Multi-day low dose ketamine infusion for the treatment of complex regional pain syndrome

Article in Pain physician · May 2005
Source: PubMed

8 authors, including:

- **Robert Hirsh**
  Cooper University Hospital
  5 PUBLICATIONS  114 CITATIONS
  [SEE PROFILE]

- **Jessie Mae Dotson**
  Cooper Hospital
  1 PUBLICATION  85 CITATIONS
  [SEE PROFILE]

- **Marc Torjman**
  Thomas Jefferson University
  164 PUBLICATIONS  1,564 CITATIONS
  [SEE PROFILE]

- **Robert J Schwartzman**
  Drexel University College of Medicine
  183 PUBLICATIONS  5,393 CITATIONS
  [SEE PROFILE]

Some of the authors of this publication are also working on these related projects:

- **Efficacy of combo therapy with ketamine and mindfulness for chronic pain**
  View project

All content following this page was uploaded by Marc Torjman on 14 July 2014.
The user has requested enhancement of the downloaded file.
Complex regional pain syndrome (CRPS) is characterized by pain that is out of proportion to the injury and is regional in distribution (1). It is primarily caused by peripheral trauma although approximately 10% occurs from lesions in central pain pathways. A large body of literature now exists both from animal and human studies in CRPS (2). There are clear changes in the central, peripheral, and autonomic systems. The incidence has not been determined although it occurs more frequently in females (2).

Recent evidence suggests that a persistent nociceptive barrage maintains a state of central sensitization in central pain projecting neurons (3, 4). The consequences of central and peripheral sensitization are a lower threshold to fire C and A delta nociceptors, a spread of cutaneous receptive fields of central project- ing neurons, a change in spinal cord and cortical pain maps, and spontaneous pain (5). There are clear changes in the central, autonomic, and motor systems that evolve concomitantly with changes in pain pathways in CRPS (1). Central in this process is the NMDA receptor. The release of the magnesium block at the NMDA receptor with influx of calcium and initiation of intracellular cascades, appears to be a critical factor in initiating and maintaining neurons mediated through the N-methyl-D-aspartate (NMDA) receptor. The clinical elements include autonomic dysregulation, spontaneous pain, evoked pain and movement disorder, and in severe cases, trophic changes. The incidence has not been determined although it occurs more frequently in females (2).

Present evidence suggests that a persistent nociceptive barrage maintains a state of central sensitization in central pain projecting neurons (3, 4). The consequences of central and peripheral sensitization are a lower threshold to fire C and A delta nociceptors, a spread of cutaneous receptive fields of central project- ing neurons, a change in spinal cord and cortical pain maps, and spontaneous pain (5). There are clear changes in the central, autonomic, and motor systems that evolve concomitantly with changes in pain pathways in CRPS (1). Central in this process is the NMDA receptor. The release of the magnesium block at the NMDA receptor with consequent influx of calcium and consequent initiation of intercellular cascades, appears to be a critical factor in initia- tion of central sensitization (6, 7). Ex- perimental and clinical literature supports the effectiveness of ketamine in blocking central sensitization by its effects on the NMDA receptor (8). Ketamine is a drug that is rapidly distributed into the brain and other highly perfused tissues, with about 10% of the drug bound to plasma. The bioavailability of ketamine is dependent on the route of administration, being as high as 93% for an intramuscular dose, 20-50% for an intranasal dose, and approximately 20% for an oral dose.

Recent treatment with anesthetic doses of ketamine for severely ill, general- ized CRPS patients has shown some ef- ficacy and prompted its use in less severe- ly ill patients by low dose infusion (9). The results of this therapy are reported for 40 patients with moderate to severe long- standing CRPS.
Table 1. Patient treatments prior to ketamine protocol

<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>0%</td>
<td>0%</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% (29)</td>
<td>24%</td>
<td>83% (31)</td>
<td>0%</td>
</tr>
<tr>
<td>30–50%</td>
<td>46% (17)</td>
<td>57%</td>
<td>81% (30)</td>
<td>59% (22)</td>
<td>3% (1)</td>
<td>76% (28)</td>
<td>43%</td>
<td>41% (16)</td>
<td>0%</td>
</tr>
<tr>
<td>≥50%</td>
<td>8% (3)</td>
<td>3%</td>
<td>22% (8)</td>
<td>5% (2)</td>
<td>14% (5)</td>
<td>24% (9)</td>
<td>22%</td>
<td>12% (4)</td>
<td>6%</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: After indicates chronic pain relief >8 weeks in duration. Three patients’ clinical records could not be located which explains n=37.

