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Optimizing the Treatment of CRPS With Ketamine

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Objective: This study aimed to develop a method that objectively measures the clinical benefits of ketamine infusions to treat complex regional pain syndrome (CRPS), thus making it possible, for the first time, to determine the optimal dosing of ketamine and duration of treatment to treat CRPS.

Materials and Methods: All patients were diagnosed with hyperalgesia associated with CRPS. Patients underwent an outpatient, 4-day, escalating dose ketamine infusion. Hyperalgesia was measured using pain thresholds. Clinical outcome was determined without knowledge of the patient's pain thresholds throughout treatment.

Results: We found a correlation between pain thresholds and the intensity of pain reported by the patient at various sites of the body. We found that clinical outcomes correlated with improvement in pain thresholds. There was a plateau in pain thresholds between days 3 and 4 for the lower extremities. There was no plateau in pain thresholds observed for the upper extremities.

Discussion: Our findings suggest that 4 days of treatment are sufficient for the treatment of CRPS of the lower extremities. For the upper extremities, >4 days may be required. Our study is the first to utilize quantitative sensory testing to direct the treatment of a chronic pain disorder.

Key Words: complex regional pain syndrome, hyperalgesia, ketamine, pain thresholds, reflex sympathetic dystrophy

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The safety and efficacy of ketamine to treat complex regional pain syndrome (CRPS) have been demonstrated in controlled studies for over a decade.[1,2] "Ketamine Clinics" have sprouted up worldwide with uncertainty about the optimal dose to treat CRPS.[3] Human studies designed to seek the optimal dose and duration of ketamine for treating CRPS may be subject to Investigational New Drug (IND) application requirements, which can be cumbersome for individual investigators. Previous studies attempting to establish a standardized protocol have been limited by sample size and a method to objectively quantify the efficacy of ketamine during treatment.[4]

The primary goal of this study was to determine if it was possible to observe a plateau response in relieving pain due to CRPS over 4 days of treatment. Such a determination is critical in preventing the overtreatment of patients with ketamine, which would have significant economic and safety consequences. For example, ketamine can cause adverse hallucinations when used in procedures requiring sedation in 10% to 20% of adults.[5] Medications for sedation, such as midazolam, can manage adverse hallucinations. However, these medications can lead to life-threatening respiratory depression and thereby limit the amount of ketamine that can be administered to the patient.

Unfortunately, a method does not exist to measure the intensity of pain from a quantitative standpoint. For more than a decade, we have found it useful to record quantitative sensory testing using an algometer to determine the magnitude of hyperalgesia on the surface of the body. Hyperalgesia is a condition in which a person with chronic pain develops an increased sensitivity to a painful stimulus. Approximately 5 million Americans experience hyperalgesia due to fibromyalgia.[6] CRPS is a chronic pain disorder also characterized by tactile and deep pain hyperalgesia.[7,8] In this study, we aimed to determine if utilizing pain thresholds to measure hyperalgesia could be used to monitor this component of chronic pain. A pain threshold is defined as the amount of stimulation required before the sensation of pain is experienced.

MATERIALS AND METHODS

This study was reviewed and approved by the Institutional Review Board at the University of Florida.

Patient Demographics

All patients were diagnosed with CRPS based on the Budapest Diagnostic Criteria.[9] This study did not distinguish between CRPS 1 and 2. All patients exhibited hyperalgesia. Patients were evaluated by the attending physician (A.F.K.). Our experience with administering ketamine in patients with CRPS is that the response is highly variable. The average age of female patients was 39 years, ranging from 9 to 50 years. The average age of male patients was 43 years, ranging from 13 to 59 years. The study included 89 females and 25 males after exclusions. Rather than giving a fixed-dose based height and weight, we

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selected at a relatively low dose as a starting dose and titrated upwards.

Exclusion Criteria

(1) Patients who had a primary location of CRPS above the neck were excluded (6 patients). These patients were excluded from this analysis since the sites where pain thresholds were measured would not address this area of the body reliably.
(2) Patients who failed to experience pain when >5 kg of force was applied to the skin at the primary location of CRPS were excluded (27 patients). The force was measured using a device (algometer by Wagner Instruments. Greenwich, CT) that is limited to a maximum reading of 5 kg. Therefore, readings above this point would not be quantifiable.

