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# Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: A double-blind placebo controlled study

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ABSTRACT

Complex regional pain syndrome (CRPS) is a severe chronic pain condition that most often develops following trauma. The pathophysiology of CRPS is not known but both clinical and experimental evidence demonstrate the important of the NMDA receptor and glial activation in its induction and maintenance. Ketamine is the most potent clinically available safe NMDA antagonist that has a well established role in the treatment of acute and chronic pain. This randomized double-blind placebo controlled trial was designed to evaluate the effectiveness of intravenous ketamine in the treatment of CRPS. Before treatment, after informed consent was obtained, each subject was randomized into a ketamine or a placebo infusion group. Study subjects were evaluated for at least 2 weeks prior to treatment and for 3 months following treatment. All subjects were infused intravenously with normal saline with or without ketamine for 4 h (25 ml/h) daily for 10 days. The maximum ketamine infusion rate was 0.35 mg/kg/h, not to exceed 25 mg/h over a 4 h period. Subjects in both the ketamine and placebo groups were administered clonidine and versed. This study showed that intravenous ketamine administered in an outpatient setting resulted in statistically significant ($p < 0.05$) reductions in many pain parameters. It also showed that subjects in our placebo group demonstrated no treatment effect in any parameter. The results of this study warrant a larger randomized placebo controlled trial using higher doses of ketamine and a longer follow-up period.


## 1. Introduction

Complex regional pain syndrome most often develops following trauma [13]. In a number of patients it evolves into a severe chronic pain condition. The illness most likely is inhomogeneous and factor analysis reveals its signs and symptoms to cluster into four distinct subgroups: (1) abnormalities of pain processing (allodynia, hyperalgesia, hyperpathia); (2) skin color and temperature changes (warm or cold) vasomotor and sudomotor dysfunction; (3) neurogenic edema; and (4) a motor syndrome and trophic changes [12]. The syndrome frequently spreads in specific patterns [36]. It has recently been suggested that warm CRPS at presentation may represent peripheral pathophysiology while cold CRPS is a manifestation of its centralization [9,20].

The pathophysiology of the syndrome is not known but both clinical and experimental evidence demonstrate the important of the NMDA receptor and glial activation in the establishment of central sensitization in nociceptive systems that seem critical for its induction and maintenance [8,32,42,43,45,60,62]. Ketamine is the most potent clinically available safe NMDA antagonist that has a well established role in the treatment of acute and chronic pain [2,4,14,16,32,43]. There have been several recent publications demonstrating its effectiveness in sub-anesthetic and anesthetic doses for the treatment of CRPS [7,10,23,24,27].

This randomized double-blind placebo controlled trial, in primarily severe long standing CRPS patients, was designed to evaluate its effectiveness in sub-anesthetic doses in an outpatient setting.

## 2. Methods

### 2.1. Inclusion criteria

Subjects diagnosed with CRPS based on the revised IASP (International Association for the Study of Pain) criteria [13], whose condition was intractable for a minimum of 6 months and had failed at least three of the following therapies; nerve blocks, opioid analgesics, non-opioid analgesics, non-steroidal anti-inflammatory drugs, anti-seizure medications, antidepressants, muscle relaxants or physical therapy were included in this study. Study subjects were ketamine naive and were of either gender including all racial or

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minority groups. The subject's age was between 18 and 65 years. All subjects were on a stable dose of CRPS medications for 28 days prior to entry and remained on the same medications and dosage throughout the duration of the study. This study was approved by the Drexel University College of Medicine Institutional Review Board.

### 2.2. Exclusion criteria

Subjects who were pregnant or had known substance abuse issues, glaucoma or thyrotoxicosis were excluded. Any subject that was unable to provide consent due to cognitive difficulties was not enrolled in this study. Subjects that could not provide the means to be transported home following daily infusions, those with active litigation, compensation or disability issues related to their CRPS, and subjects on calcium channel or beta blockers due to the need to utilize clonidine with ketamine were excluded. Subjects with major medical problems including but not limited to; uncontrolled hypertension, hypotension, cardiac failure, renal failure or liver failure were not enrolled.

### 2.3. Pre-treatment

Prior to treatment, after informed consent was obtained, each subject was randomized into the ketamine or placebo infusion group. Both the subject and all other individuals involved in the subject's care or evaluation were blinded as to the treatment. The subject received a complete neurological examination and pain evaluation. The pain evaluation assessed overall pain level, joint pain, pin hyperalgesia, touch allodynia, cold allodynia and deep pressure evoked pain (at the supraclavicular fossa and the posterior popliteal fossa), strength and facility of movement. The subject was also asked to complete a short form McGill questionnaire [38], quality of life questionnaire (American Chronic Pain Association) and a seven question pain questionnaire weekly until the start of the infusions.

The seven question pain questionnaire asked patients to evaluate on an (0–10) (0 = no pain and 10 unbearable pain) numerical rating scale (NRS): (1) your current pain in your most affected area; (2) pain when you are touched or brushed lightly; (3) pain when deep pressure or squeezing is applied; (4) burning pain; (5) joint pain; (6) the degree your pain interferes with your general activity and (7) your overall pain.

All subjects wore an activity watch for at least 2 weeks prior to treatment and 2 weeks following treatment. The watch evaluated the subject's level of activity and at random programmed intervals recorded the subject's pain on a 0–10 NRS scale (0 = no pain and 10 = unbearable pain). In addition, the subjects were instructed to enter their pain scores during the night if they awoke.

Two weeks before treatment, 1 and 3 months post-treatment the following sensory and motor tests were performed.