Methods

After approval from the local Institutional Review Board, 40 American Society of Anesthesiologists, Physical Status Classification I or II patients with a primary diagnosis of CRPS I or II gave written informed consent to participate in this prospective study.

The patients had a history of long-standing or rapidly spreading CRPS, refractory to conventional therapy which included: a) Physical therapy; b) drug combinations of NSAIDS, tricyclic antidepressants, anticonvulsants, and opioids; c) sympatholysis either by intermittent superior cervical or paravertebral block, or five days intrapleural or epidural block. Four patients had failed a therapeutic trial of dorsal column stimulation. The patients referred for therapy were diagnosed to have persistent and/or progressive severe disease, and no known contraindications to ketamine, clonidine, or midazolam. Prior to entering the ketamine protocol, these patients had been treated for a period of three months to three years.

The ketamine infusion was administered on an outpatient basis under the supervision of an Anesthesiologist/Pain Specialist. The same neurologist (RJS) made the diagnosis of CRPS based on the International 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 assessment 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 monitored with continuous ECG, pulse oximetry, and non-invasive blood pressure every 15 minutes. Forty-80 mg of ketamine was mixed in 500 cc of a normal saline solution. All of the patients were started on a 40 mg infusion lasting four hours, and the infusion was increased over a ten-day period to a maximum of 80 mg. Each patient also received clonidine 0.1 mg orally prior to the infusion to prevent a hypertensive response and possible muscle pain, as well as midazolam (2-4 mg) to relieve anxiety.

Throughout the treatment period, patients were monitored for side effects including: hypertension, tachycardia, dysphoria, hallucinations, dreams, and headaches. The infusion was spread over a two-week period excluding weekends. Patient journal entries were made each day prior to infusion. The subjects were asked to rate the intensity of their pain using a verbal analog pain scale of 0-10 (0 = no pain, 10 = worst pain possible) and the affective component of their pain using a verbal scale of 0-4 (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Pain data were analyzed using the Kruskal-Wallis test with p<0.05 considered statistically significant. Data are presented as mean ± standard deviation.

Results

Thirty-six female and four male patients participated in the study. Mean demographic data for age, weight, and height were 42 ± 10 years, 156 ± 45 lbs., and 65 ± 3.5 inches respectively. Compared to baseline there were significant (p=0.001) reductions 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” experienced revealed a significant reduction (p<0.001) in this measure by the 10th day of infusion (8.77 ± 1.33 vs. 6.63 ± 2.72) (Fig. 1).

Compared to the first day of treatment, 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 punishing, we found that a significant reduction (p=0.007) in the incidence of “punishing pain” was achieved by the 10th day of infusion (1.61 ± 1.22 to 0.82 ± 1.13) (Fig. 3).

In addition, patients were asked to summarize their pain level over the previous 24 hours as another measure over time of treatment efficacy. By the 10th day of infusion this pain measure had also decreased significantly (7.88 ± 2.02 vs. 5.5 ± 2.75) (Fig. 1) (p<0.001).

Patients’ ability to initiate movement showed significant improvement (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...
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 autonomnic 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.

AUTHOR AFFILIATION:

Michael E. Goldberg, MD
Chief, Department of Anesthesiology
Professor of Anesthesiology
UMDNJ – Robert Wood Johnson
Medical School at Camden
Cooper University Hospital
One Cooper Plaza
Camden, NJ 08103
E-mail Goldberg-mike@cooperhealth.edu

Richard Domsky, MD
Co-Director, Division of Pain Management, Cooper University Hospital, One Cooper Plaza
Camden, NJ 08103

Denise Scaringe, MD
Attending Anesthesiologist
Cooper University Hospital
One Cooper Plaza
Camden, NJ 08103

Robert Hirsh, MD
Co-Director, Division of Pain Management, Cooper University Hospital, One Cooper Plaza
Camden, NJ 08103

Jessie Dotson, MSN
Advance Practice Nurse, Division of Pain Management, Cooper University Hospital, One Cooper Plaza
Camden, NJ 08103

Imran Sharaf, MD
Resident in Anesthesiology
Cooper University Hospital
One Cooper Plaza
Camden, NJ 08103

Marc C. Torjman, Ph.D.
Director of the Division of Research
Department of Anesthesiology
Cooper University Hospital
Education and Research Building, Suite 394, 401 Haddon Avenue, Camden, NJ 08103

Robert J. Schwartzman, MD
Professor and Chairman, Department of Neurology
Drexel University College of Medicine
245 N. 15th Street Mail Stop 423
Philadelphia, PA 19102
REFERENCES