Classification of Primary, Secondary, and Tertiary Locations of CRPS

During the initial evaluations of patients, they were asked where they experienced pain most intensely. An effort was made to identify whether it was on the right or left side and if the pain involved a specific region of the body. Information about the location and intensity of the pain is identified in the chief complaint portion of the medical report. On the basis of the patients' presentation of pain at their initial baseline evaluations, pain threshold locations were classified as primary, secondary, and tertiary. The primary location was defined as the area of the body where the patient reported the greatest amount of pain. Secondary locations were reported as painful but not as severe as primary locations. Tertiary sites were least affected by pain.

Treatment Technique

The treatment timeline is displayed in Figure 1. Each day the patient had pain thresholds measured using an algometer. The algometer was pressed against the skin, and the pressure was slowly increased until the pressure sensation became painful to the patient. Pain thresholds were measured on the extremities of the body at 4 sites: the right and left thumb pads and the right and left great toe pads. The final threshold value at each site was calculated as an average of 3 consecutive measurements. The measurement of pain thresholds at all 4 sites took <1 minute. The patients were blinded to the value of the pain thresholds during quantitative sensory testing.

The day before the first infusion, patients had their pain thresholds measured. Next, patients were videotaped demonstrating their strength and range of motion by completing the following exercises: placing each arm behind the head, opening and closing a fist as fast as he or she can, ankle rotation, flexing the great toe of each foot, walking normally, walking on toes, and walking on heels.

The ketamine infusions took place on an outpatient basis. Patients were required to have a surrogate present throughout the infusion. The surrogate was required to be a part of the patient's long-term memory, such as a spouse, family member, or long-time friend. Prior experience demonstrated that having a surrogate present decreases the risk of an adverse hallucination. The surrogate acted as the proxy for the patient while the patient was under the influence of ketamine. Also, the surrogate transported the patient home or to a hotel after the infusion. Patients were not allowed to sleep during the ketamine infusion because we have found that sleeping is associated with adverse hallucinations.

During the infusion, the surrogate asked the patient a simple long-term memory question every 15 minutes.

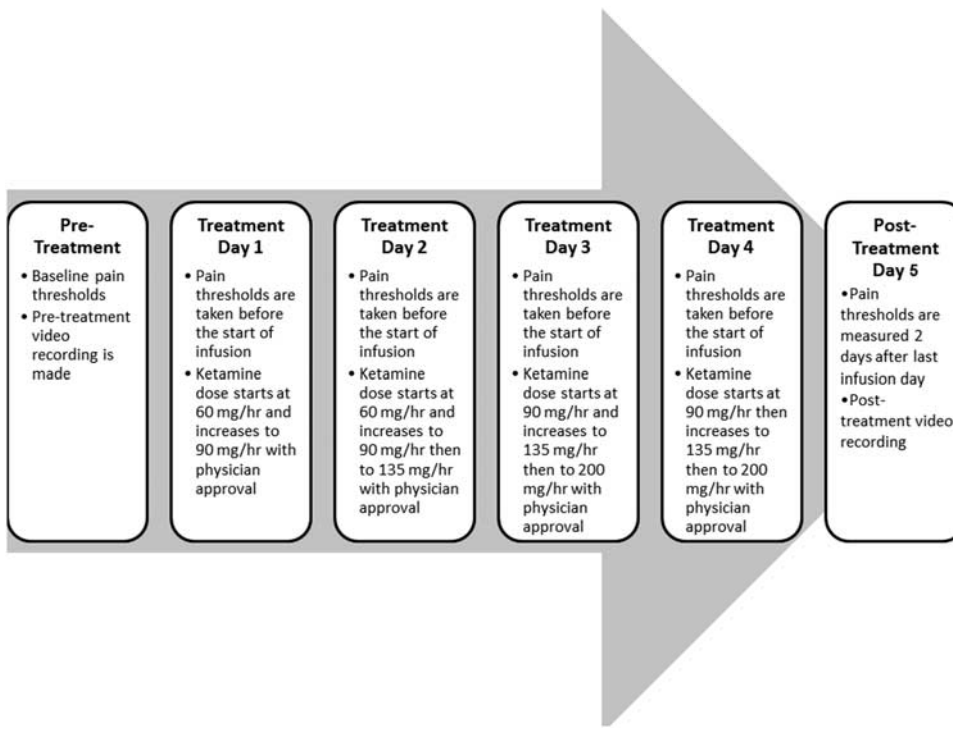

FIGURE 1. Timeline displaying the protocol for the 4-day ketamine treatment.

