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PRELIMINARY RESEARCH

A Pilot Open-Label Study of the Efficacy of Subanesthetic Isomeric S(+)-Ketamine in Refractory CRPS Patients

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ABSTRACT

Objective. Complex regional pain syndrome (CRPS) is a severe neuropathic pain state that is often disproportionate to the initial trauma. Associated features are autonomic dysregulation, swelling, motor dysfunction, and trophic changes to varying degrees. Despite a multitude of treatment modalities, a subgroup of CRPS patients remain refractory to all standard therapies. In these patients, the disease may spread extraterritorially, which results in severe disability. A critical involvement of N-methyl-D-aspartate receptors (NMDARs) has been demonstrated both clinically and by animal experimentation. NMDA antagonists may be effective in many neuropathic pain states. In long-standing, generalized CRPS, we investigated the effects of S(+)-ketamine on pain relief and somatosensory features, assessed by quantitative sensory testing (QST).

Methods. Four refractory CRPS patients received continous S(+)-ketamine-infusions, gradually titrated (50 mg/day–500 mg/day) over a 10-day period. Pain intensities (average, peak, and least pain) and side effects were rated on visual analogue scales, during a 4-day baseline, over 10 treatment days, and 2 days following treatment. QST (thermo-, mechanical detection, and pain thresholds) was analyzed at baseline and following treatment.

Results. Subanesthetic S(+)-ketamine showed no reduction of pain and effected no change in thermo- and mechanical detection or pain thresholds. This procedure caused no relevant side effects. The lack of therapeutic response in the first four patients led to termination of this pilot study.

Conclusion. S(+)-ketamine can be gradually titrated to large doses (500 mg/day) without clinically relevant side effects. There was no pain relief or change in QST measurements in this series of long-standing severe CRPS patients.

Key Words. CRPS; NMDA-Antagonists; S(+)-Ketamine; Quantitative Sensory Testing

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Introduction

At the present time, there are a variety of pharmacological, interventional, and physical therapy approaches to the treatment of complex regional pain syndrome (CRPS) that are partially effective [1,2]. A subgroup of patients remain refractory to all modes of treatment and suffer

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progression of the disease [3]. The disease may spread in specific patterns and at times becomes generalized. Therapy for these patients at present is most often ineffective [2,3].

A great deal of progress has been achieved in understanding the neurobiology of the syndrome utilizing experimental models but there are differences in these models and the specific aspects of the illness [4]. Recent experimental and clinical studies suggest a major role of the central nervous system in much of the symptomatology seen in CRPS patients [4,5]. Peripheral and central sensitization of nociceptive pathways appears to be a major mechanism [6]. There is solid evidence that the N-methyl-D-aspartate receptor (NMDAR) is involved in central sensitization [7].

Beneficial therapeutic effects of various NMDA antagonists have been suggested for several neuropathic pain conditions [8]. However, available data on the efficacy of NMDAR-antagonists mainly derives from animal experimental and uncontrolled clinical studies, and randomized controlled clinical studies are highly warranted. CRPS is generally regarded as a neuropathic condition and thus might be benefited by NMDA blockade. This thesis is supported by a growing number of clinical trials, suggesting a clinical response to ketamine in CRPS [9–12]. The best results of ketamine therapy to date have been demonstrated in early and well-localized CRPS. The efficacy of ketamine in long-standing CRPS patients who have been refractory to all standard modes of therapy has not been investigated to the same degree as early less severely affected patients.

S(+)-ketamine, as well as racemic ketamine, is a potent analgesic in the low-dose range (0.125–0.25 mg/kg), and potent anesthetic in the high-dose range (above 0.5 mg/kg). The main adverse effects are directly dependant on dosage and above all consist in cardiovascular stimulating (tachycardia, hypertension) and psychotropic (agitation, nervousness, hallucinations) side effects. In chronic pain therapy, beneficial pain-relieving effects of ketamine have been suggested by several clinical studies and randomized controlled trials [7,8].

This study was undertaken to investigate the effectiveness of S(+)-ketamine in a group of severely affected, long-standing CRPS patients who had failed all conventional methods of therapy. The isomeric S(+) entomere of ketamine was selected because of its higher NMDAR-affinity, its twofold higher analgesic potency, and its side-effect profile compared with the racemic form [13].

