Multi-Day Low Dose Ketamine Infusion for the Treatment of Complex Regional Pain Syndrome

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Background: Complex regional pain syndrome (CRPS) is characterized by pain that is out of proportion to the injury and is regional in distribution. A large body of literature supports a dynamic change in the physiology and structure of central pain projecting neurons mediated through the N-methyl-D-aspartate (NMDA) receptor. A critical factor in central sensitization seems to be the release of the magnesium block on the NMDA receptor with influx of calcium and initiation of intracellular cascades. Current literature supports the effectiveness of ketamine in blocking central sensitization through its effects on the NMDA receptor. Recent treatment with anesthetic doses of ketamine in severely ill patients with generalized CRPS prompted our interest in a lower dose therapy.

Objective: To report on the efficacy of low dose outpatient ketamine infusion for the treatment of CRPS diagnosed by International Association for the Study of Pain (IASP) criteria in patients who have failed conservative treatment.

Design: Open label, prospective, pain journal evaluation of a 10-day infusion of intravenous ketamine in the CRPS patient.

Methods: Patients diagnosed with CRPS by a single neurologist were assigned to receive a 10-day outpatient infusion of ketamine supervised by an Anesthesiologist/Pain Management Specialist. The infusion was administered in a short procedure unit after each patient had been instructed on how to complete a pain questionnaire. Monitoring consisted of continuous ECG, pulse oximetry, and non-invasive blood pressure every 15 minutes. Patients made journal entries each day prior to the infusion of 40-80 mg of ketamine. The subjects were also asked to rate their pain intensity using a verbal analog pain scale of 0-10 and the affective component using a verbal scale of 0-4.

Results: There was a significant reduction in pain intensity from initiation of infusion (Day 1) to the 10th day, with a significant reduction in the percentage of patients experiencing pain by Day 10 as well as a reduction in the level of their “worst” pain. The nadirs of pain were lower by Day 10 with a significant reduction in the incidence of “punishing” pain. Moreover, there was a significant improvement in the ability to initiate movement by the 10th day.

Conclusion: A four-hour ketamine infusion escalated from 40-80 mg over a 10-day period can result in a significant reduction of pain with increased mobility and a tendency to decreased autonomic dysregulation.

Keywords: Complex regional pain syndrome (CRPS), ketamine, neuropathic pain...
1.33 vs. 6.63 +

2.72)

3.2) (Fig. 4). A trend to-

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national Association for the Study of Pain

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superior cervical or paravertebral block,

c) sympatholysis either by intermittent

depressants, anticonvulsants, and opioids;

combinations of NSAIDS, tricyclic anti-

including: a) Physical therapy; b) drug

standing or rapidly spreading CRPS, re-

spective study.

diagnosis of CRPS I or II gave written in-

of Anesthesiologists, Physical Status Clas-

METHODS

After approval from the local Institu-

tional Review Board, 40 American Society

of Anesthesiologists, Physical Status Class-

ification I or II patients with a primary
diagnosis of CRPS I or II gave written in-

formed consent to participate in this pro-

pective study.

The patients had a history of long-

standing or rapidly spreading CRPS, re-

fractory to conventional therapy which included: a) Physical therapy; b) drug

combinations of NSAIDS, tricyclic anti-
depressants, anticonvulsants, and opioids;
c) sympatholysis either by intermittent

s superior cervical or paravertebral block,
or five days intrapleural or epidural block.
Four patients had failed a therapeutic tri-

al of dorsal column stimulation. The pa-

ents referred for therapy were diagnosed
to have persistent and/or progressive se-

disease, and no known contraindica-
tions to ketamine, clonidine, or midazol-
am. Prior to entering the ketamine proto-

col, these patients had been treated for a

period of three months to three years.

The ketamine infusion was adminis-
tered on an outpatient basis under the su-
pervision of an Anesthesiologist/Pain Spe-
cialist. The same neurologist (RJS) made
the diagnosis of CRPS based on the Inter-
national Association for the Study of Pain
(IASP) criteria. Patients were maintained
on their usual medications/treatments and
those were not altered during the

infusion period (Table 1). The baseline
physical exam also included a general as-

essment of the patient’s ability to initiate

movement of the affected extremity using a

10-point scale.

Prior to ketamine infusion, subjects

were admitted to a short procedure unit

and instructed on proper completion of a

pain questionnaire. They were moni-

tored for side effects in-

1.13) (Fig. 3).

2.75) (Fig. 1).

Patient treatments prior to ketamine protocol

Table 1.

<table>
<thead>
<tr>
<th>Proportion of Patients</th>
<th>Physio-Therapy</th>
<th>NSAID</th>
<th>Anti-Depressants</th>
<th>Anti-Convulsants</th>
<th>Spasmolytics</th>
<th>Sodium Channel Blocker</th>
<th>Opioids</th>
<th>Sympathetic Block</th>
<th>Lidocaine Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10%</td>
<td>3% (1)</td>
<td>0%</td>
<td>8% (3)</td>
<td>3% (1)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>9% (3)</td>
<td>6% (2)</td>
</tr>
<tr>
<td>10-30%</td>
<td>43% (16)</td>
<td>97%</td>
<td>13% (5)</td>
<td>97% (36)</td>
<td>16% (6)</td>
<td>79% (9)</td>
<td>83% (31)</td>
<td>0%</td>
<td>35% (13)</td>
</tr>
<tr>
<td>30-50%</td>
<td>46% (17)</td>
<td>0%</td>
<td>57% (21)</td>
<td>0%</td>
<td>81% (30)</td>
<td>8% (3)</td>
<td>3% (1)</td>
<td>76% (28)</td>
<td>43% (16)</td>
</tr>
<tr>
<td>≥50%</td>
<td>8% (3)</td>
<td>3%</td>
<td>22% (8)</td>
<td>0%</td>
<td>3% (1)</td>
<td>5% (2)</td>
<td>14% (5)</td>
<td>14% (5)</td>
<td>24% (9)</td>
</tr>
</tbody>
</table>

Patients reported initial and long-term quality of analgesia for their various therapies prior to entry into the intravenous Ketamine protocol.