Example questions might include "In what state were you born?" or "What country are we in right now?" On the basis of the patient's ability to answer the question, the patient's level of consciousness (LOC) was recorded from levels 1 to 3. A LOC of 1 indicates the patient was able to answer the question without hesitation. A LOC of 2 means the patient responded to the question but may have required the question to be repeated several times or struggled to recall the answer immediately. A LOC of 3 indicates the patient could not provide the correct answer or did not respond to the question, even after it was repeated. The attending physician would pause the infusion for 5 to 10 minutes or decrease the dose if the patient received a LOC of 3. Blood pressure, pulse, oxygen saturation, and electrocardiogram were monitored continuously throughout the infusion.

Each infusion treatment lasted 4 hours. Patients were given 1 to 2 mg of intravenous midazolam at the beginning of each infusion. On day 1 of the infusion, the infusion rate of ketamine started at 60 mg/h. The rate was increased to 90 mg/h based on a patient's comfort, the stability of vital signs, and LOC. On day 2, the rate was initiated at 60 mg/h and was increased to 90 mg/h, then to 135 mg/h. On days 3 and 4, the rate was initiated at 90 mg/h and was increased to 135 mg/h, then to 200 mg/h. Near the end of the infusion on day 4, a video recording of the patient was completed that documented both short-term and long-term memory at the highest dose of ketamine.

The final infusion took place on a Friday. Three days later (Monday), patients returned to the surgery center to have their strength and range of motion tested and to have their pain thresholds recorded. These pain threshold measurements served as the day 5 readings. The patients were video-recorded completing the same strength and range of motion exercises they performed before the first treatment. Also, in this video, patients are interviewed about how their quality of life and abilities have changed since the infusion. Posttreatment clinical outcome of strength and range of motion was determined by the attending physician (A.F.K.) to be one of 3 clinical outcomes (strong, weak, or no clinical improvement) using the information documented in the video. The attending physician determined the clinical outcome without knowledge of the patient's pain thresholds throughout treatment.

Control Participants

To determine if conditioning to the stimulus caused by the application of force to the thumbs and the great toes took place over time, we recruited a population of volunteers to be tested over the same period as the experimental group. Control participants were healthy volunteers who did not have a history of a neurological or pain disorder. Participants had their pain thresholds measured in the same areas of the body as patients receiving ketamine treatment. Volunteers came on Tuesday to Friday and the following Monday for their appointments to have their thresholds measured.

Statistics

Due to the broad range of baseline readings for pain thresholds among patients with CRPS, results were analyzed using the percent change in pain thresholds from the baseline. This method allowed the patient to be used as his or her control. The normal control participants also served as his or her control at baseline. Confidential identifiers were used in place of the patient and volunteer names. The analysis of data was completed utilizing Microsoft Excel and IBM SPSS. Longitudinal changes between groups were tested using the mixed-effect model repeated-measures analysis of variance, after applying normality transformations.[10,11] Follow-up post hoc comparisons were made using the Bonferroni adjustment for multiple comparisons.