Methods

The Ethical Committees of the Medical Faculties at the University of Tuebingen, and at the University of the Saarland in Saarbrücken, approved the study protocol and the use of increased doses of ketamine for severe and refractory CRPS. Informed written consent was obtained by all patients.

Study Design

The study was designed and performed as a prospective open-label pilot study. The objective was to determine clinical effectiveness and effective dosage as a basis for a power-calculation of subsequent randomized controlled trials.

CRPS-Diagnosis

All patients met both the 1993 IASP–CRPS and the 1999 modified research diagnostic criteria for CRPS [14].

Inclusion Criteria

Inclusion was limited to severe, long-standing or fulminantly progressive CRPS patients. Their average pain intensity had to exceed 70 mm on a 100-mm visual analogue scale (VAS: endpoints: 0—no pain, 100—worst pain imaginable). All patients had to have failed recognized pharmacological and interventional treatments. These included: 1) pharmacological therapy with recommended drugs or their combinations; and 2) at least three unsuccessful interventional treatments. Failure was defined as: 1) no response to treatment, or 2) no lasting relief of pain (>2 months); and 3) persistence, recurrence, or steady progression of the disease. Inclusion was limited to, apart from their pain-related disability, physically healthy patients who fulfillled the American Society of Anesthesiologists (ASA) Physical Status Classification Class I–III. Patients with known contraindications or allergies to ketamine, a history of substance or drug abuse, psychatric illness, suspected somatoform pain disorder, or legal issues were excluded.

Treatment Protocol

S(+)-ketamine was continuously infused via a central line, in gradually increasing dosage over 10 days. The starting dose was 50 mg/day S(+)-ketamine, with a daily increase by 100 mg/day, if there were no side effects. Ketamine was titrated to a final target dose of 500 mg/day. Infusions were slowly tapered on treatment day 10. In the presence of side effects, dosage was reduced step-

wise by 50 mg/day until they ceased. The dose was slowly titrated upwards again to the final target dose. Clonidine (150–450 μg/day, as clinically needed) was coadministered to alleviate sympathomimetic, psychomimetic, and potential neurotoxic ketamine side effects [13,15].

Side effects and Safety Issues

Prior, during, and following therapy blood work was performed, which included a complete blood cell count, coagulation parameters, liver enzymes, creatine phosphokinase (CPK), and C-reactive protein.

Pain Assessment

Patients rated their subjective pain intensities three times daily on 100-mm VASs (endpoints: 0—no pain, 100—worst pain imaginable) using a pain diary. Diaries contained a 4-day baseline assessment, 10 treatment days, and 2 days following treatment. The diary assessed the intensities of the following pain components: 1) average pain; 2) peak pain; 3) least pain; and 4) degree of pain relief (endpoints: 0—no pain relief, 100—total pain relief).

Side Effects

Patients used a symptom diary once daily to rate occurrence and intensity of side effects on 100-mm VASs (endpoints: 0—not at all, 100—intolerable) during the same time period as their pain diaries. The diary contained specific items for psychotropic NMDAR-antagonist side effects (dizziness, euphoria, anxiety, disorientation, hallucinations, nightmares, feeling faint), as well as general symptoms (tiredness, nausea, headaches, heartburn, weakness, insomnia). Other nonpsychiatric side effects of NMDAR-antagonists (blurred vision, altered hearing, tinnitus or buzzing in the ears, perioral numbness, metallic taste, and throbbing heart) were also recorded.

Quantitative Sensory Testing

Quantitative sensory testing (QST) was performed in the area of the patients' worst pain, which corresponded in these patients to the forearms and hands. QST was performed on the medio-dorsal aspect of the hand for the mechanosensory tests and the palmar thenar aspect for thermosensory testing.

Mechanosensory Detection Threshold

Mechanosensory detection thresholds (touch thresholds) were investigated using standardized and force-graded (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128 and 256 millinewton [mN]) optical VonFrey Hair filaments (Optihair, Marstock, Germany). Using the method of limits, 5-stimulation series of increasing and decreasing stimulation intensities were performed. The calculated geometrical mean represents the detection thresholds. Patients were instructed to report only a touch sensation [16].

Mechanosensory Pain Thresholds

These were determined by the method of limits using a standardized force-graded set of pinprick probes (8, 16, 32, 64, 128, 256 and 512 mN), with a standardized plane contact area (0.2 mm). Five-stimulation series with increasing and decreasing stimulation intensities were performed, with the calculated geometrical means representing the thresholds. Patients were instructed to indicate the stimulation intensity at which the sensation of touch changed to "needle prick" [17].

