This analgesic effect of S-ketamine is achieved through its antagonistic-actions on the N-methyl-D-aspartate (NMDA) receptor.^{11–13} Activation of the NMDA receptor is thought to be a major contributor to the wind-up phenomenon, which leads to central sensitization.^{14–17} Central sensitization can develop symptoms like spontaneous pain, allodynia, and hyperalgesia to nociceptive stimuli.^{15–17} These symptoms can be reduced when the wind-up phenomenon and central sensitization are blocked by S-ketamine administration.^{14–17}

What is known about the clinical effects of S-ketamine administration in CRPS is that the analgesic effects have not only been observed during administration, but also seem to last for a period of time after the administration.^{18,19} A meta-analysis by Zhao et al.¹⁹

Key Points

- In a group of patients with CRPS with refractory pain, low-dose intravenous S-ketamine treatment resulted in effective pain relief during infusion
- Responders started to observe treatment effect within 2 days
- The median effective S-ketamine dose was 6 mg/h
- At ~ 4 weeks postinfusion, almost half of the patients were still responders
- Further research is needed to understand which pathophysiological mechanisms are targeted by S-ketamine infusion in order to predict treatment responders

showed that intravenous S-ketamine therapy can provide clinically effective pain relief in short term for less than 3 months. Zhao and colleagues¹⁹ used a 30% pain relief event rate to evaluate efficacy of S-ketamine in CRPS and found an effect of 69% immediately after S-ketamine treatment and an effect of 58% at the 1–3 months of follow-ups.

In our experience, the effectiveness of S-ketamine therapy in our patients with CRPS is not as great or as long lasting as described in the meta-analysis. However, in our infusion protocol, the S-ketamine dose is relatively lower than the dose used by most studies included in the meta-analysis by Zhao et al.¹⁹ This could be a reason for the discrepancy between our clinical results and the findings in the meta-analysis. Therefore, we conducted this retrospective cohort study in which we aimed to assess the effectiveness of our lower dose intravenous S-ketamine treatment for pain intensity in our patients with CRPS.

METHODS

Ethical approval

Ethical approval for this study was obtained from Medical Ethics Committee of Erasmus University Medical Center Rotterdam (MEC-2019-0209).

Patients

We searched the electronic medical record database for patients with CRPS who received a low-dose intravenous S-ketamine treatment in the period between March 2010 and April 2019 at the Center for Pain Medicine (CPM) at Erasmus MC University Medical

Center. Only patients aged 18 years or older during the time of treatment were included in this study. Of patients who had multiple S-ketamine treatments during the study period, only data from the first treatment were included in this study. At the CPM, CRPS is diagnosed using the IASP clinical diagnostic criteria for CRPS.⁵ Patients with CRPS who were treated with S-ketamine in an emergency setting, and thus not in an elective setting, were excluded. Furthermore, patients who were admitted to the hospital for combination treatments of S-ketamine with another drug were also excluded from this study.

Treatment with S-ketamine

S-ketamine is administered intravenously in patients with CRPS according to the protocol which was derived from the study by Sigtermans et al.¹⁸ Although a maximum dose of 0.43 mg/kg/h is described in the literature,¹⁸ we maintain a maximum dose of 14 mg/h (0.2 mg/kg/h normalized to a 70 kg patient) on our ward.

A synopsis of our protocol is the total inpatient treatment duration is 7 days. S-ketamine is started at 3 mg/h. The dose is increased twice a day (usually in the late morning and late afternoon) with steps of 1–2 mg/h. The increase depends on whether the patient experiences pain reduction or side effects. Once the patient notices a reduction in pain, the S-ketamine dose is not increased further for the duration of admission, we call this the “effective dose.” In case the patient experiences severe side effects, the dose is reduced until the side effects disappear. If the side effects reduce, the S-ketamine dose is increased again and effect and side effects are closely monitored.

Measurements, data collection, and management

Data for this study were extracted from electronic medical records. Data were obtained at baseline before treatment (T0), at discharge from the hospital (T1), and at the first follow-up outpatient appointment (T2), which was at a variable time interval, depending on individual appointments of patients in the outpatient clinic. The primary outcome parameters were pain scores (Numeric Rating Scale [NRS]) at T0, T1, and T2.

