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Efficacy of Ketamine in Anesthetic Dosage for the Treatment of Refractory Complex Regional Pain Syndrome: An Open-Label Phase II Study

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Original Research Article

ABSTRACT

Objective. Advanced complex regional pain syndrome (CRPS) remains very difficult to treat. While subanesthetic low-dose ketamine has shown promise in early localized CRPS, its use in advanced CRPS has

not been as effective. Since ketamine's analgesic potency and duration of effect in neuropathic pain are directly dose-dependant, we investigated the efficacy of ketamine in anesthetic dosage in refractory CRPS patients that had failed available standard therapies.

Methods. Twenty ASA I-III patients suffering from refractory CRPS received ketamine in anesthetic dosage over 5 days. Outcome criteria were pain relief, effect on the movement disorder, quality of life, and ability to work at baseline and up to 6 months following treatment.

Results. Significant pain relief was observed at 1, 3, and 6 months following treatment (93.5 ± 11.1%, 89.4 ± 17.0%, 79.3 ± 25.3%; $P < 0.001$). Complete remission from CRPS was observed at 1 month in all patients, at 3 months in 17, and at 6 months in 16 patients. If relapse occurred, significant pain relief was still attained at 3 and 6 months (59.0 ± 14.7%, $P < 0.004$; 50.2 ± 10.6%, $P < 0.002$). Quality of life, the associated movement disorder, and the ability to work significantly improved in the majority of patients at 3 and 6 months.

Conclusions. This open-label trial suggests benefit in pain reduction, associated CRPS symptoms, improved quality of life and ability to work following anesthetic ketamine in previously refractory CRPS patients. However, a randomized controlled trial will be necessary to prove its efficacy.

Introduction

The understanding of the pathophysiology of mechanisms underlying complex regional pain syndrome (CRPS) has vastly progressed in the recent years [1]. Recent evidence has been presented that suggests focal small-fiber axonal degeneration and alteration of the cutaneous innervation by small-diameter afferent and postganglionic sympathetic efferent fibers are important for its induction and maintenance [2, 3].

Caveats of this hypothesiz have been raised by Janig and Baron 4, who propose that patients with CRPS have concomitant peripheral changes in the microenvironment at the site of injury that induce peripheral afferent sensitization, neurogenic inflammation, and sympathetic afferent coupling in addition to functional reorganization of the somatosensory, motor, and autonomic circuits in the central nervous system (CNS) 5-7.

There is general agreement that the pain in CRPS is disproportionate to the extent of the primary triggering injury that does not respect a root or nerve territory. Characteristic symptoms include severe unrelenting burning and deep pain, associated with mechano- and thermal allodynia, hyperalgesia, and hyperpathia. Swelling, autonomic dysregulation, a movement disorder, atrophy, and dystrophy are associated to varying degrees 8. The syndrome may progress with time, and signs and symptoms may spread to sites that were not primarily affected. In some patients, it is generalized 9, 10. Current standard therapy consists of a variety physical, psychological, behavioral, pharmacological and interventional treatments 11-13. Unfortunately, a subgroup of CRPS patients remains refractory to all standard therapy. For these refractory patients, no effective treatment exists 8.

Ketamine, the currently most potent clinically available N-methyl-D-aspartate (NMDA)-antagonist, has a well-established role in the treatment of acute and chronic pain 14, 15. Its main action is through inhibition of NMDA-receptors, which are thought to play a crucial role in the generation and maintenance of chronic pain 16, 17. In addition to its acute analgesic effects, systemic ketamine modulates correlates of central sensitization in chronic pain states on a long-term basis. Wind-up and punctuate hyperalgesia were shown to be significantly reduced up to 7 days after surgery 18. Ketamine administered at higher intraoperative dosage for major abdominal surgery reduced the area of wound hyperalgesia and significantly prevented the initiation and maintenance of chronic pain 19,

20. Possible mechanisms are that these effects are mediated through NMDA-receptor inhibition, which may be critical for central sensitization, and anti-inflammatory modulation of the immune system 17, 21. Proinflammatory cytokines are involved in the processes of peripheral and central sensitization and are inhibited by ketamine 22. In the management of chronic pain, the use of ketamine at higher dosages has been limited by psychotropic side effects. The incidence and severity of ketamine side effects are dose-dependent as are its analgesic potency and duration of action 15.