*Thermal detection thresholds:* Cool detection thresholds were determined using the TSA-II NeuroSensory Analyzer (Medoc Advanced Medical Systems US, Minneapolis, MN). The device consists of a computer controlled thermoelectric probe with a surface area of 9 $cm^2$ that is attached using a Velcro strap to the area of skin to be tested (thenar eminence and hypothenar eminence in the hands and the dorsal foot). For each trial the thermal stimulator starts at the thermo-neutral baseline temperature of 32 °C, and increases for warming thresholds, or decreases for cooling thresholds, linearly at a rate of 1 °C per second, until the subject pushes a button that stops and records the temperature and returns the unit to baseline temperature. Three trials are averaged for cool and for warm threshold for each site tested.

*Thermal pain:* Thermal pain tolerance was determined at the same sites and using the same method described above for thermal detection thresholds. The only difference is that for thermal pain trials, the subject was instructed to push the control button (which immediately resets the stimulator back to baseline temperature) when the thermal stimulus (cold or hot) becomes painful. The TSA-II hardware automatically resets if the temperature reaches −10 °C (for cooling) or 50 °C (for heating) and the control button has not been pushed. This temperature range has been determined not to cause damage to skin or underlying tissue.

*Dynamic and static mechano-allodynia:* Dynamic mechano-allodynia was determined by stroking the skin three times within 5 s at a rate of 5 cm/s with a 2.5 cm wide standard foam paintbrush. Allodynia severity was determined by the subject's response using a numerical rating scale. The subject reported both the amount of pain on a 0–10 scale (0 = no pain; 10 = unbearable pain) and the extent to which the sensation spread. Static allodynia was determined with a 20 g bending force monofilament. The subject was instructed to report the level of pain on a 0–10 scale (0 = no pain; 10 = worst pain ever experienced).

*Deep pressure pain thresholds:* Deep pressure pain thresholds were determined with a pressure algometer (Wagner Instruments, Greenwich, CT) which is a hand held device with a 1 $cm^2$ rubber tip capable of measuring applied pressures of 0–5 kg. The device was held at a 90° angle to the body surface being tested. The pressure is gradually increased by 1 kg/s until the subject reports that the stimulus is painful or a pressure of 4 $kg/cm^2$ was reached. In the upper extremity thresholds to pain were determined at: (1) second costosternal joint; (2) acromioclavicular joint; (3) lateral epicondyle; (4) radial styloid; (5) ulnar styloid; (6) second metacarpal; and (7) fifth metacarpal. In the lower extremity thresholds to pain were determined at: (1) greater trochanter; (2) lateral femoral condyle; (3) tibial tubercle; (4) mid-shin; (5) medial malleolus; (6) lateral malleolus; (7) first metatarsal; and (8) fifth metatarsal.

*Quantification of motor function (finger tap):* Finger tap rate was determined using a computer program developed by our group. The subject was instructed to press the spacebar of a standard computer keyboard as fast as possible with the index finger of each hand respectively for 30 s.

*Cutaneous temperature:* Skin temperature was measured with an infra-red thermometer (Dermatemp Infrared Temperature Scanner, model DT-1001, Exergen Corp., Watertown, MA).

### 2.4. Preinfusion

On the first day of treatment but prior to the start of the infusions, the subjects were weighed, underwent a neurologic exam, had vital signs evaluated and an intravenous line inserted.

### 2.5. Infusion plan

On all 10 infusion days, subjects in both the ketamine and placebo group were monitored for cardiac rhythm, blood pressure, pulse and oxygen saturation. In addition, clonidine (0.1 mg p.o.) and midazolam (2 mg prior to and 2 mg following the 4 h infusion by i.v. push) was administered. Clonidine has been shown, in animals, to potentiate the neuropathic pain-relieving action of NMDA receptor blockers like ketamine while preventing their neurotoxic side effects [21]. Midazolam, at this dose, provides mild sedation and relieves anxiety.

All subjects were infused intravenously with 100 ml of normal saline with or without ketamine for 4 h (25 ml/h) daily for 10 days (5 days on, 2 days off, 5 days on). The maximum intravenous ketamine infusion rate for this study was 0.35 mg/kg/h, not to exceed 25 mg/h (100 mg of ketamine over a 4 h period). On the first day, the intravenous ketamine infusion was set to 50% of the maximum rate. On the second day, the intravenous ketamine infusion was increased to 75% of the maximum rate. On the third day, the

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intravenous ketamine infusion was increased to the maximum rate and maintained at this level for the duration of the 10 day study.

### 2.6. Post infusion

Following the last (10th) infusion, the subjects were seen at 2 weeks and then monthly at the Neurology Pain Clinic for the following 3 months. All subjects were asked to wear an activity watch from the time of the last infusion until the 2 week post-treatment visit. Subjects were also instructed to complete the short form McGill, quality of life and pain questionnaires weekly until the end of the study (3 months after the last infusion).

### 2.7. Blood ketamine level determination

Blood plasma was obtained from whole blood collected into EDTA coated tubes and spun at 3000 RPM for 15 min at 4 °C. Equal volumes of plasma and acetonitrile–phosphoric acid (85%)–water (20:2:78, v/v/v) (200 μl each) were mixed, followed by ultrafiltration through a 10,000 molecular mass cut-off filter (Millipore Microcon YM-10) [49]. The plasma ketamine level was determined from the ultra filtrate by high performance liquid chromatography (HPLC) [6]. The chromatographic system consisted of a Micromeretics 760 HPLC pump, a mobile phase of 77% sodium phosphate pH 7.2, 23% $CH_3CN$ at a flow of 1.2 ml/min. Separation was performed on an octadecylsilane (C18) column (Purosphere 5μ RP-18e 80A, 125 × 4 mm) and detection at a wavelength of 210 nm with a Shimadzu SPD-20A UV–vis detector [6,52].

### 2.8. Statistical analysis

The sample size was calculated by power analysis using data from our infusion clinic that suggested a 35% reduction in overall pain for the ketamine group. We estimated a 15% improvement for the placebo group. With a power of 80% and a type I error of 0.05, 34 patients (17 for each arm) had to complete the study. To account for dropouts we planned to enroll 20 patients for each arm.