Patients were categorized as either a responder or nonresponder to S-ketamine at T1 and T2. Patients were considered a responder if there was a reduction in their pain score of greater than or equal to 2 points from baseline²⁰ and/or if treatment was reported as successful in the electronic medical record. In case the patients met neither of these 2 conditions, they were categorized as nonresponders.

The following data were also extracted: maximum dose, “effective dose,” side effects, and the day the patient first noticed treatment effect.

Statistical analysis

Descriptive statistics were used to determine the frequency distributions of the variables and to describe measures of central tendency and variability of the continuous parameters dependent on the shape of their distribution. The Shapiro-Wilk test was used to analyze whether or not continuous parameters were normally distributed. A Related-Samples Friedman’s Two-Way analysis of variance by ranks was used for finding a difference in the skewedly distributed pain scores across the 3 moments of measurement. The Wilcoxon signed-rank was used to assess the difference between these scores before and after treatment and before treatment and at first follow-up. The McNemar test was performed to compare paired proportions of the non-responders at T1 and T2. No correction for multiple testing was made. The alpha level for statistical significance was set at the traditional level of 0.05. The study was analyzed using a per-protocol analysis. Data analysis was performed using IBM SPSS statistics for Windows, version 25.0.

RESULTS

Patients

Data from 60 patients were identified and extracted from electronic medical records. A total of 12 patients were excluded from the study because of 2 reasons. First, 9 patients were admitted to the hospital for a combination treatment of S-ketamine with another drug. These other drugs were mannitol, tadalafil, or pamidronic acid. Second, 3 patients received S-ketamine in an emergency setting. Thus, a total of 48 patients were included in this study (Figure 1). Patients’ baseline characteristics are shown in Table 1.

S-ketamine treatment

Characteristics of the S-ketamine treatment are depicted in Table 2. The median time interval between discharge (T1) and the first follow-up appointment (T2) lasted 4 weeks (interquartile range [IQR] = 5).

Pain scores

At T0, the pain score was available of 42 of the 48 patients and their median NRS before treatment was 8

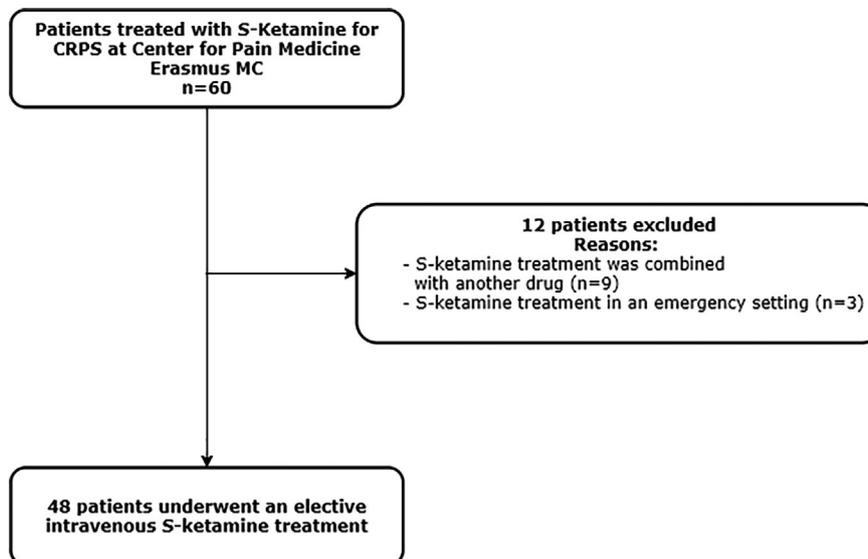


FIGURE 1 Flowchart of patient selection. MC, Medical Center; CRPS, Complex Regional Pain Syndrome

TABLE 1 Patients' baseline characteristics

	<i>n</i> = 48
Age (years)	39 (SD ± 14)
Gender	
Male	7 (15%)
Female	41 (85%)
Duration of diagnosis (years)	
Median (IQR)	5 (6)
NRS before treatment	
Median (IQR)	8 (2)
Medication at start treatment	
Paracetamol	17 (35%)
NSAIDs	11 (23%)
Opioids	30 (63%)
Antidepressants	12 (25%)
Anti-epileptics	16 (33%)

Abbreviations: IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; NRS, Numeric Rating Scale; SD, standard deviation.