Several series and case reports have documented reduction of pain intensity, allodynia and associated CRPS signs of autonomic dysregulation and motor dysfunction following the administration of subanesthetic systemic, epidural, and topical ketamine 23-26. A recent case report and larger series demonstrated long-term pain relief from subanesthetic ketamine infusions, particularly in early and well localized CRPS 27, 28. However, in a subgroup of refractory CRPS with spreading disease, subanesthetic continuous S(+)-ketamine infusions were ineffective 29.

This suggested that ketamine in anesthetic dosages might be effective in this refractory CRPS subgroup. Excellent clinical results were obtained with anesthetic doses of ketamine administered on a compassionate care basis to several refractory CRPS patients (unpublished). Based on this limited clinical experience, a standardized treatment regime was developed, and utilized in the present trial. The therapeutic efficacy of ketamine in anesthetic dosage was studied in a Phase II study in 20 refractory CRPS-patients, who suffered either longstanding or rapidly progressive disease that had failed standard therapy. The primary outcome parameter was acute and long-term relief of pain. Other measures included effects on the movement disorder, quality of life, social integration, and the ability to work at 6 months following treatment.

Methods

Patients

The human investigation committees in Tübingen and Saarbrücken, Germany, approved the study. Patients were recruited in the pain clinics of the Department of Neurology of Drexel University College of Medicine (Philadelphia, PA) and pain clinics of the Teaching Hospital University of the Saarland (Saarbrücken, Germany). Informed consent emphasized the experimental nature of this treatment. Special emphasis was placed on the risks associated with the intensive care component of this treatment which includes respiratory and urinary tract infections and other infectiouscomplications such as systemic inflammatory response syndrome and sepsis. Organ failure (single or multi-organ failure), cardiovascular complications as well as the associated high morbidity and mortality rates of all of these serious complications were stressed. All patients gave their informed written consent.

Inclusion Criteria

All patients fulfilled the 1993 IASP–CRPS diagnostic criteria, the 1999 modified research diagnostic CRPS criteria, and the proposed modified research diagnostic criteria of the 2005 Budapest conference in at least one limb [30]-[32]. Other associated CRPS factors [1]-[4] were noted to varying degrees in contiguous areas of the extremity, the face or in a mirror distribution. Cluster analysis placed all patients in subgroup; and [3] a florid CRPS syndrome [32].

The average daily pain intensity had to be 7 points or greater on a numerical rating scale (Numeric Rating Scale [NRS] endpoints 0: no pain, 10: worse pain imaginable) over a period of at least 6 months while on standard therapy. The CRPS symptomatology had to be either longstanding and spreading, or rapidly progressive. Standard

conventional nonmedical (physical therapy, psychological approaches), or pharmacological and interventional treatment modalities had to have failed. Failure of therapy was defined as: 1) no benefit from treatment, or 2) no lasting pain relief (>2 months). The designation “refractory” included documented failure of: 1) nonmedical; 2) pharmacological mono-, or combined therapy with nonsteroidal antiinflammatory drugs, tricyclic antidepressants, anticonvulsants, low or high potency opioids; 3) at least three interventional procedures, including selective nerve blocks, epidural analgesia, brachial plexus blocks, sympathetic ganglion blocks, intravenous regional sympathetic blocks, spinal cord stimulation, surgical sympathectomy, or intrathecal drug delivery systems; and 4) unchanged or progressing state of disease despite these efforts.

Inclusion was limited to ASA I-III patients (ASA: American Society of Anesthesiologists Physical Status Classification), which apart from their pain-related disability, did not suffer from clinically relevant systemic disease. Patients that presented with a history of significant cardiovascular, pulmonary, renal disease or mental disorders were excluded. Further exclusion criteria included known contraindications to ketamine use (severe arterial hypertension, hyperthyroidism, ischemic heart disease or heart failure), as well as allergies to ketamine or midazolam. All patients during the course of their treatments were evaluated by a psychiatrist for counseling and support and 9 underwent detailed neuropsychological testing prior to and following treatment [33]. All patients had difficulty falling and staying asleep but this feature of their illness was not studied systematically. Patients with a history of substance or drug abuse, or a suspected somatoform pain disorder were excluded. The inclusion criteria were evaluated by three physicians, a neurologist (RJS), and two anesthesiologists (RTK, PR).