Analysis of variance (ANOVA) was used to compare differences between groups in age, disease duration, limb temperature, cold evoked pain, heat evoked pain, finger tap and pressure evoked pain. The Kruskall–Wallis test was used to compare differences between groups for the McGill pain questionnaire scores. The Wilcoxon Signed Rank Test was used to compare differences between pre- and post-treatment for all NRS scores. Calculations were accomplished with the aid of statistical data analysis software, SYSTAT version 11 (SYSTAT Software Inc., Richmond, CA). The data was considered significantly different if $p < 0.05$.

## 3. Results

Although originally powered for 20 subjects per arm, the study was stopped at the halfway point for the following reasons. An interim analysis of the study results was performed after 19 subjects completed the study. The data showed little placebo effect allowing for statistical significance to be reached on many of the study parameters with a smaller number of study subjects than originally predicted. In addition, when this study was designed, our experience with outpatient intravenous ketamine was limited to doses of 25 mg/h (100 mg/4 h). Over the duration of this study (2 years) our further experience with outpatient intravenous ketamine showed that 50 mg/h (200 mg/4 h) provided much greater pain relief for a longer period of time without any complications. Since it was clear that a higher ketamine dose was having a much greater effect in other CRPS patients, it was felt that a randomized study at higher doses would be justified at this time.

Twenty-six subjects with CRPS were evaluated for this study. There were 5 screen failures and 2 subjects did not complete the study. Nineteen subjects, 1 male and 18 female completed this study. Ten of the subjects were in the placebo group and nine in the ketamine group. All subjects provided written informed consent prior to participating in the study. The subject's treatment group, age, gender, location of initial injury, spread of symptoms and their overall pain level at their initial evaluation are tabulated in Table 1. There was no significant difference ($p > 0.05$) in age, initial pain level or duration of disease between the ketamine and placebo groups.

All study subjects met the CRPS revised International Association for the Study of Pain (IASP) criteria [13]. Their condition was intractable with disease duration varying between 0.8 and 20 years. At their initial exam, the average overall pain level on a 0–10 numerical rating (±SE) scale was 7.5 ± 1.9 for the placebo group and 7.9 ± 0.9 for the ketamine group. This difference was not statistically significant ($p > 0.05$). In the ketamine group, the average plasma ketamine level (±SE) was 188.4 ± 20.9 ng/ml. Using linear regression, no correlation was found ($r = 0.04$, $p = 0.93$) between subject plasma level and symptom improvement.

### 3.1. Pain questionnaire

The subjects completed at least two pain questionnaires prior to treatment and one every week for the 12 weeks following treatment. The subjects' responses to the pain questionnaire are tabulated in Table 2. The placebo group scores demonstrated small non-significant ($p > 0.05$) differences for both better and worse following treatment. The ketamine treated group demonstrated consistent decreases for all parameters at all post-treatment time points that lasted for the 12 week post-treatment evaluation period. None of the parameters, in the ketamine treated group, returned to their pre-treatment levels by the 12 week post-treatment visit. There was a statistically significant ($p < 0.05$) decrease in scores in some parameters (pain in the most affected area, burning pain, pain when touched or brushed lightly and overall pain level). Whereas the other parameters (joint pain, pain when deep pressure or squeezing was applied and the degree their pain interfered with general activity) the reduction in scores did not reach statistical significance ($p > 0.05$).

### 3.2. The short form McGill pain questionnaire in CRPS

The subjects completed at least two short form McGill pain questionnaires [32] prior to treatment and one every week for the 12 weeks following treatment. The responses to the short form McGill pain questionnaire are tabulated in Table 3. The average total score (±SE) prior to treatment was 23.1 ± 1.4 for the ketamine group and 28.17 ± 1.7 for the placebo group. This difference was not statistically significant ($p > 0.05$). In the placebo group, both the sensory and the affective component demonstrated a slight but not statistically significant ($p > 0.05$) increase following treatment. In the ketamine group, both the sensory and the affective component demonstrated a significant ($p < 0.05$) decrease that lasted for the 12 weeks follow-up period (Fig. 1). The decrease in total McGill score was approximately 35% with the affective component demonstrating a larger decrease (50%) than the sensory component (31%), Table 3.

### 3.3. Activity watch data

The watch evaluated the subject's level of activity and at random programmed intervals recorded the subject's pain on a 0–10 NRS scale (0 = no pain and 10 = unbearable pain). The watch was worn for at least 2 weeks prior to and following treatment. The subjects average pain score (±SE) as entered in the activity watch

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**Table 1**
Study subject treatment group, age, gender, location of initial injury, spread of symptoms and their overall pain level at their initial evaluation.