TABLE 2 Characteristics of S-ketamine treatment

Duration of treatment (days)	6 (SD ± 2)
Maximum dose (mg/h)	7 (SD ± 3)
Side effects	<i>n</i> = 30 (63%)
Headache	6 (20%)
Drowsiness	11 (37%)
Dizziness	14 (47%)
Nausea	8 (27%)
Hallucinations	0 (0%)

Abbreviations: mg, milligram; h, hour.

(IQR = 2). At T1, the pain score of 36 patients was available and their median NRS at discharge was 6 (IQR = 4). At T2, the pain score of 18 patients was available and their median pain score was 7 (IQR = 3).

Thus, the median NRS score changed from 8 (IQR = 2) before treatment to 6 (IQR = 4) at discharge and 7 (IQR = 3) at first follow-up, ($p < 0.001$); see Figure 2. Pairwise comparison yielded a significant difference between the scores before treatment and both those at discharge ($p < 0.001$) and those at first follow-up ($p = 0.015$).

Responder versus nonresponder

At T1, data of 47 of the 48 patients were available for classification as responder or nonresponder as of 1 patient, the response to S-ketamine treatment was unknown. After S-ketamine infusion at discharge from the hospital (T1), 29 (62%) of 47 patients were classified as responders, and 18 (38%) of 47 patients as nonresponders. At the first follow-up appointment (T2), data were available for 40 of the 48 patients. At T2, 19 (48%) of these 40 patients were responders, all of them were also responders at T1. At T2, 21 (53%) of the 40 patients were classified as nonresponders. None of the patients who were originally nonresponders to S-ketamine treatment at T1 became responders at T2. Six of the 40 patients (15%) turned from a responder at T1 into a nonresponder at T2. This implies that a statistically significant proportion of responders at T1 turned into nonresponders at T2 ($p = 0.03$; see Table 3).

For responders at T1, the median NRS before treatment was 8 (IQR = 1) and at discharge 5 (IQR = 4). Pairwise comparison yielded a significant difference between the scores before treatment and at discharge ($p < 0.001$). At follow-up (T2), in 9 of the 19 responders,

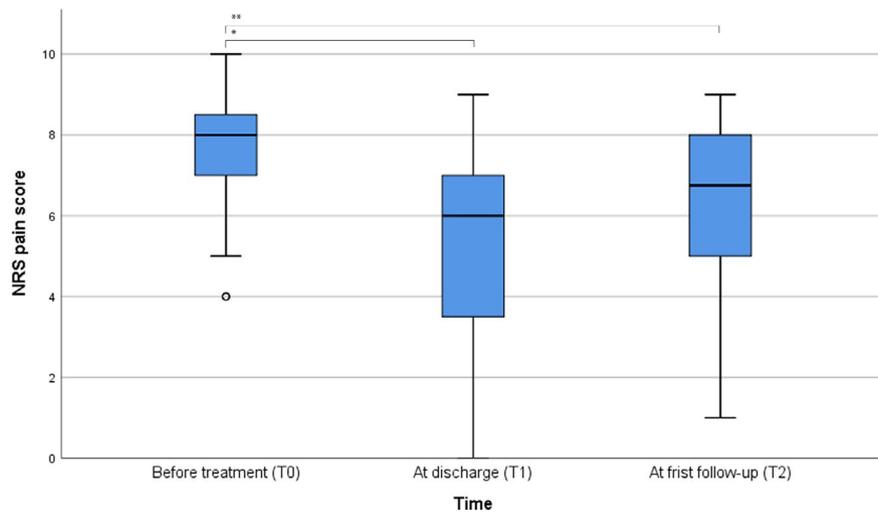


FIGURE 2 Pain scores of patients with CRPS before start of the S-ketamine infusion (T0, $n = 42$), at discharge of the treatment (T1, $n = 36$), and at first follow-up visit to the clinic after treatment (T2, $n = 18$) NRS, Numeric Rating Scale. * $p < 0.001$, ** $p = 0.015$

TABLE 3 (Non)responders at T1 and T2 (n [% of total])

	T2		Total
	Responder	Nonresponder	
T1			
Responder	19 (48)	6 (15)	25 (63)
Nonresponder	0 (0)	15 (38)	15 (38)
Total	19 (48)	21 (53)	40 (100)

the NRS was available and for these patients the median NRS score was 6 (IQR = 3). Unfortunately, we encountered too many missing NRS scores at follow-up to statistically compare these scores with baseline and discharge.