Ketamine Treatment Protocol

Anesthesia was induced by bolus injection of ketamine (1–1.5 mg/kg) and midazolam (2.5–7.5 mg). Tracheal intubation was facilitated by vecuronium (0.1 mg/kg). Treatment was maintained by infusions of ketamine over 5 days, starting at 3 mg/kg/h, followed by gradual daily titration up to a final dose of 7 mg/kg/h. Midazolam was co-administered and adjusted as clinically required (0.15–0.4 mg/kg/h) to obtain a stable level of deep sedation (Ramsay-Score 4–5), and to attenuate ketamine-specific side effects, i.e., agitation [34]. The first three patients were not intubated and spontaneous ventilation was allowed. The remaining 17 patients were electively intubated, to limit the risk of aspiration. These 17 patients were mechanically ventilated. After 5 days, infusions were slowly tapered, first by reducing the ketamine dosage by 20% every four hours, followed by gradual reduction of midazolam in the same manner. Patients were then weaned from mechanical ventilation and extubated once adequate spontaneous ventilation, sufficient gas exchange, and the appropriate level of consciousness together with intact protective reflexes was attained.

Ketamine and Norketamine Plasma Concentrations

Blood samples were drawn into prefabricated EDTA-tubes (S-Monovette®, Sarstedt AG & Co., Nürnbrecht, Germany) from all patients every eight hours to determine ketamine and norketamine (the primary ketamine metabolite) plasma concentrations during anesthesia and for 3 days following treatment. Blood samples were centrifuged and plasma aliquots stored until analysis at −80°C. Ketamine and norketamine plasma concentrations were analyzed by simultaneous high-pressure liquid chromatography (HPLC) [35].

Standardized Additional Drugs

Deep Venous Thrombosis and Ulcer Prophylaxis

All patients received intravenous unfractionated low-dose heparin 7.500–15.000 I.E./day (Liquemin®, Roche, Germany) under regular aPTT monitoring, and the proton pump inhibitor pantoprazole 40 mg/day (Pantozol®, Altana Pharma, Germany).

Clonidine

Clonidine (Catapresan®, Boehringer Ingelheim, Germany) was administered intravenously (0.20–0.85 µg/kg/h) to control cardiovascular stimulation and the psychomimetic and potential neurotoxic side effects of ketamine. It was dosed as clinically required (0.20–0.85 µg/kg/h) to control tachycardia and hypertension. The coadministration of clonidine at a minimum dose of 0.15 µg/kg/h was maintained throughout the intensive care treatment.

Alimentation and Glycemic Control

Alimentation

The first three unintubated patients received full parenteral nutrition (25 kcal/kg/day) with a ternary mixture of aminoacids (40 g/L), glucose (160 g/L), and fat (40 g/L), containing 1040 kcal/L glucose-fat calories (Oliclinomel® 4.0% GF-E Baxter, Germany). Intubated patients received full enteral nutrition (25 kcal/kg/day) via nasogastral tube (Nutrison Standard®, Nutrisone Multifibre®, Pfrimmer Nutrica, Germany, containing 1.000 kcal/L, proteins 40 g/L, carbohydrates 123 g/L, fat 39 g/L).

Glycemic Control

Intensified insulin-therapy (Actrapid®, Novo Nordisk A/S, Denmark) was applied, and insulin dosed as clinically needed to maintain normoglycemia (blood glucose concentrations: 90–150 mg/dL) [36].

Patient Safety

Monitoring

Continuous standard intensive care monitoring (arterial blood pressure monitoring, ECG and ST-segment analysis, core temperature, pulse oximetry, capnometry, central venous pressure) was performed in all patients. All patients had bladder catheterization.

Blood Gas Analysis and Blood Chemistry

Blood gas analysis was routinely performed every 8 hours and additionally when clinically warranted to adjust mechanical ventilation, insulin therapy, acid-base balance, and electrolytes. Detailed blood tests were performed before the treatment, daily during treatment, and for the first 2 weeks thereafter. Laboratory evaluation included cell counts, electrolytes, coagulation parameters, liver enzymes, C-reactive protein (CRP), creatine phosphokinase (CPK), and CKMB-isoenzyme activity.