Temperature Detection Thresholds

Cold and warm detection thresholds were analyzed using a computerized thermosensory analyzer (TSA, Medoc, Israel). Thermoneutral temperature was set at 32°C. Detection thresholds were determined with the method of limits in 4-stimulation series with decreasing (cold detection), and increasing (warm detection) temperatures. The ramp for temperature changes was set at $\Delta t = 1°C/s$. Patients were instructed to stop the stimulation as soon as they noticed a temperature change. The calculated means represent the thresholds.

Temperature Pain Thresholds

These were determined for cold pain and heat pain thresholds by a similar method as for thermal detection thresholds. Patients were instructed to stop the stimulation as soon as the quality of a temperature change became painful, burning or stabbing.

Ketamine Plasma Levels

Blood samples were collected on each treatment day. Samples were centrifuged at 4,500 r.p.m. over 10 minutes. Plasma aliquots were stored at –80°C until high-pressure liquid chromatography-analysis.

Statistics

Pain intensities and side effects are presented as means ± SD. Using the Kolmogorov-Smirnov test, data were found to be not normally distributed. Analyses of differences between baseline,

during, and following therapy, the nonparametric Wilcoxon rank sum tests were used with Bonferroni correction for multiple comparisons. Alpha was set at 0.05. Due to the small sample size, results for QST were only presented descriptively. Temperature detection and pain thresholds are presented as means ± SD; mechanosensory detection and pain thresholds were shown as geometrical means ± 95% CI.

Results

Demographics

Four female patients aged 25.3 ± 10.3 years old (mean ± SD; range 18–43 years) were included in the study. All patients belonged to ASA Physical Status Classification I-II. The mean duration of CRPS was 58 ± 20 months. Three patients suffered generalized CRPS. One patient had severe CRPS of the distal aspects of the arm (wrist and hand), following hand surgery, which showed rapid regional spread up the entire arm within the first months following injury. At inclusion, disease had spread to the arm, the ipsilateral shoulder, with early mirror spread to the contralateral upper trunk brachial plexus distribution. A movement disorder, deterioration in all aspects of daily living, was present in all patients (Table 1). All patients had failed numerous medical and invasive treatments (Table 2).

Course of S(+)-Ketamine Treatment

A gradual daily upward titration of S(+)-ketamine was performed without relevant side effects in patients 1–3. The maximal dosage of 500 mg/day S(+)-ketamine was reached in these patients on treatment day 8, without relevant side effects. In patient 4, the S(+)-ketamine dosage had to be titrated more slowly due to dizziness during the initial three treatment days. This resulted in a reduced maximal S(+)-ketamine dose of 300 mg/day in this patient.

Pain Relief

During the 4-day baseline observation period, all patients reported severe pain with an average pain intensity of 81.7 ± 4.5 mm, a peak pain intensity of 86.3 ± 3.2 mm, and a least pain intensity 74.2 ± 4.7 mm on 100-mm VASs. The reported subjective pain relief by the medication they were taking on a regular basis was 6.4 ± 3.2 mm on a 100-mm VAS.

Over the 10 days of ketamine treatment, patients showed no relief from their intense pain,

Table 1 Patient demographics

Patient No.	Age (Years)	Gender	ASA Class	Height (cm)	Weight (kg)	Triggering Injury/Site of Primary CRPS Manifestation	CRPS Duration (Months)	Status of Spread	Average Pain Intensity over Baseline (VAS)
1	20	F	II	174	68	Trauma to neck, shoulder and lower back/sciatic nerve distribution right, shoulder, neck and arm right	48	Generalized	82.5 ± 12.6
2	43	F	III	170	128	Traumatic injury to lower back, operative fusion of L4/5-S1/2/entire sciatic nerve distribution left	72	Generalized	85.1 ± 4.64
3	18	F	II	178	61	Trauma to right foot (no fractures)/right foot	84	Generalized	82.1 ± 5.73
4	19	F	I	168	65	Soft tissue trauma to right hand (no fractures)/right hand	30	Contiguous (entire right arm, shoulder, neck, and face)	82.1 ± 5.32

Shown are age, gender, ASA Physical Status Classification, triggering original injury and primary site of CRPS manifestation, duration of CRPS and the status of CRPS-spread at inclusion in the investigation. The average pain intensity shown represents mean ± SD over the 4-day baseline.
ASA = American Society of Anesthesiologists; CRPS = Complex regional pain syndrome; F = female; VAS = visual analogue scale.