For nonresponders at T1, the median NRS before treatment was 8 (IQR = 2) and at discharge 8 (IQR = 1). Pairwise comparison yielded no significant difference between the scores before treatment and at discharge ($p = 0.125$).

Responders at T1 started to observe a treatment effect at a median of 2 (IQR = 1) days after starting treatment. The median effective dose of these responders was 6 (IQR = 4) mg/h S-ketamine.

Regarding demographic parameters, no statistically significant differences were found between responders and nonresponders after S-ketamine infusion.

DISCUSSION

This retrospective cohort study included patients with CRPS with therapy-resistant pain who were treated with a low-dose 7-day intravenous S-ketamine infusion. It showed a statistically significant reduction in median pain scores between admission (T0) and discharge (T1) and between admission and follow-up (T2) at a median

of 4 weeks. At T1, 62% of the patients were responders. For a significant proportion of patients, from whom data were available at both T1 and T2, 48% still were a responder at T2.

As mentioned in the introduction, the S-ketamine dose in our infusion protocol is relatively lower than the dose used by most studies included in the meta-analysis by Zhao et al.¹⁹ This was one of the reasons why our research group believed that the effect of our S-ketamine infusions was not as large or as long-lasting as described by Zhao et al.¹⁹ Zhao and colleagues reported an effective treatment by using a 30% pain relief event rate in 69% of the patients immediately after S-ketamine treatment and in 58% of the patients at the 1–3 month's follow-up.¹⁹ Despite our low-dose regimen, the results of our study still show that about half of our patients benefit from low-dose S-ketamine administration for up to 4 weeks on average (T2). This is in line with the 58% of patients with an effective treatment effect at the 1–3 month's follow-up described by Zhao et al.¹⁹ However, most studies included in the meta-analysis do not have a retrospective design and are therefore methodologically not comparable to our study.

For the responders to S-ketamine treatment, we did a post hoc analysis on pain relief beyond T2. Data on duration of pain reduction were available from 12 of 19 patients who were responders at both T1 and T2. The median duration of their treatment effect was 9 weeks (IQR = 7) and 1 patient even reported a duration effect of 27 weeks. Despite the low number of patients, the treatment effect of 9 weeks is roughly in line with the reported pain relief of 11 weeks by Sigtermans and colleagues.¹⁸ In addition, our results fit in the range of 1–3 months effective pain relief after S-ketamine infusion reported by the meta-analysis by Zhao et al.¹⁹

Interestingly, we found that a considerable proportion of responders at T1 turned into nonresponders at

T2. For these patients, continued treatment might be necessary and therefore follow-up therapy with an oral NMDA-receptor antagonist might be proposed.

Furthermore, it is notable that responders noticed a positive treatment effect within 2 days and that the effective dose—median of 6 mg/h—was relatively low. These findings raise the following questions: (1) whether long hospital admissions are necessary and (2) whether relatively high dosing greater than 14 mg/h is required. First, as an alternative to lengthy inpatient hospital admissions, outpatient day care treatments with multiple clinic visits could be proposed.^{21–23} Second, although the current study suggests that an S-ketamine dose less than 14 mg/h might be sufficient to achieve pain relief, Sigtermans et al. and the consensus guidelines of the United States recommend a higher dose of ~ 22 mg/h for patients with CRPS.^{18,21} Altogether, there is no sufficient evidence yet to define a “gold standard” protocol.

This study has several limitations. First and foremost, is the retrospective design of this cohort study. We encountered missing data and the outcome assessment was not standardized. Unfortunately, we encountered too much missing data to draw valid conclusions after the 4-week post-treatment period. Prospective studies are needed that study the duration of pain relief and other factors, such as return to work, pain medication reduction, and the need of repeating the intravenous S-ketamine treatments.^{21,24} Furthermore, our patients were treated in a tertiary referral hospital, were suffering from CRPS for several years, and were therapy-refractory to several other treatments. Therefore, these results might not be generalizable to patients who are newly diagnosed with CRPS. Another limitation is that we cannot compare our intravenous low-dose regimen with relatively high-dose regimens recommended by, for instance, Xu and colleagues.²⁵ Finally, the focus on pain relief is a common limitation in pain research and deserves more attention. Not only is pain perception a subjective outcome parameter, it is also heavily influenced by multiple interrelated biological, psychological, and social factors.²⁶ For future research, it would be advisable to obtain objective parameters, such as quantitative sensory testing^{27,28} and the emerging diagnostic and prognostic biomarkers of small noncoding RNAs (microRNAs)²⁹ alongside additional subjective parameters, like the quality of life and the measurement of the global perceived effect of the treatment.^{30,31}