Screening for Infectious Complications

When admitted patients were screened with pharyngeal, nose and rectal swabs for the presence of multiresistant pathogens (methycillin resistant *S*. aureus [MRSA]; vancomycin resistant enterococci [VRE]). During the treatment screening included continuous monitoring of core body temperature, and laboratory parameters (daily leukocyte count, CRP), urine status, and tracheal secretion and urine cultures on the first day of treatment and when respiratory or urinary tract infection was suspected clinically. In the presence of fever blood cultures were collected.

Outcome Criteria

The patients' progress during the study, the times and nature of assessments at baseline, 1 week, 1, 3, and 6 months after treatment are summarized in a flow chart shown in Figure 1.

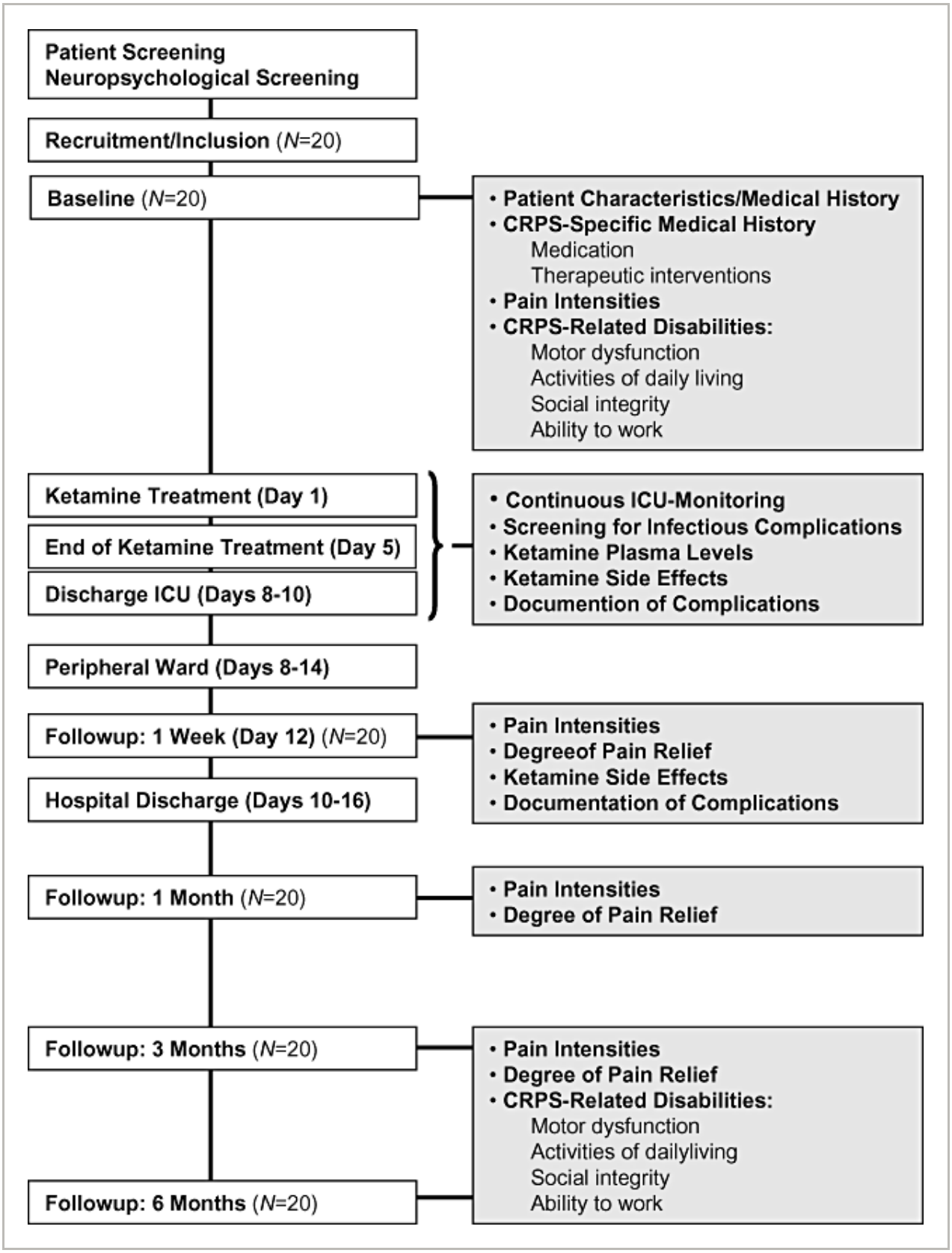

Figure 1

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Flow chart summarizing patients' progress through the study. The left side of the diagram shows the timing of the