Table 2 Failed standard modalities of therapy: summary of the previously failed conventional treatment attempts

(A) Physical and pharmacological treatments

		Oral Pharmacological Treatment							Topical Treatments	
Patient No.	Physiotherapy	NSAID	Antidepressants	Anticonvulsants	Spasmolytics	Sodium-Channel-Blocker	Low-Potent Opioids	High-Potent Opioids	Lidocaine	DMSO
1	+	+	+	+	+	+	+	+		
2	+	+	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+	+	+
4	+	+	+	+	+	+	+	+	+	+

The "+" indicates for each patient, which prior treatment was performed without initial or lasting (>2 months) relief of pain.
NSAID = nonsteroidal anti-inflammatory drugs; DMSO = dimethylsulfoxid.

(B) Interventional therapies

		Nerve Blocks		Sympathetic Blocks								
Patient No.	Trigger-Point Infiltrations	Selective Nerve Blocks	Brachial Plexus Blocks	IVRSB	Intrapleural	Stellate Ganglion	Lumbar Epidural	Lumbar Sympathetic Chain	Sympathectomy	intravenous Lidocaine	Spinal Cord-Stimulation	Intrathecal Treatment
1	+ (>4)	+ (>3)	+ (1)	+ (2)	+ (2)	+ (>6)	+ (2)			+ (1)		
2	+ (>8)	+ (>6)		+ (>4)			+ (>4)	+ (2)	+	+ (2)	+	+
3	+ (>4)	+ (>5)	+ (1)		+ (1)		+ (1)			+ (2)		
4	+ (>6)	+ (>3)	+ (1)	+ (2)	+ (2)	+ (>4)						

The "+" indicates which intervention was performed in each patient. Additionally approximate number of procedures performed in each patient is in parentheses.
IVRSB = intravenous regional sympathetic blockade.

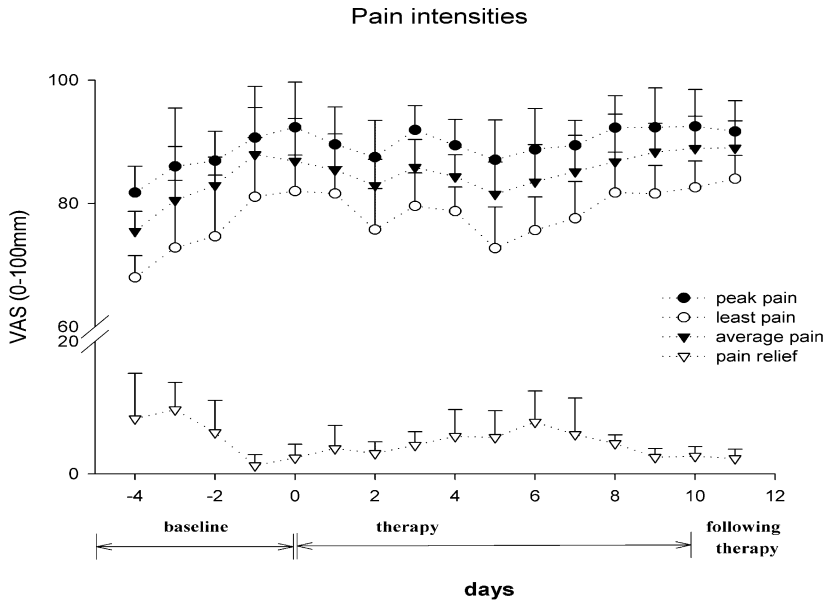

Figure 1 Pain intensity and subjective relief from pain: results of the pain diaries assessing different pain intensities (endpoints: 0—no pain, 100—worst pain imaginable), and the subjective relief from pain (endpoints: 0—no relief, 100—total relief) on 100-mm VAS. Results are shown as means + SD for average pain, peak pain, and least pain and for the subjectively reported degree of pain relief from treatment. Data were assessed over a 4-day baseline, 10 treatment days and 2 days following therapy. There were no significant differences for the relief of pain over baseline. VAS = visual analogue scale.