To determine when the patients obtain a peak response to treatment, it was necessary to employ a statistical analysis for longitudinal data. It was not possible to use the percent change in pain thresholds for this task. Instead, the observed pain threshold changes from baseline at the primary location were studied. Analyses were conducted using R, version 3.4.3. The longitudinal mixed-effect models were used to characterize pain threshold changes over time for each participant. In the model, patient groups (control vs. CRPS), extremity type (lower vs. upper), sex, age, body mass index, time, time2, and the interaction terms of all the above terms are used as predictors. In the model, time2 is considered to allow a quadratic trend of the response over time. To perform model selection, the backward variable selection technique was used to decide which predictors should be included in the final model. The 95% confidence intervals of the peak responses were obtained using a bootstrap procedure with 1000 bootstrap samples. The bootstrap method is a widely used statistical technique for constructing confidence intervals without making unreasonable assumptions about the data.[12,13]

RESULTS

Correlation Between Pain Thresholds and Intensity of Pain Reported by Patient

The primary location of CRPS represents the area with the most severe pain reported by the patient during the initial evaluation. The primary location of CRPS with the most severe pain shows the highest percent improvement in pain threshold, followed by the secondary then by the tertiary locations (Fig. 2). Throughout the 4-day infusion, readings at the primary and secondary locations showed significantly greater improvement than tertiary locations and control locations ($F = 98.80$, $P < 0.001$). We found a correlation between pain thresholds and the level of pain reported by the patient at various sites of the body ($\eta = 0.701$), where η is the correlation ratio commonly used to measure the strength of association between a nominal explanatory and a continuous outcome.

Correlation Between Pain Thresholds and Clinical Outcome

Of the 114 patients that were evaluated, 101 had a strong clinical outcome, 6 had a weak outcome, and 7 had no clinical improvement (Fig. 3). Pain threshold changes in the primary location were analyzed based on the patients' clinical outcomes. Patients that received a strong clinical outcome posttreatment showed a significant, robust increase in pain thresholds throughout treatment ($F = 66.49$, $P < 0.001$). We found that clinical outcomes correlated with improvement in pain thresholds ($\eta = 0.801$).

Separate Analysis of Upper and Lower Extremities

We analyzed the difference in response in the upper and lower extremities in the strong responders (Fig. 4). Doing so eliminated the data points from the patients with a

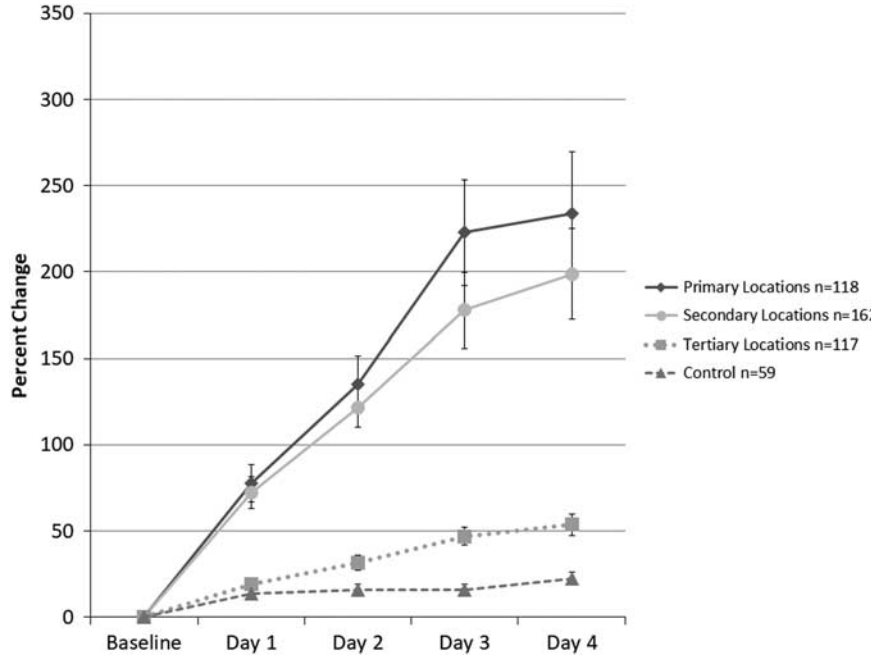

FIGURE 2. Graph showing the percent change from baseline in pain threshold readings for each location classification (primary, secondary, tertiary). Error bars represent the SEM.

weak clinical outcome or no clinical improvement. By only analyzing the strong responders, the variability of the data was reduced. From a clinical standpoint, the physician is more interested in knowing whether there is a difference in response to treatment in the upper and lower extremities in patients that had a strong clinical outcome after ketamine treatment than those who showed a weak response or who had no clinical improvement. Figure 4 displays a plateau in response for the lower extremities but not in the upper extremities.