| Pat# Rx group | Age/ gender | Duration of CRPS | Location of the initial injury | Spread of symptoms | Pain quality/intensity/modality |
|---|---|---|---|---|---|
| 001 Ketamine | 44 F | 6.8 | R ankle fracture | R foot regionally; L5–S1 pain; neuroma 4th 5th metatarsal | 6/10 spontaneous pain (burning, numbness, tingling); mechano-allodynia; deep sensitization (d/s); articular pain, deep muscle sensitization R foot and legs in regional distribution; hyperalgesia to pinprick (PP) R foot and legs |
| 003 Ketamine | 40 F | 2.5 | R knee injury; blunt trauma | Mirror spread to L knee; ipsilateral spread to R arm; sensitization of L5–S1 R | 8/10 spontaneous pain (deep ache; burning; lancinating features into L5–S1); + Tinel's brachial plexus distributions; mechano-allodynia d/s R side; cold allodynia; hyperalgesia; loss of surround inhibition to pinprick R leg |
| 004 Placebo | 48 F | 7.1 | Torn L posterior tibial tendon following leg surgery | Mirror spread to R leg; regional both lower extremities to midthigh | 9/10 spontaneous pain (burning; deep muscle ache); Tinel's signs brachial plexus; sciatic nerves; mechano-allodynia d/s lower extremities; deep muscle sensitization lower extremities; hyperalgesia to PP lower extremities |
| 005 Placebo | 49 M | 12.1 | Crushed L foot; plantar nerve injuries | Mirror distribution to R leg; brachial plexus distributions; generalized pain | 8/10 (burning, deep ache, lancinating); mechano-allodynia d/s; PP hyperalgesia lower extremities |
| 006 Ketamine | 47 F | 9.4 | Twisted R ankle; torn ligaments | Mirror distribution to L ankle; brachial plexus distributions; generalized | 8/10 (burning; deep ache, lancinating): mechano-allodynia d/s; hyperalgesia to PP; cold allodynia |
| 007 Placebo | 60 F | 2.9 | Tripped on steps twisted R ankle; multiple surgical procedures | Contiguous | 4/10 spontaneous pain (hot burning pain), dynamic allodynia; static allodynia; no joint pain; pain in R leg |
| 008 Placebo | 27 F | 3.8 | L ankle fracture | Mirror spread to the R ankle; sensitization of L L5–S1 | 6/10 (aching, burning) regionally in the L lower extremity; long-term depression; cannot feel PP; no mechanical allodynia |
| 009 Ketamine | 44 F | 4.2 | Radicular pain from HNP Ll5–S1 | Mirror spread to R foot; bilateral brachial plexus distributions; generalized | 8/10 (burning, throbbing, shooting) mechano-allodynia d/s (generalized) cold allodynia lower extremities; + Tinel's upper brachial plexus distributions; PP hyperalgesia throughout |
| 011 Placebo | 40 F | 3.4 | L lower extremity; she fell striking L flank on stove | Area around the original injury | 5/10 (burning) pain in the area of the injury; dynamic and static allodynia; joint pain |
| 012 Ketamine | 40 F | 1.3 | Brachial plexus traction injury (middle trunk posterior cord) | Shoulder pain; contiguous then regional pain the entire R arm | 8/10 (burning, aching) severe mechano-allodynia R arm; severe hyperalgesia to PP R arm; + Tinel's all brachial plexus distributions R arm |
| 013 Placebo | 50 F | 20 | Brachial plexus traction injury of L arm | L brachial plexus to L cervical plexus-entire L upper quadrant | 8/10 (burning, tingling, aching) + Tinel's brachial plexus distributions L; mechano-allodynia d/s; hyperalgesia to PP; cold allodynia of L upper quadrant |
| 016 Ketamine | 37 F | 9.9 | Fracture of L 5th metatarsal | L foot-spread in a regional distribution to entire L leg; L brachial plexus distributions | 9/10 (burning, throbbing, sharp stabbing); + Tinel's all L brachial plexus distributions; mechano-allodynia d/s; hyperalgesia to PP; cold allodynia L leg regionally |
| 018 Ketamine | 38 F | 3.0 | Brachial plexus traction injury R arm | R brachial plexus; ipsilateral R leg; L leg regional distribution | 8/10 (burning; deep ache; joint pain, lancinating); mechano-allodynia d/s; hyperalgesia to PP; cold allodynia throughout |
| 019 Placebo | 31 F | 1.1 | Surgical procedure (ablation for supra ventricular tachycardia) | L intercosticobrachial nerve; L plexus distributions; L leg-generalized | 9/10 (burning, severe joint pain, deep ache, lancinating components); severe mechano-allodynia d/s; deep muscle sensitization; joint pain to pressure; cold allodynia; hyperalgesia to PP |
| 021 Ketamine | 28 F | 13.2 | Fractured foot, ankle-CRPS 1990–1991 that resolved; 1997 probable traction injury of the brachial plexus | R foot and ankle soft tissue injury (resolved incompletely); reoccurrence 1997 with R leg regional pain; R brachial plexus-generalized pain | 9/10 (sharp, stabbing, burning); + Tinel's R side; mechano-allodynia d/s generalized; generalized cold allodynia; joint pain throughout; hyperalgesia to PP R leg and arm |
| 023 Ketamine | 24 F | 2.7 | Rack of clothes fell on brachial plexus on R | Pain in the hand; spread to brachial/cervical plexus on the R | 7/10 (aching, burning, deep); R upper quadrant regionally; mechano-allodynia d/s; deep muscle pain; joint pain; cold allodynia, hyperalgesia to PP |
| 024 Placebo | 56 F | 0.8 | probable brachial plexus injury R arm (possible iv. infiltration) | R hand then spread to all brachial plexus distributions of R arm | 8/10 (burning, shooting components); mechano-allodynia d/s; deep muscle sensitization; cold allodynia; PP hyperalgesia |
| 025 Placebo | 42 F | 18.7 | L brachial and cervical traction injuries | L brachial/cervical plexus regional distribution; sensitization of L5–S1 roots | 8/10 (burning, lancinating, deep ache, numbness); mechano-allodynia d/s L plexus distributions; hyperalgesia to PP and cold allodynia L upper quadrant |
| 026 Placebo | 52 F | 3.2 | Fracture dislocation of R ankle | R ankle; spread to sciatic nerve distribution R; then to L; L brachial plexus distributions | 10/10 (deep ache, throbbing stabbing, burning in R leg); mechano-allodynia d/s R lower leg; cold allodynia; PP hyperalgesia R lower leg |

Mechano-allodynia – d, dynamic; s, static; PP, pinprick hyperalgesia.