as demonstrated by the mean pain intensities over the treatment period: 1) average pain: 85.1 ± 1.9 mm; 2) peak pain: 90.0 ± 1.9 mm; and 3) least pain: 78.7 ± 3 mm. The subjective pain relief during ketamine treatment was rated at 4.6 ± 1.6 mm. During the 10-day observation period after initiation of the ketamine infusion, the average pain intensity was 89 ± 0.1 mm, the peak pain intensity 92.1 ± 0.4 mm, the least pain intensity 83.3 ± 0.7 mm with a reported general pain relief of 2.5 ± 0.2 mm. There were no significant differences for all investigated components of pain compared with baseline (Figure 1).

Side Effects

Relevant (>30 mm on 100-mm VASs) general side effects were already observed at baseline under their current analgesic medication: nausea (34.6 ± 23.16 mm), tiredness (69.1 ± 17.7 mm), dizziness (40.3 ± 25.4 mm), headaches (49.6 ± 11.4 mm), insomnia (39.6 ± 16.4 mm), and weakness (45.4 ± 38.65). Typical NMDAR side effects and side effects unrelated to ketamine were reported and were minimal (<30 mm) extent.

During the course of the infusion, the intensity of general symptoms decreased (nausea, tiredness, insomnia, headaches, and weakness). Ketamine side effects (hallucinations, nightmares) showed either no change with treatment, or only an insignificant increase compared with baseline over the first two to four treatment days (euphoria, disorientation). At the maximal infusion dose, euphoria and disorientation increased moderately (<40 mm). No severe psychotropic side effects were observed during ketamine treatment. All groups of side effects showed no significant changes compared with baseline.

Safety Issues

There were no changes in complete blood cell counts, coagulation parameters, liver enzymes, CPK or C-reactive protein.

QST

Mechanosensory Detection and Pain Thresholds

The ability to discriminate light touch was intact in all patients. Severe static mechanical allodynia was present in all patients, who also demonstrated low mechanosensory detection thresholds. A small increase of stimulus intensity caused pain. Following S(+)-ketamine treatment, a slight but insignificant increase in mechanosensory detection thresholds was seen in all patients, especially in patient 2.

Mechanosensory pain thresholds were found to be very low, especially in patients 1–3, which matched their extreme mechanoallodynia. Following ketamine treatment, patients 2 and 3 described a minor reduction in their touch allodynia, congruent with a slight increase in their mechanosensory pain thresholds. Patients 1 and 4 described no subjective change in touch allodynia following ketamine. Compared with baseline, mechanosensory pain thresholds remained unchanged in these patients.