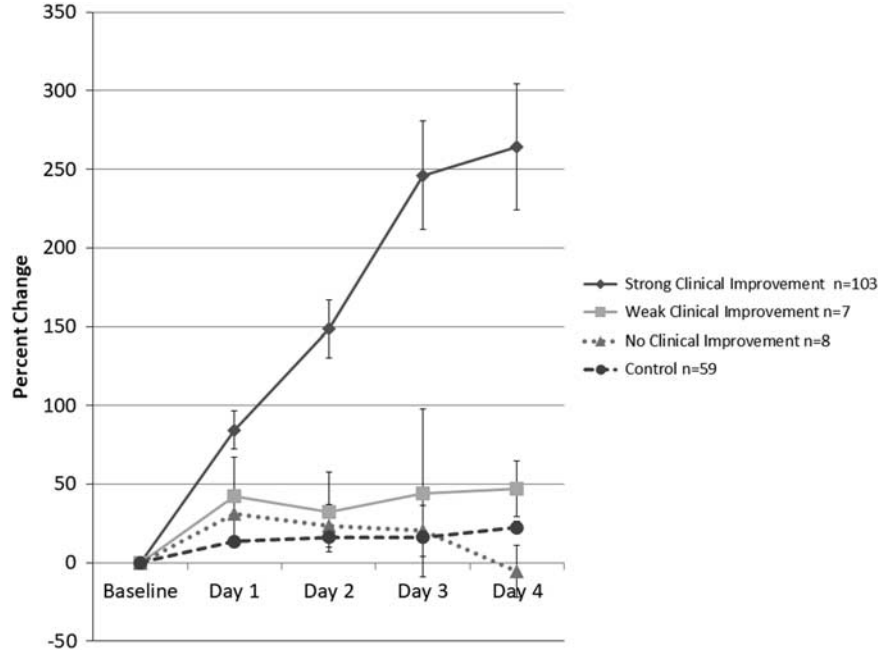

FIGURE 3. Comparison of the percent changes in pain threshold readings at the primary location for patients with a strong clinical outcome, weak clinical outcome, and no clinical improvement. Posttreatment clinical outcome was based on determining improvements strength and range of motion in video recordings by the attending physician (A.F.K.). The attending physician determined the clinical outcome without knowledge of the patient's pain thresholds throughout the treatment. Error bars represent the SEM.

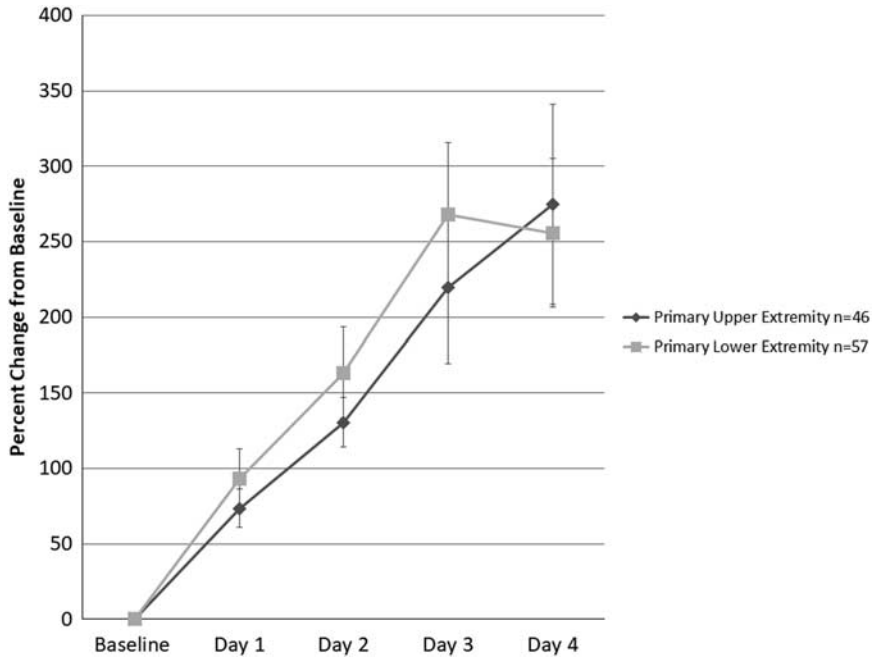

FIGURE 4. Percent change in pain thresholds from baseline of the primary upper and lower extremities in strong responders.