**Table 2**
Study subject responses to the pain questionnaire.

| Pain questionnaire NRS (0–10) | Group | Pre | Post Wk 1–2 | Post Wk 3–4 | Post Wk 5–8 | Post Wk 9–12 |
|---|---|---|---|---|---|---|
| Pain in the most affected area | Placebo | 7.73 ± 0.4 | 7.61 ± 0.6 | 7.50 ± 0.6 | 7.52 ± 0.6 | 7.56 ± 0.7 |
| | Ketamine | 7.66 ± 0.4 | **6.06 ± 0.9*** | **6.13 ± 1.0*** | 6.49 ± 1.1 | 6.69 ± 0.9 |
| Burning pain | Placebo | 8.05 ± 0.7 | 7.67 ± 0.9 | 7.70 ± 0.8 | 7.63 ± 0.8 | 7.57 ± 0.9 |
| | Ketamine | 7.12 ± 0.9 | 5.33 ± 1.2 | **4.21 ± 1.6*** | 5.04 ± 1.2 | 5.44 ± 1.1 |
| Pain when touched or brushed lightly | Placebo | 7.88 ± 0.5 | 6.50 ± 0.9 | 7.55 ± 0.6 | 7.14 ± 0.6 | 6.95 ± 0.9 |
| | Ketamine | 7.90 ± 0.4 | **5.94 ± 0.9*** | **5.86 ± 1.2*** | **5.91 ± 1.0*** | 6.28 ± 0.9 |
| Overall pain level | Placebo | 7.62 ± 0.6 | 7.61 ± 0.6 | 7.60 ± 0.5 | 7.72 ± 0.6 | 7.59 ± 0.7 |
| | Ketamine | 7.76 ± 0.4 | **6.28 ± 0.9*** | 6.43 ± 1.0 | 6.66 ± 1.0 | 6.81 ± 0.9 |
| Pain when deep pressure or squeezing is applied | Placebo | 8.51 ± 1.9 | 8.06 ± 0.5 | 8.00 ± 0.6 | 8.40 ± 0.5 | 8.17 ± 0.6 |
| | Ketamine | 7.99 ± 0.6 | 6.78 ± 0.8 | 6.64 ± 1.2 | 6.36 ± 1.1 | 6.53 ± 0.9 |
| Joint pain | Placebo | 7.51 ± 0.5 | 7.28 ± 0.7 | 7.15 ± 0.7 | 7.12 ± 0.7 | 7.40 ± 0.7 |
| | Ketamine | 5.91 ± 0.9 | 4.61 ± 1.1 | 5.21 ± 1.2 | 5.35 ± 1.2 | 5.69 ± 1.1 |
| Degree your pain interferes with your general activity | Placebo | 8.11 ± 0.6 | 7.61 ± 0.7 | 7.55 ± 0.6 | 7.70 ± 0.7 | 7.87 ± 0.7 |
| | Ketamine | 6.92 ± 0.7 | 5.50 ± 1.0 | 5.79 ± 1.1 | 6.07 ± 1.0 | 6.28 ± 0.8 |

The table entries are given as (means ± SE). Statistically significant (*$p < 0.05$) scores are marked in bold. In four of the seven inquiries, the ketamine treated group demonstrated significant ($p < 0.05$) differences between pre- and post-treatment scores. Most of the differences were noted during the first month post-treatment. The placebo group scores demonstrated small non-significant ($p > 0.05$) differences between pre- and post-treatment scores at all time points in the 12 week post-treatment evaluation period.

for the time period prior to treatment was 7.51 ± 0.4 for the ketamine group and 7.20 ± 0.4 for the placebo group, this difference was not statistically significant ($p > 0.05$). Following treatment, the ketamine group showed a 21.4% reduction of pain score to 6.01 ± 0.6 ($p < 0.01$) whereas the placebo group demonstrated a non-significant ($p > 0.05$) 3.1% reduction to 6.98 ± 0.5. There were no significant changes between pre- and post-treatment values ($p > 0.05$) in the level of activity, as recorded by the accelerometers in the watch in either the placebo or the ketamine group. In addition to evaluating activity, the subjects were instructed to enter their pain scores during the night if they awoke. The number of awakenings decreased by 85% in the ketamine group. This decrease was statistically significant ($p < 0.05$). There was no significant decrease ($p > 0.05$) in the number of awakenings in the placebo group. The difference in pain scores entered during the night between pre- and post-treatment decreased in the ketamine group and remained the same for the placebo group, however the changes were not statistically significant ($p > 0.05$).

### 3.4. Quantitative sensory testing

Quantitative sensory tests (QST) were administered to all subjects prior to treatment and at 1 and 3 months following treatment. Average skin temperatures were normal in all extremities and the average difference between the affected limb and its contralateral extremity was less than 0.5 °C in both the placebo and ketamine groups. Both cold and warm detection thresholds were at the upper range of normal in both groups when compared to control subjects evaluated at our QST laboratory [50]. There were no significant changes ($p > 0.05$) in skin temperature, cold or warm detection thresholds following treatment. A number of tests evaluating evoked pain and motor function were also performed. The results of these tests are tabulated in Table 4. Following treatment, the ketamine group showed improvement in all categories (pressure evoked pain, brush allodynia, stimulation with a 20 g monofilament, cold evoked pain, heat evoked pain and finger tap), however, none of the improvements were statistically significant ($p > 0.05$). The majority of patients demonstrated reduced tap test scores (7 of 9 in the ketamine group, 8 of 10 in the placebo group). Following treatment the ketamine group showed a small not statistically significant ($p > 0.05$) improvement whereas the placebo group showed no change. Most patients demonstrated cold allodynia (8 of 9 in the ketamine group, 6 of 10 in the placebo group). Of the QST tests, cold evoked pain (on the most affected extremity) demonstrated the greatest improvement. The ketamine group demonstrated a 5.8 °C improvement whereas the placebo group showed a 1.1 °C worsening. However, this difference did not reach statistical significance ($p = 0.06$). All subjects had low thresholds to pressure evoked pain when compared to control subjects evaluated at our QST laboratory (control subjects do not report pressure of less than 4 kg as painful) [50]. In the ketamine group, pressure evoked pain and finger tap demonstrated the least improvement of all parameters tested.