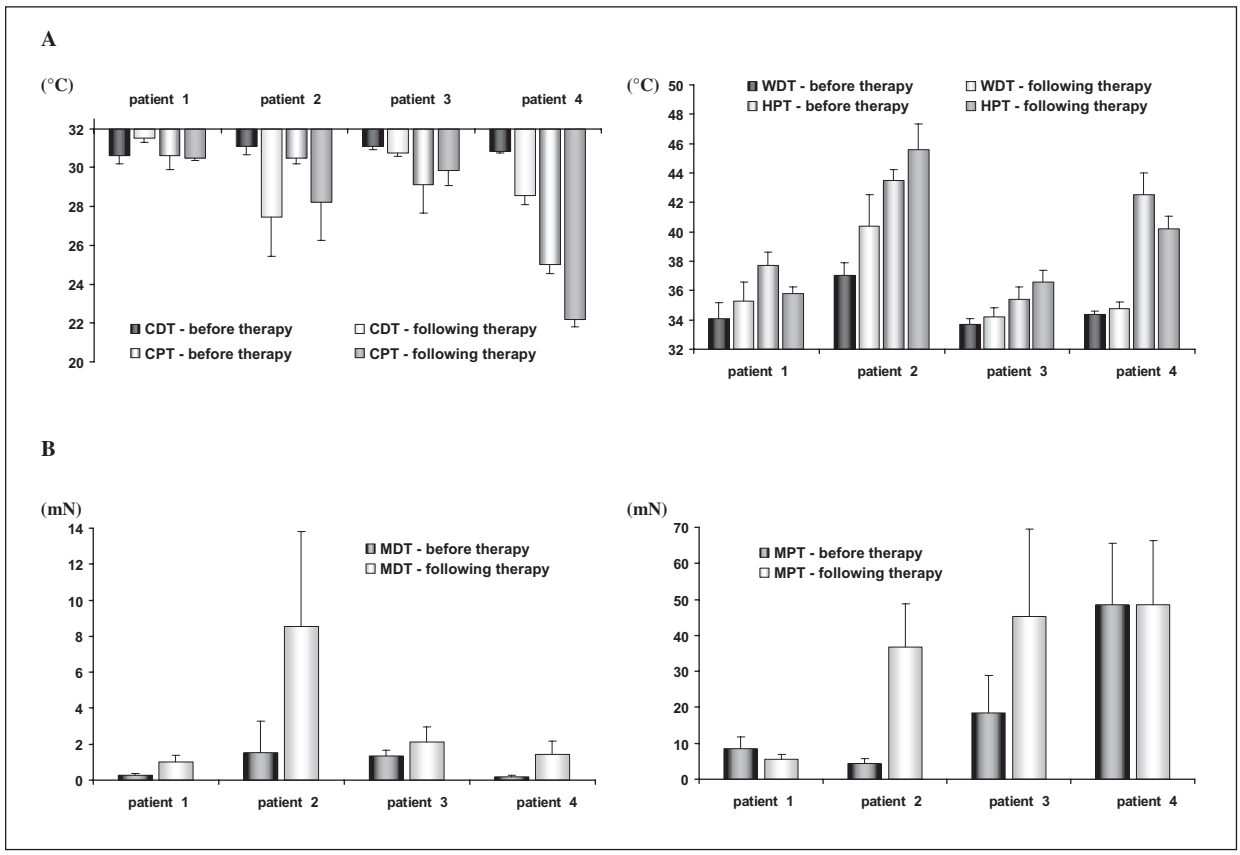

Figure 2 Thermosensory (A) and mechanosensory (B) detection and pain thresholds. (A) Results for thermosensory analysis: cold detection (CDT), and cold pain threshold (CPT) as mean – SD, in degrees Celsius, for each patient before and following therapy. Warmth detection (WDT), and heat pain threshold (HPT) as mean + SD for each patient before and following therapy. (B) Mechanosensory detection (MDT) and pain thresholds (MPT). Results are shown as geometrical mean + 95% CI for each patient in millinewton (mN) before and following therapy.

Thermosensory Detection and Pain Thresholds

Warm and cold detection thresholds were normal in all patients. There were no paradoxical sensations to a cold stimulus during detection or pain threshold evaluation. There were no significant changes in warm and cold detection thresholds following S(+) ketamine treatment. Severe cold allodynia was found in patients 1, 2, 3, and to a lesser degree in patient 4. Following S(+)-ketamine, a decrease in cold pain thresholds was observed in patients 2 and 3. No change in thresholds was noted in patients 1 and 4. Heat pain thresholds were greatly decreased in patients 1 and 3, and were diminished in patient 2 and 4. Following ketamine infusion, no relevant changes were noted for heat detection and pain thresholds (Figure 2).

Ketamine Plasma Levels

The S(+)-ketamine plasma levels, determined by HPLC, are shown in Figure 3. The maximal mean S(+)-ketamine plasma levels of 777.5 ± 372.41 ng/mL were reached on treatment day 7. The highest individual plasma peak concentration observed was 1,200 ng/mL in patient 3 at 450 mg/day S(+)-ketamine. The lowest plasma peak concentration of 320 ng/mL at the maximal dosage of 500 mg/day S(+)-ketamine was observed in patient 2 on day 9.

Discussion

The results of this trial suggest that subanesthetic infusion of S(+)-ketamine is ineffective in generalized, long-standing CRPS patients who have failed conventional therapy. However, the trial demonstrates that S(+)-ketamine dosages of up to 500 mg/day can be given without clinically relevant side effects if titration is gradual over several days. The lack of response to pain parameters was mirrored by the results of QST. The decreased detection and pain thresholds for mechanical and thermal stimuli were also unchanged.