B - Before indicates pain relief achieved for up to 8 weeks while on any one of the above therapies

A: After indicates chronic pain relief ≥8 weeks in duration. Three patients’ clinical records could not be located which explains n=37.

RESULTS

Thirty-six female and four male pa-

tients participated in the study. Mean de-

mographic data for age, weight, and height

were 42 ± 10 years, 156 ± 45 lbs., and 65 ± 3.5 inches respectively. Compared to base-

line there were significant (p=0.001) re-

ductions in pain intensity (7.54 ± 1.93 vs.

5.44 ± 2.87) (Fig. 1) and in percentage of

overall pain relief by the 10th day (43.61 ±

27.79) (Fig. 2). Analysis of each patient’s

journal for levels of “worst daily pain” ex-

perienced revealed a significant reduction

(p<0.001) in this measure by the 10th day

of infusion (8.77 ± 1.33 vs. 6.67 ± 2.72)

(Fig. 1).

Compared to the first day of treat-

ment, patients also had a lower “least daily

pain” score (p<0.006) by the 10th infusion

day (5.91 ± 2.19 vs. 4.24 ± 2.75) (Fig. 1).

In this population where pain was also
described as burning, aching, and pun-

ishing, we found that a significant reduc-

tion (p=0.007) in the incidence of “punishing

pain” was achieved by the 10th day of infu-

sion (1.61 ± 1.22 to 0.82 ± 1.13) (Fig. 3).

In addition, patients were asked to sum-

marize their pain level over the pre-

vious 24 hours as another measure over
time of treatment efficacy. By the 10th day

of infusion there were significant (p=0.012)
by the 10th day of infusion (6.4 ± 2.6 vs.

4.4 ± 3.2) (Fig. 4). A trend to-
wards a reduction in skin color changes was noted by the 10th day of infusion although this observation did not reach statistical significance. Overall, side effects were minimal with 4/40 and 5/40 patients reporting headaches and restlessness respectively with infusion. There were no episodes of desaturation (SpO2 < 93%) and 3/40 patients experienced a 20% increase over their baseline heart rate during the infusion of ketamine. None of these side effects required intervention. No patient reported hallucinations or nightmares over the duration of exposure to ketamine.

All of the patients expressed positive feelings about the treatment, the quality of their pain relief, and confirmed that they would have no objection to repeating this mode of therapy if necessary. Finally, all of the changes recorded in the variables measured appeared to be progressive over the days of infusion (Figs. 1-4).

**DISCUSSION**

Complex regional pain syndrome is often described by patients as burning, throbbing, or aching pain, as well as mechano- and thermal allodynia (1). The syndrome is often debilitating and can result in complete disability. Multiple treatment modalities have been attempted including physical therapy, psychotherapy, behavior modification, surgery, interventional pain therapies, and medications (16, 17). All were reported to have some degree of success, but with great variability in the quality of the response. In the most severe cases, the interventional treatments are short lived and may not show positive effects.

Multiple studies have suggested that
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the use of N-methyl-D-aspartate receptor antagonists can reduce the pain response in patients with neuropathic pain (18-21). These receptors are phosphorylated and their channel properties are altered, thereby changing the physiology of central pain projecting neurons (22, 23).

The goal of our treatment modality was to expand on the technique previously described by Kiefer et al (15). In that study, patients with severe CRPS who had been resistant to conservative therapies successfully underwent high dose (coma inducing) ketamine therapy in an ICU setting (15). This procedure may have significant risks and other difficulties resulting from five days of immobilization, risk of nosocomial infection, need for invasive monitoring, parenteral nutrition, endotracheal intubation, and mechanical ventilation. Therefore, our rationale for the treatment of these less severely affected patients was to use a technique of low dose ketamine administration, and a longer infusion. The maximum dose used in this study (20 mg/hr) was well below the reported doses associated with psychomimetic effects (5, 24).

The results indicate that the use of an escalated infusion, from 40 mg over four hours to 80 mg over four hours/day for 10 days, can result in significant reduction of pain with increased mobility and a tendency to decreased autonomic dysregulation. Our patients reported a significant increase in pain relief and a decrease in their worst episodes of pain that we believe to be clinically significant. Furthermore, patients reported that the pain, when reduced, was much more tolerable over a given 24-hour period. The improvement was noted to be progressive over the infusion period and suggests that continued treatment (longer than 10 days) might produce a more significant response. At the time of publication of this manuscript we report that four patients (10%) had a return of “worst” and “punishing” pain to pre-infusion levels by two weeks post treatment. Twenty-five patients (62%) had at least a 70% reduction of “worst” and “punishing” pain for six weeks and were back to baseline pain levels by nine weeks post treatment. Eight patients (20%) had a >70% reduction in those same pain measures for 11-12 weeks. Three patients remain CRPS free at 15 months following treatment.

CONCLUSION

The results of this study demonstrated clinically significant benefits of the technique in this specific patient population. Although pain data showed some variability, the results are encouraging and point to the need for additional studies (i.e., oral medication, longer therapy, more specific therapies) with specific NMDA receptor antagonists in this population. Further studies with specific NMDA receptor antagonists would be beneficial in this population.

ACKNOWLEDGMENTS

The authors wish to thank the editors of Pain Physician for peer review and constructive criticism, which ultimately improved the quality and understanding of the manuscript.

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