In the search for optimal pain management, Woolf et al.³² advocated as early as 1999 for a shift in pain medicine from a symptom-based treatment toward a mechanism-based treatment. For CRPS treatment, it is currently advised to target the underlying pathophysiological mechanisms deemed most prominent during history taking and physical examination.^{33,34} However, in clinical practice, S-ketamine is still prescribed for therapy-resistant pain without thorough consideration of the pathophysiological mechanism causing the pain. In

addition, awareness of the mechanisms underlying pain reduction by S-ketamine need to be explored because they can be used to predict response on the treatment. If more insights on these mechanisms were to be revealed, S-ketamine might be prescribed in a more mechanism-based and individually tailored manner.

Various mechanisms of action have been proposed for the therapeutic effects of ketamine. The most prominent rationale is the antagonism of the NMDA receptor causing a weakening of central neuroplastic changes like the wind-up phenomenon and central sensitization.^{14,15,35} However, effects of ketamine on CRPS might not be restricted to only its antagonistic actions on the NMDA receptor. For instance, Sorel et al.³⁶ showed that the analgesic effect of ketamine in CRPS is related to changes in GABA/glutamate balance in the cerebral cortex. Furthermore, ketamine also has immunomodulatory and anti-inflammatory properties.^{37,38} Therefore, ketamine might modulate inflammation and interact with the closely linked immune and nervous system in the pathophysiology of CRPS. Finally, ketamine has been prescribed for its antidepressant properties.^{39,40}

Further research is needed in order to determine the underlying mechanism(s) for which it is beneficial to give S-ketamine to patients with CRPS and to predict responsiveness to S-ketamine treatment. Given the exploratory nature of this retrospective study, we did not consider it achievable to look for predictors of response to S-ketamine. In search of predictors, Birklein et al. and our research group previously mentioned the potential use of systemic microRNAs as a biomarker in the diagnosis and management of CRPS.^{29,41} These small noncoding RNA molecules can negatively regulate gene expression and their dysregulation is revealed in several diseases.^{42,43} For patients with CRPS, it seems that microRNA profiling could be used as a prognostic biomarker to identify responders to treatment with ketamine.⁴⁴ Besides microRNAs, there are other potential biomarkers, however, results are preliminary and more research is needed for their validation.⁴¹

Besides intravenous administration of S-ketamine, other routes of administration have to be studied for future recommendations. With regard to iontophoresis, Vranken et al.⁴⁵ administered ketamine via iontophoresis to patients with intractable central pain, but this did not result in pain reduction after 1 week. For treatment of chronic neuropathic pain states with topical ketamine, studies show conflicting results.⁴⁶ In a small double-blind placebo-controlled trial, Finch et al.⁴⁷ reported that topical ketamine does not result in pain relief in patients with CRPS, but does cause a reduction in allodynia. Furthermore, promising results are available for sublingual ketamine in depression and should be studied further for CRPS.^{48–50}

In addition, we would also like to highlight the responsibility to reduce health care costs and acknowledge that a 7-day inpatient S-ketamine infusion has

considerable economic implications. Ideally, intravenous S-ketamine therapy should result in long-term pain relief and, for instance, decrease opioid consumption, improve functionality, and help patients return to work. Unfortunately, no economic studies have been conducted to determine the cost-effectiveness for treating CRPS with S-ketamine and these studies are warranted in the future.

CONCLUSION

This study showed that our low-dose intravenous S-ketamine treatment resulted in effective pain relief for a subgroup of patients with CRPS with refractory pain. At ~ 4 weeks after infusion, almost half of the patients were still responders. It is notable that responders to low-dose intravenous S-ketamine treatment started to observe treatment effect within 2 days and that the median effective S-ketamine dose was 6 mg/h. More research is needed to understand which pathophysiological mechanisms are targeted by S-ketamine infusion in order to predict treatment responders.

CONFLICT OF INTEREST

None of the authors have any conflict of interest.

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