assessment of patients and the investigated treatment with anesthetic ketamine. The right side of the diagram shows he investigated outcome parameters at the different assessment times throughout the study. CRPS = complex regional pain syndrome; ICU = intensive care unit.

Pain Assessment and Degree of Pain Relief

The degree of a patient's subjective pain intensities was rated by a numeric scale (NRS, endpoints: 0—no pain, 10—worst pain imaginable) at baseline and at follow-up examinations. The degree of pain relief following treatment was calculated as: percent pain relief = $(NRS_{baseline} - NRS_{follow\ up})/NRS_{baseline} \times 100$.

Movement Disorder

Data were obtained at baseline and 1, 3, and 6 months after treatment for both upper and lower extremities.

Upper Extremity Motor Evaluation

Assessment of active range of motion was based on norms described by Kendall et al. [37]. Arm movement was quantified by utilizing a combination of the performance of specific motor tasks (placing a book in a shelf above shoulder level, ability to comb one's hair, putting on a sweater, tying an apron) in addition to the results of the range of motion evaluation. Hand movement assessment combined grip function (gripping and holding a cup) and pinch grip ability (gripping, holding and use of a key, pencil and writing). Based on the observed range of movement combined with performance in the described functional tasks, the movement disorder was quantified utilizing a 4-point rating scale: 0: normal movement; 1: moderate disability (moderately reduced active range of motion, muscular strength, initiation, and completion of motor tasks); 2: severe disability

(severely restricted active range of motion, weakness, poor initiation, and completion of motor tasks); 3: total disability (only residual movement, severe weakness, and inability to perform motor tasks).

Lower Extremity Motor Evaluation

The assessment of motor function of the lower extremity was based on the ability to walk and was scored on a 4-point rating scale: 0: normal movement (unimpaired walking); 1: moderate disability (inability to walk 500 meters); 2: severe disability (inability to walk 200 meters); 3: total disability (ability to walk <50 meters or inability to walk).

Quality of Life

The assessments to estimate disease-related impairments in activities of daily living, social integration, and the ability to work represent recognized aspects of quality of life. The assessments were performed at baseline and at 3, and 6 months following therapy.

Activities of Daily Living

Patients were asked to rate their performance of typical activities of daily living. The representative tasks of everyday life were based on selected key items contained in valid questionnaires, such as the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) and the Stanford Health Assessment Questionnaire (HAQ) [38], [39]. Patients were instructed to rate their ability to independently perform the following tasks: self-care (preparing meals and eating [cutting food], drinking, dressing, washing, drying, and combing), and household activities (house cleaning, grocery shopping, washing dishes, and gardening). The degree of impairment was rated using a 4-point numeric scale: 0: no impairment (all tasks can be performed independently), 1: moderate impairment (tasks can be accomplished but with difficulty), 2: severe impairment (<50% of activities can be performed independently); 3: total impairment (majority of tasks

cannot be performed; dependent on the help of others).

Social Integration

Patients were queried in regard to their ability to function socially and rated their overall impairment. Representative activities were chosen from the aforementioned validated questionnaires (WHYMPI, HAQ). Patients were asked to rate their ability to perform recreational activities (pursuing hobbies, playing sports, taking trips, seeing friends/relatives, reading, going out), cultural activities (attending concerts, movies, theatre). The degree of impairment was rated using a 4-point numeric rating scale: 0: no impairment, 1: moderate impairment (all activities can be performed, but with difficulty), 2: severe impairment (<50% of activities can be performed independently), 3: total impairment (majority of activities cannot be performed and the patient is dependent on the help of others).

Ability to Work

The ability to work was rated on a 4-point scale: 0: no impairment, 1: moderate impairment (able to work more than 4 h/day but less than 8 h/day), 2: severe disability (able to work up to 4 h/day), 3: total impairment (able to work only 2 h/day or totally unable to work).