Statistical Analysis Using A Computer-based Program

To further investigate the differences between the response in the upper and lower extremities, it was necessary to use a computer-based program. (See the Materials and Methods section). Figure 5 demonstrates that a plateau is evident for the changes in pain thresholds for the lower extremity between days 3 and 4, but not for the upper extremity. From this statistical model, we can calculate the estimated position of the peak response to treatment. Also, we can calculate the 95% confidence intervals of these positions by the bootstrap procedure. The results are presented in Table 1.

Patient Demographics and Medication Intervention

Table 2 lists the side effects experienced by patients, patient demographics, and medications that were required during the infusion. The most common side effect was nausea. Females were affected by nausea more frequently than males. Dexamethasone was used to alleviate nausea. Glycopyrrolate was used to control excessive salivation caused by ketamine during the infusion. All patients received 1 to 2 mg of midazolam at the beginning of each infusion. Additional midazolam was used to alleviate patient anxiety during the infusion. Anxiety was also alleviated in some instances by pausing the infusion for 5 to 10 minutes without having to use midazolam intervention. No adverse hallucinations or serious complications were observed.

DISCUSSION

When comparing the percent change in pain thresholds in primary, secondary, and tertiary locations (Fig. 2), the primary location of CRPS exhibited the greatest average percent increase. This observation suggests that ketamine has its most potent effect in areas of the body that are most affected by pain due to CRPS.

Patients with a strong clinical outcome exhibited the greatest improvement in pain thresholds (Fig. 3). This finding suggests that pain thresholds are a valid method to measure pain in CRPS as well as to measure clinical outcomes after treatment with ketamine. These results introduce pain thresholds as a tool to optimize the treatment of CRPS.

We were surprised to find that the upper and lower extremities respond differently to ketamine (Figs. 4, 5). When analyzing the lower extremities, there is a plateau in pain thresholds seen between days 3 and 4 of treatment, which suggests that the patients may have received the maximum ketamine benefit. However, for patients with CRPS of the upper extremities, a plateau is not conspicuous, which suggests that >4 days of ketamine treatment may be required for an optimal clinical outcome.

Ketamine treatment has been shown to increase blood pressure.[14] Therefore, elevated blood pressure was expected (Table 2). Some patients required additional midazolam during the infusion to counteract anxiety. Additional midazolam should be used with caution due to its ability to cause respiratory depression, which could limit the amount of ketamine a patient can receive.[15] No adverse hallucinations were observed. Nausea was the most common side effect and was effectively treated with dexamethasone and, if necessary, glycopyrrolate. Ketamine increases salivation, which can trigger the gag reflex and cause discomfort for the patient.[16] Glycopyrrolate was given to patients experiencing excess salivation. A treatment protocol for ketamine infusions should include the availability of intravenous midazolam, dexamethasone, and glycopyrrolate (Table 2).

The intensity of pain experienced by patients influences a physician's clinical judgment, decision-making, selection of treatment modalities, potential surgical indications, and the subsequent prognosis. An objective method of