### 3.5. Quality of life

The subjects completed at least two American Chronic Pain Association quality of life (QOL) questionnaires (Appendix 1) prior

**Table 3**
Study subject responses to the short form McGill questionnaire.

| Short form McGill questionnaire | Group | Pre | Post Wk 1–2 | Post Wk 3–4 | Post Wk 5–8 | Post Wk 9–12 |
|---|---|---|---|---|---|---|
| Sensory component (0–33) | Placebo | 21.62 ± 2.4 | 21.75 ± 2.3 | 23.70 ± 2.2 | 22.63 ± 2.6 | 22.63 ± 2.9 |
| (Questions 1–11) | Ketamine | 17.07 ± 1.6 | **12.83 ± 2.3*** | **11.17 ± 2.0*** | **11.69 ± 1.8*** | **11.75 ± 2.1*** |
| Affective component (0–12) | Placebo | 6.56 ± 1.2 | 7.55 ± 1.3 | 7.45 ± 1.3 | 6.98 ± 1.4 | 7.46 ± 1.5 |
| (Questions 12–15) | Ketamine | 6.10 ± 0.9 | **3.39 ± 1.0**** | **2.67 ± 0.9**** | **3.03 ± 1.0*** | **3.28 ± 1.0*** |
| Total McGill Score (0–45) | Placebo | 28.17 ± 3.4 | 29.30 ± 3.5 | 31.15 ± 3.4 | 29.60 ± 3.9 | 30.09 ± 4.3 |
| (Questions 1–15) | Ketamine | 23.14 ± 2.4 | **16.22 ± 2.6*** | **13.39 ± 2.1**** | **14.81 ± 2.3*** | **15.44 ± 2.6*** |

The table entries are given as (means ± SE). Statistically significant (*$p < 0.05$; **$p < 0.001$) scores are marked in bold. Both the affective and sensory components in the ketamine treated group demonstrated significant differences between pre- and post-treatment scores for all time points in the 12 week post-treatment evaluation period. The placebo group scores demonstrated small non-significant ($p > 0.05$) differences between pre- and post-treatment scores at all time points in the 12 week post-treatment evaluation period.

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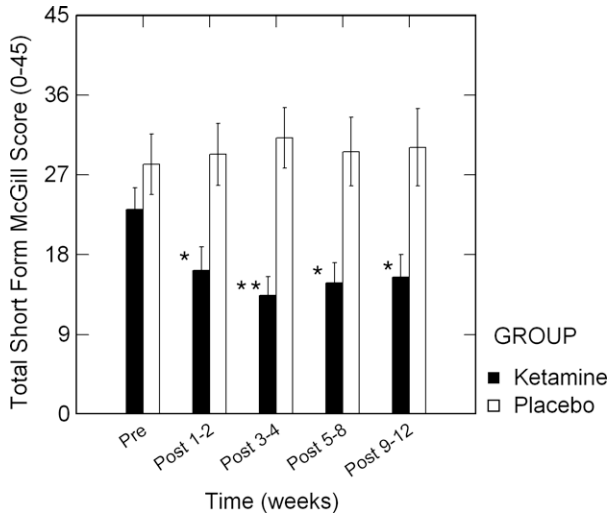


**Fig. 1.** Changes in the total McGill questionnaire score (means ± SE) at five time periods (the period prior to treatment (at least 2 weeks), weeks 1 and 2 post-treatment, weeks 3 and 4 post-treatment, weeks 5 to 8 post-treatment and weeks 9 to 12 post-treatment) in both the ketamine treated and the placebo group. In the ketamine treated group, the McGill pain questionnaire scores showed significant ($p < 0.05$) improvements when compared to either the baseline measurements or the placebo scores that lasted for the 12 week follow-up period. In the placebo group, the total McGill score demonstrated a slight but not statistically significant ($p > 0.05$) increase following treatment.

to treatment and one every week for the 12 weeks following treatment. The possible score ranges from 0 (non-functioning) to 10 (normal quality of life). The subjects average quality of life score (±SE) for the time period prior to treatment was 5.4 ± 1.0 for the ketamine group and 3.6 ± 0.4 for the placebo group, this difference was not statistically significant ($p > 0.05$). There were no significant changes in the QOL scores ($p > 0.05$) following treatment in either the placebo or the ketamine group.

### 3.6. Side effects

Six of the 19 subjects that completed the study complained of nausea, headache, tiredness or dysphoria at some point during the trial (4/9 in the ketamine group and 2/10 in the placebo group). All subjects were queried by the clinical staff (neurologist and infusion nurses) and none reported agitation, blurred vision or any psychomimetic side effects such as; hallucinations, delusions or out of body experiences. The concomitant use of midazolam and clonidine during this study may have controlled the hallucinogenic and dysphoric effects of ketamine.

### 3.7. Percent change between pre- and weeks 1–4 post-treatment

The percent change between baseline values and mean values for week's 1–4 post-treatment in parameters evaluating the subject's pain are listed in Table 5. On average, parameters evaluating pain decreased by approximately 27% in the ketamine group and 2% in the placebo group. Following treatment, not all individuals improved to the same degree. In the ketamine group, one subject demonstrated greater than 50% improvement, 4 subject's 20–30% improvement, 3 subject's 10–20% improvement and 1 subject less than 10% improvement. The subjects demonstrated the same pattern of improvement across all test parameters.

Several pain parameters were evaluated in multiple ways. Overall pain was evaluated with the activity watch score, the pain questionnaire and the sensory component of the McGill questionnaire and provided similar values (decreases of 21.4%, 18.1% and 29.7% in the ketamine group and decreases of 3.1 and 0 and an increase of 5.1% in the placebo group). Dynamic allodynia was evaluated on exam (brush allodynia) and by questionnaire. They also provided similar values, decreases of 34.2% and 25.3% in the ketamine group and 7.1 and 10.9 in the placebo group. Evaluating parameters in multiple ways provided redundancy in the determination of the subject's pain level which increases our confidence in these results.