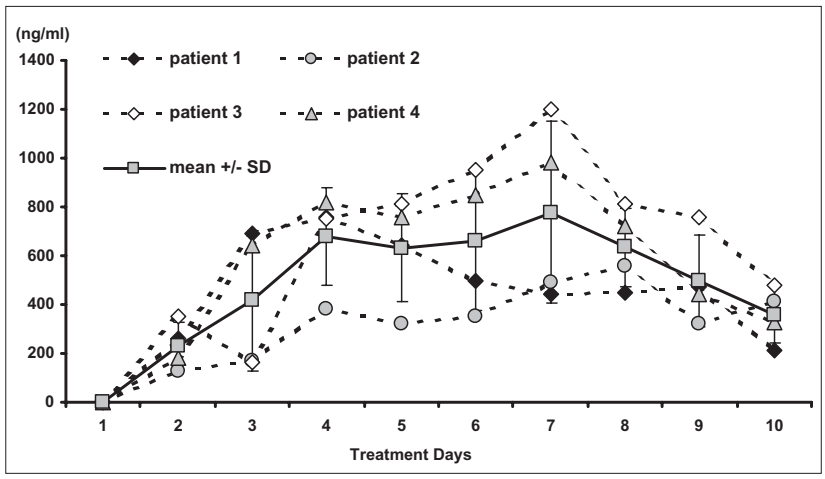

Figure 3 S(+)-ketamine plasma concentrations. The figure shows the individual S(+)-ketamine plasma concentrations (ng/mL) for patients 1–4 (dotted lines) and the calculated mean S(+)-ketamine plasma concentrations ± SD (solid line) for the 10-day treatment period.

Several trials and case studies have suggested the efficacy of ketamine in CRPS. Takahashi et al. demonstrated complete remission of CRPS after epidural ketamine administration [9]. Effective relief of severe pain and motor dysfunction has been reported for epidural ketamine in combination with morphine and bupivacaine [10]. The topical administration of ketamine ointment is effective in relieving pain and swelling in CRPS type I and CRPS type II patients [11]. Correll and colleagues reported significant pain relief in CRPS patients after prolonged infusions of subanesthetic racemic ketamine [12]. All of these reports suggest that ketamine may be more effective in earlier and more localized CRPS.

A systematic investigation of the analgesic potency of ketamine for severe, long-standing, spreading refractory CRPS has not been reported. We sought to investigate this question with this pilot study. After completion of a series of four patients who showed no clinical or positive response by quantitative sensory parameters, the investigation was terminated. The discrepancy of the therapeutic efficacy of ketamine in different groups of patients might be explained by the degree of severity of the CRPS that they suffer. Our patients had either long-standing and generalized CRPS or a rapidly spreading form (one patient). All of our patients had failed numerous standard treatments. The extent of prior treatment in the previously reported trials has not been reported in detail. In Correll's study, CRPS was of relatively short duration (8 months or less in 20/33 patients), which suggests that these patients were less severely affected than those comprising this series. The determination of spread is not reported in detail in many of the previous trials. The clinical characteristics of Takahaski et al.'s patient suggest that this patient suffered disease of the distal aspect of one extremity [9–11]. Spread is discussed in detail in Correll's series where the majority of patients suffered well-localized CRPS of the distal extremity. Two of their 33 patients suffered from bilateral involvement of the hands and shoulders (relatively circumscribed). Three of their patients suffered long-standing CRPS with generalization and one patient had mirror distribution spread. These patients responded to ketamine as well but their severity of illness is hard to compare with our series. The clinical characteristics of Takahashi's patient suggest that she suffered well-localized disease limited to the distal aspects of one extremity.

All previous studies utilizing ketamine for CRPS have used the racemic isomeric mixture of the drug. We investigated the S(+)-ketamine isomer. It is unlikely that the lack of therapeutic effect is due to this isomer because it has an approximate fourfold NMDAR-affinity than that of the racemic mixture, which should make it more effective in blocking the NMDAR.

In addition, the S(+)-isomer has a two- to threefold higher affinity for opioid receptors and less severe psychomimetic side effects at equianalgesic dosages. The S(+)-isomer may still not be as effective as the racemic mixture.

Comparing the equianalgesic doses, the S(+)-ketamine dosage utilized in this study was 30–50% higher than for racemic ketamine used in Correll's study, but failed to produce an equivalent effect. The prolonged treatment over 10 days in this study compared with 4.7 ± 3.86 days in Correll's investigation suggests that the length of the infusion does not explain the differences in outcome.