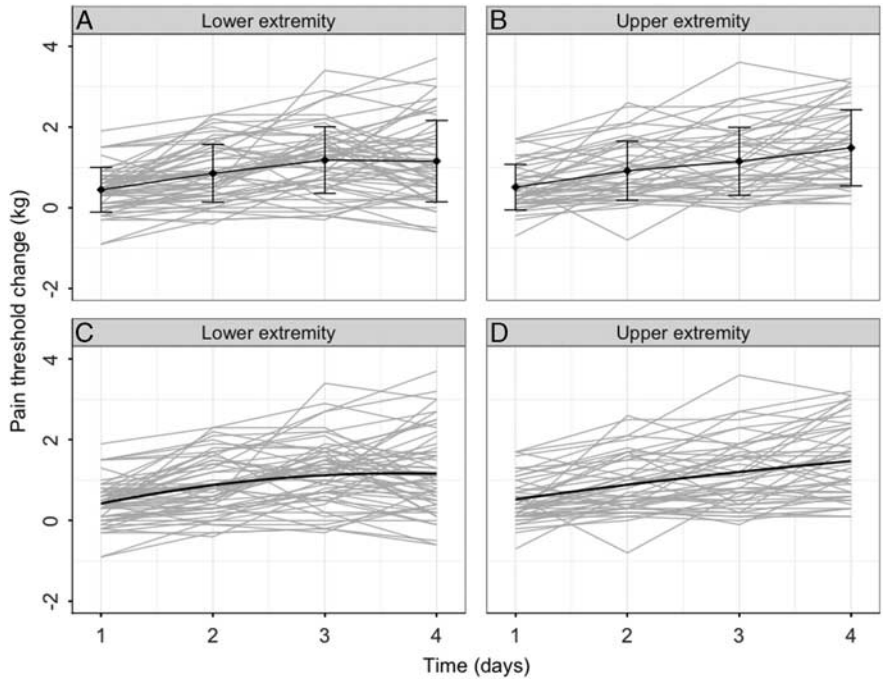

FIGURE 5. A and B, The observed pain threshold changes from baseline (gray lines) at the primary location for pain. Solid points denote mean values calculated from the raw data, while the bars indicate mean ± SD. C and D, The estimated pain threshold changes from the final model (black line), together with the observed values (gray lines).

measuring pain would be a significant advancement for all medical specialties in the treatment of chronic pain. Existing clinical pain assessment instruments are restricted to the patient's subjective perception of the intensity of pain. The Numerical Rating Scale, Verbal Descriptor Scale, Visual Analog Scale, and other methods are solely dependent upon the patient's opinion. These methods are useful for assessing acute pain, but not chronic pain.[17,18]

This report introduces a method for collecting quantitative sensory data concerning chronic pain that can be subjected to quantification. The data provides the opportunity to confirm, validate, or refute the patient's assertions concerning pain magnitude. This study validates the use of pain thresholds to offer quantitative sensory testing of clinical outcome during the treatment of chronic pain.

The measurement of pain thresholds provides a means to quantitate the spreading of CRPS throughout the body. Patients who report their symptoms of CRPS are often not aware of the syndrome spreading elsewhere on the body. Pain thresholds identify other affected areas of the body, which otherwise would be overlooked. Such identification of spreading is essential for determining the appropriate treatment options.[19] For example, if CRPS is localized to a specific extremity, sympathetic nerve blocks would be an appropriate treatment option. Alternatively, if CRPS is generalized throughout the body, a more generalized treatment, such as a ketamine infusion, might be more appropriate. While all patients achieved a CRPS diagnosis using the Budapest Criteria, this criterion, unfortunately, does not address the spreading of signs and symptoms as a hallmark of the disorder.

The question of the optimal dose and duration of ketamine for treating CRPS was raised a decade ago with little response.[4] Previous studies attempting to satisfy this need for a standardized protocol have been limited by sample size and a method to objectively quantify the efficacy of ketamine during treatment. This study suggests that 4 days of escalating dose ketamine infusions might be adequate to treat hyperalgesia associated with CRPS in the lower extremities. In contrast, there was no plateau in pain threshold improvement for hyperalgesia in the upper extremities (Figs. 4, 5).

This was a prospective study without placebo control. Given that 2 previous studies demonstrated the efficacy of ketamine utilizing placebo-controlled methods, it would have been difficult to employ a placebo control from the standpoint of recruiting patients for the current study.[1,2]

TABLE 1. Display of the Estimated Plateau Positions and Their 95% CIs, the *P*-value for the Quadratic Term, and the Estimated Coefficient of the Quadratic Term for Primary Lower and Upper Extremities in Patients With a Strong Clinical Outcome

	Estimated Plateau Position	95% CI	*P* for Quadratic Term	Estimated Coefficient of the Quadratic Term
Lower extremity	3.68	3.11, 4.45	0.0397	−0.1083
Upper extremity	9.37	4.41, 17.90	0.7557	−0.0179

CI indicates confidence interval.