## 4. Discussion

Several intravenous ketamine regimens have been reported to provide significant amelioration of pain in subjects with CRPS [7,10,24]. Ketamine has been administered at anesthetic doses for 5 days [24] or at sub-anesthetic doses administered for several days either continuously [7] or for several hours a day [10]. In general, the higher the ketamine dose the greater the reduction of symptoms and duration of relief. In our experience, only the 5 day intravenous ketamine regimen at anesthetic doses with midazolam and clonidine [24] provide complete remission of CRPS symptoms lasting for over 5 years in approximately half of the subjects. Ketamine at sub-anesthetic doses provides significant relief, however overtime the symptoms return. We chose the sub-anesthetic multi-day low dose intravenous ketamine regimen for this study because we felt it was the most amenable paradigm for con-

**Table 4**
Study subject scores in the quantitative pain examination.

| Quantitative pain examination | Group | Pre | Post 1 month | Post 3 months |
|---|---|---|---|---|
| Pressure evoked pain of affected limb (kilograms) | Placebo | 1.56 ± 0.2 | 1.14 ± 0.1 | 1.49 ± 0.3 |
| | Ketamine | 1.56 ± 0.3 | 1.62 ± 0.1 | 1.63 ± 0.3 |
| Brush allodynia of affected limb (NRS, 0–10) | Placebo | 5.50 ± 1.0 | 5.11 ± 1.3 | 5.30 ± 1.1 |
| | Ketamine | 3.89 ± 1.0 | 2.56 ± 1.1 | 3.33 ± 1.2 |
| Twenty gram monofilament on affected limb (NRS, 0–10) | Placebo | 5.40 ± 1.1 | 5.44 ± 1.4 | 5.60 ± 1.0 |
| | Ketamine | 5.56 ± 1.0 | 3.56 ± 0.8 | 3.78 ± 1.1 |
| Cold evoked pain on affected limb (change from 32 °C baseline) | Placebo | −17.6 ± 4.9 | −16.5 ± 4.8 | −12.7 ± 4.1 |
| | Ketamine | −6.9 ± 1.8 | −12.7 ± 3.8 | −6.5 ± 2.6 |
| Heat evoked pain of affected limb (change from 32 °C baseline) | Placebo | 10.7 ± 1.8 | 9.7 ± 1.8 | 8.9 ± 1.8 |
| | Ketamine | 8.9 ± 1.7 | 10.3 ± 1.7 | 8.7 ± 1.6 |
| Finger tap of affected side (taps in 30 s) | Placebo | 108.8 ± 7.1 | 98.7 ± 10.8 | 110.3 ± 10.8 |
| | Ketamine | 108.1 ± 10.0 | 116.1 ± 7.0 | 117.3 ± 8.3 |

The table entries are given as (means ± SE). Following treatment, the ketamine group showed improvement in all categories, however, none of the improvements were statistically significant ($p > 0.05$).
The placebo group scores demonstrated small non-significant ($p > 0.05$) differences between pre- and post-treatment scores at all time points in the 12 week post-treatment evaluation period.

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**Table 5**
Percent change between baseline values and mean values for weeks 1–4 post-treatment.

| Parameter | Placebo | Ketamine |
|---|---|---|
| McGill affective component | 14.3 | −50.3 |
| Twenty gram monofilament on affected limb | 0.7 | −36.0 |
| Brush allodynia of affected limb | −7.1 | −34.2 |
| Burning pain | −4.5 | −33.0 |
| McGill Sensory component | 5.1 | −29.7 |
| Pain when touched or brushed lightly | −10.9 | −25.3 |
| Pain score (activity watch) | −3.1 | −21.4 |
| Pain in the most affected area | −2.3 | −20.5 |
| Degree your pain interferes with your general activity | −6.5 | −18.4 |
| Overall pain level | 0.0 | −18.1 |
| Joint pain | −4.0 | −16.9 |
| Pain when deep pressure or squeezing is applied | −5.6 | −16.1 |
| Average | −2.0 | −26.7 |

The table entries are gives as percent. Negative values show decreases (improvement) and positive values increases (worsening) from the pre-treatment score. Parameters are listed in decreasing order (most improvement in the ketamine group listed first). The activity watch entries evaluate the percent change between baseline values and mean values for weeks 1–2 post-treatment.

ducting a randomized double-blind placebo controlled trial to evaluate the effectiveness of intravenous ketamine for the treatment of CRPS.

In this randomized, double-blind, placebo controlled study of primarily severe longstanding CRPS patients treated with a low dose multi-day infusion of ketamine, statistically significant reduction of pain ($p < 0.05$) was demonstrated in the ketamine treated group on: (1) the short form McGill pain questionnaire for the 3 month length of the study following treatment; (2) in several of the parameters evaluated in the pain questionnaire (pain in the most affected area, burning pain, pain when touched or brushed lightly and overall pain level; (3) data from the activity watch demonstrated fewer nighttime awakenings as well as lower daytime pain scores (only measured for 2 weeks following the last infusion); and (4) spontaneous burning pain decreased ($p < 0.05$) for 1 month. The subjects in the placebo group demonstrated no significant improvement between pre- and post-treatment values in any of these parameters. The changes in the other parameters queried: (1) overall pain; (2) deep muscle pain; (3) joint pain; (4) quantitative sensory testing; and (5) quality of life issues did not reach statistical significance ($p > 0.05$), however they trended toward improvement in the ketamine group and remained unchanged in the placebo group.