Noteworthy, the results of this study are not solely based on patients' subjective pain ratings, but also on analyses of somatosensory parameters, evaluated by QST. The severity of pain together with the intense sensitization of peripheral somatosensory nerves supports the severity of disease in this subgroup of CRPS patients. The failure of S(+)-ketamine to produce relevant relief from pain, together with unaffected severe mechano- and thermal allodynia and persisting significant reduction of the thermal and mechanical pain thresholds, mirrors the patients' subjective complaints [17–19].

Several possibilities exist to explain the failure of subanesthetic S(+)-ketamine for severe refractory CRPS. In these patients, additional mechanisms, other than those that are NMDAR-mediated, may be crucial for maintenance of the disease. Second, the length of time a patient has suffered the disease prior to NMDAR-antagonist intervention may be important for successful NMDAR-antagonist therapy. The dosage of ketamine utilized in this study may have been insufficient to block NMDAR-mediated hyperexcitability of central pain projecting neurons.

The first hypothesis that other mechanisms than those effected through the NMDAR may be important on CRPS is supported by failure of a complete translation of the animal data, which supports a crucial role of the NMDAR, in initiation of some neuropathic pain states with clinical experience [6–8]. Low-affinity, noncompetitive NMDAR-antagonists have failed in clinical randomized controlled trials, to produce significant therapeutic benefit in chronic phantom limb pain, as well as posttraumatic neuropathic pain [20–23]. Dextromethorphan and memantine have failed in clinical randomized controlled trials to benefit diabetic peripheral nerve and post-herpetic neuralgia [23]. Therapeutic efficacy with dextromethorphan has been demonstrated in clinical randomized controlled trials for facial neuralgia, diabetic polyneuropathy, and post-herpetic neuralgia [24–26]. Ketamine has been shown to be effective for ischemic pain, cancer pain, and CRPS [27–29].

The importance of the time of administration of ketamine and its effect on pain is suggested by the success of memantine and ketamine in reducing phantom pain if given perioperatively but its failure to modify established pain [30–32]. The effectiveness of ketamine in early vs established long-standing CRPS pain has not been studied by randomized controlled trials.

The optimal dosage of NMDAR-antagonist therapy has not been established. Animal experiments suggest that the analgesic potency and effectiveness of NMDAR-antagonists for neuropathic pain is dose-dependent, which is also supported by human clinical trials [33–36]. As well, the optimal duration of treatment with NMDAR-antagonists remains to be established. Firs and limited evidence from prior uncontrolled case reports and case series suggested prolonged treatment periods might lead to an enhanced beneficial effect [9–11]. However, this question has not been systematically investigated by randomized controlled trials. Therefore, it can not be excluded that maintaining (S+)-ketamine over a longer treatment period might have resulted in a beneficial therapeutic effect.

The use of NMDAR-antagonists in pain medicine has been limited by their psychiatric side effects [6,7]. Another serious concern in the use of ketamine is its potential neurotoxicity. Neurodegenerative effects were shown for not only high-dosed NMDAR-antagonists, but also combinations of other common general anesthetics, in the developing brain of the rat, and in the adult rat brain [37,38]. Effective prevention of these neurodegenerative effects of NMDAR-antagonist was demonstrated in animal experimental work, when either clonicin or $GABA_A$ agonists were coadministered [39,40]. To date, these neurotoxic effects have only been described in the animal experiment. To our knowledge, neurotoxic of ketamine in the clinical use has not been described in more than 30 years of clinical use [40]. A recent randomized controlled trial demonstrated the safety of high-dosed ketamine sedation in intensive care for severely head-injured patients [41].

This study supports the earlier work by Correll and colleagues that large doses of ketamine can be administered safely by gradual upward titration over several days without serious side effects [12].

In this series, we posit that the dosage of S(+)-ketamine was insufficient for a beneficial therapeutic response in these long-standing severe patients. Ketamine in anesthetic doses has been effective in severe long-standing patients in whom all conventional methods of treatment have failed [36].

In conclusion, subanesthetic S(+)-ketamine was ineffective in four severe long-standing CRPS patients who were refractory to standard therapy. The data suggest that increased doses of S(+)-ketamine can be administered by upward titration without relevant psychiatric side effects. S(+)-

ketamine did not alter QST that determined detection and pain thresholds of thermal and mechanical stimuli. QST of these modalities may be a helpful diagnostic tool to analyze the severity of disease, which might mirror patients' subjective pain ratings.

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