TABLE 2. Average Age, the Average Time Between the Onset of CRPS and First Infusion, Average Ketamine Received, Side Effects, and Medication Intervention

	All Patients (N = 114)	Females (N = 89)	Males (N = 25)
Age (y)			
Mean	39.7	38.7	43.2
Median	40.0	38.0	47.0
Average time between onset of CRPS and infusion (y)			
Mean	5.9	5.4	7.9
Median	4.0	4.0	5.3
Average total ketamine (mg) received over 4 d			
Mean	1501.6	1501.0	1503.9
Median	1516.0	1517.0	1499.0
Most common side effects			
Nausea	46 patients (40%)	40 female patients (45%)	6 male patients (24%)
Respiratory depression	9 patients (8%)	5 female patients (6%)	4 male patients (16%)
Elevated blood pressure	9 patients (8%)	5 female patients (6%)	4 male patients (16%)
Anxiety	6 patients (5%)	6 female patients (7%)	0 male patients (0%)
No side effects	44 patients (39%)	31 female patients (35%)	13 male patients (52%)
Medications			
Dexamethasone	40 patients (35%)	35 female patients (39%)	5 male patients (20%)
Glycopyrrolate	27 patients (24%)	5 female patients (6%)	6 male patients (24%)
	Total infusions (114 patients×4 infusions) (n = 456)	Female infusions (89 females×4 infusions) (n = 356)	Male infusions (25 males×4 infusions) (n = 100)
Infusions where additional midazolam was needed to treat anxiety	34 infusions (7%)	27 female infusions (8%)	7 male infusions (7%)

CRPS indciates complex regional pain syndrome.

There is no "gold standard" for the objective measures of pain-related physical or functional capacity in use within the health care system. Practitioner ratings are subject to the standard range of observer biases[20] and often lack consistent rating scales used to rate performance, which reduces their reliability and validity. In addition, despite their apparent objectivity, practitioner ratings are highly subjective since they rely on their clinical experience and internalized schema, which may account for their poor interrater reliabilities.[21–23] Also, pain intensity, functionality, and quality of life may not match, especially in chronic pain. Our study validates the use of the algometer for quantitative sensory testing for hyperalgesia in patients with chronic pain in settings where rapid and cost-effective assessment is necessary.

Our study has several strengths. First, a physician experienced in the treatment and diagnosis of CRPS evaluated research participants, thus limiting interobserver variance. Second, this is the first study to show that it is possible to direct the treatment of chronic pain using a tool that measures quantitative sensory testing. Furthermore, determining the intensity of pain experienced by the patient using pain thresholds under blinded conditions is more objective than in previous studies that depend on self-reporting of pain by the patient. Third, video documentation of results has not been previously done for CRPS or other chronic pain afflictions. Video documentation (and evaluation by a blinded interpreter) adds to the validity of our findings. Fourth, for the first time, ketamine was given to conscious patients, and there were no adverse hallucinations documented. Last, we believe that utilizing pain thresholds in the treatment of other chronic pain disorders will broaden the applicability of this tool across many specialties and facilitate research into chronic pain.

In summary, our findings suggest that 4 days of treatment with ketamine are sufficient for the treatment of hyperalgesia of the lower extremities associated with the diagnosis of CRPS. But for the upper extremities, >4 days may be required. This study demonstrated that there is a strong correlation between clinical improvements in hyperalgesia and improvements in strength and range of motion of patients on a short-term basis during the 4-day ketamine infusion (Fig. 3). However, the effects of treating CRPS has to be associated with the improvement of quality of life in the long term. Future studies are in progress to determine if pain thresholds are predictive of the long-term efficacy of ketamine in several domains such as strength, range of motion, sleep, depression, opioid use, and patient's ability to work. The use of pretreatment and posttreatment videos in this short-term study will serve as a useful baseline in assessing changes in the quality of life and abilities of the patients in the long term.

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