### 4.1. Correlations of clinical characteristics with pain parameters

There were no significant differences between those patients with a shorter duration of CRPS (11 patients with an average length of illness of 2.6 years and a range of 0.8–4.2 years) and longstanding patients (8 patients with an average length of illness of 12.2 years and a range of 6.8–20 years). This is in keeping with a recent study of 580 CRPS patients whose signs and symptoms were evaluated by regression analysis demonstrating little change in their pain scores after 1 year of illness [51]. No significant clinical differences were noted between upper or lower extremity involvement. All patients suffered various degrees of the same qualities of pain (burning, aching, deep muscle, lancinating, joint). They all demonstrated dynamic and static mechano-allodynia and most showed hyperalgesia to pinprick, and cold allodynia. CRPS symptoms have been shown to spread from the site of injury [36]. All patients in this study demonstrated spread either contiguous to the original lesion, in a mirror distribution or in some to most parts of the body. All patients had at least two extremities involved and those with greater than 8 years of illness more than 75% of their body was painful to some degree.

### 4.2. Short form McGill pain questionnaire

The McGill score of both the ketamine and placebo groups demonstrated severe pain (23.1 for the ketamine group and 28.17 for the placebo group). The ketamine group demonstrated a significant decrease ($p < 0.05$) in both the sensory and affective components. Both the sensory and the affective component were significantly reduced throughout the post-treatment part of the trial. The decrease in the total McGill score was approximately 35%, a 50% decrease in the affective component and a 31% in the sensory component. The robust decrease in the affective component may reflect the recently described antidepressant effects of ketamine as well as its demonstrated effects on NMDA dependent long-term potentiation (LTP) of pain transmission neurons of the dorsal horn [5,19,26,34,44,63].

### 4.3. Pain questionnaire

Statistically significant decreases ($p < 0.05$) were attained for pain in the most affected area, burning pain, pain when touched or brushed lightly and overall pain level in the ketamine group as compared to placebo. Although decreased for the 3 months following ketamine treatment, joint pain, muscle sensitization and the degree that pain interfered with activities of daily living, the reduction did not reach statistical significance ($p > 0.05$). This finding, a greater decrease of pain in the index area (area of original trauma), as compared to the decrease in overall pain, supports the recent evidence for NMDA involvement in homotopic hyperalgesia (mechanical or thermal hyperalgesia in a territory subserved by C-fibers conditioned by high frequency electrical stimulation). Mechanical heterosynaptic hyperalgesia (in this paradigm) occurs in contiguous or distant areas from the primary area of injury and may not be subserved by NMDA sensitive systems [25,29]. Evidence supports the general concept that homotopic hyperalgesia is a perceptual correlate of homosynaptic LTP in patients [22,61]. In addition, ketamine may act at supraspinal levels in CRPS [3,57] as well as at $Na^+$ and $K^+$ channels, L-type $Ca^{2+}$ channels, $5HT_3$ receptors [15,48], nicotinic [47], muscarinic [18], acetylcholine and μ-opioid receptors [18,53].

In superficial dorsal horn neurons, the basic pattern of tonic firing and spike repolarization is generated by voltage gated $Na^+$ and $K^+$ rather than $Ca^{2+}$ conductance's [37,41]. It is clear that in some chronic pain states NMDA receptor conductance is a major mechanism for pain maintenance and LTP of pain transmission neurons [33,35,46,49]. That ketamine did not provide greater relief of the pain in muscles or joints may be a reflection of heterogeneity of $K^+$ and $Na^+$ channels expressed on these nociceptive afferents, that enough NMDA channels were not blocked at this dosage or that this form of pain is less NMDA dependent. Recent studies have shown that muscle pain can induce central sensitization [17,39]. However, spontaneous activity of dorsal horn neurons in muscle pain afferents is not decreased by NMDA blockade [1,17]. It has been suggested that proprioceptive afferents may be the source of spontaneous muscle pain [31]. However, it has also been shown that chronic musculoskeletal pain is decreased to a greater degree with ketamine than morphine [1,54] and that muscle hyperalgesia, temporal summation and referred pain is reduced in a major subgroup of fibromyalgia patients by NMDA receptor blockade [11].

### 4.4. Activity watch data

Actigraphy has been utilized to monitor physical activity and sleep in fibromyalgia patients [28,30], psychomotor dysfunction in major depressive disorders [59] and in irregular sleep–wake rhythms [55]. This is an objective measure of sleep quality, awakenings and activity, and helps to minimize retrospective bias of

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self-reported data in which there is a tendency to report peak and most recent symptoms [56,58,59]. The statistically significant reduction in pain scores for the 2 week period following treatment corroborated the reduction of index area and burning pain as documented by self-report.

### 4.5. Conclusion

The strengths of this study are: (1) all patients met strictly defined IASP criteria for CRPS; (2) all patients were examined by the same senior clinician at all visits; (3) standardized pain (McGill short form) and quality of life questionnaires were utilized; (4) multiple pain parameters were evaluated; (5) several pain parameters were evaluated in multiple ways providing redundancy and increased confidence in the results; and (6) positive placebos (midazolam and clonidine) were utilized to effect blinding. The major limitations of this study are: (1) its small size; (2) non-stratification of patients either by length of time with the illness or by the temperature of the affected area; and (3) lack of a cross-over arm.

This study showed that i.v. ketamine, even at low dosage, administered in an outpatient setting resulted in statistically significant ($p < 0.05$) reduction in many pain parameters. Surprisingly, it also showed that subjects in our active placebo group demonstrated little treatment effect in any of these same parameters. The results of this study warrant a larger randomized placebo controlled trial using higher doses of ketamine and a 5 month follow-up in stratified patients. A recent literature review supports the use of sub-anesthetic ketamine for short term relief of refractory neuropathic pain [4]. Although several prior series utilizing sub-anesthetic multi-dose outpatient protocols [7,10,40] have been successful in treating refractory patients, this is the first randomized, placebo controlled trial to demonstrate significant reductions of some pain parameters suffered by CRPS patients.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2009.08.015.

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