Side Effects of Treatment

Ketamine-Specific Side Effects

Psychotomimetic side effects: the occurrence, duration, and severity of ketamine-specific psychotomimetic side effects were documented following treatment. These included: anxiety, hallucinations, restlessness, difficulty in concentration, disruption of sleep, dizziness, dysphoria, euphoria, and disorientation.

Other Adverse Treatment Effects

These included all potential adverse effects associated with the intensive care nature of the treatment, such as respiratory, urinary tract or systemic infection, and cardiovascular and pulmonary complications. The occurrence of these complications, their treatment and resolution were documented.

Statistics

Data were analyzed using the statistical software package JMP IN (Version 5.1.2, SAS Institute, Cary, NC). The Kolmogorov-Smirnov test was used to assess normality. Nonparametric paired *t*-tests on ranks were used to analyze differences between baseline and those obtained during and following therapy for not normally distributed data. Normally distributed data were analyzed by paired *t*-tests. Alpha was set at 0.05. For multiple comparisons the alpha correction of Bonferroni was performed.

Results

Patient Demographics

Twenty ASA-Class I–III patients were enrolled and completed the study (18 female and two male; mean age 30.4 ± 10.4 years, range: 14–48 years). The mean duration of CRPS was 49.4 ± 25.0 months (range: 6–84 months). All patients suffered from severe or spreading CRPS. Two had rapid contiguous spread affecting the entire extremity, two suffered from mirror spread, and 16 had generalized CRPS. All patients had been unresponsive to multiple conventional treatments and had failed standard pharmacological therapy and numerous invasive procedures (Tables 1–4).

Table 1. Characterization of CRPS-status at baseline: patients' age, gender, American Society of Anesthesiologists Physical Status Classification (ASA-Class), and CRPS-related characteristics at baseline: triggering injuries, sites of primary CRPS manifestation, duration of disease (months), the

type of spread, the status of disease spread at baseline, and the pain intensity at baseline (NRS: 0: no pain, to 10: worst pain imaginable)

Patient No.	Age (Years)	Gender	ASA-Class	Triggering Injury/CRPS Manifestation	CRPS Duration (Months)	Type of Spread
1	16	f	I	Sprain injury/right wrist and hand	8	Contiguous
2	26	f	I	Brachial plexus traction injury/right shoulder	12	Mirror
3	25	m	II	Hodgkin's disease, compression of brachial plexi by lymphoma/shoulders	24	Mirror
4	46	f	II	Brachial plexus traction injury/right arm	60	Contiguous, Mirror
5	29	f	II	Electrical shock/right arm	30	Contiguous
6	46	f	III	Crush injury right ankle and foot, operative	72	Contiguous

				osteosynthesis/right foot		
7	28	f	III	Trauma to lower back/right leg	60	Contiguous, Mirror
8	42	f	II	Cruciate ligament tear, tibial impression fracture/right knee	30	Contiguous
9	22	f	II	Tendon rupture digit IV, operative repair/right hand	72	Contiguous
10	19	f	II	Fracture metatarsal-V/right foot	60	Mirror, Contiguous
11	20	f	II	Trauma to right shoulder and lower back/right arm	36	Mirror, Contiguous
12	35	f	III	Trauma to right shoulder and lower back/right arm	72	Mirror
13	38	f	III	Crush injury digit-III right hand, infection and amputation/right hand	24	Mirror, Contiguous
14	19	m	II	Sprain injury wrist/right hand	84	Mirror, Contiguous

15	36	f	II	Para-venous i.v.-line/left hand, left forearm	60	Contiguous
16	25	f	II	Arnold Chiari repair operation/left shoulder, arm	25	Contiguous
17	48	f	II	Extension/distension trauma/right hand	72	Mirror
18	41	f	II	Car accident, whiplash injury/right arm	84	Contiguous
19	14	f	III	Brown recluse spider bite inner right thigh/right thigh and leg	7	Mirror, Contiguous
20	33	f	II	Tibial torsion fracture, osteosynthetic operation/left lower leg	63	Mirror, Contiguous

CRPS = complex regional pain syndrome; NRS = Numeric Rating Scale.

Table 2. Demographics: summarizes statistic data of patients'

demographics for the entire group of patients, and the analyzed subgroups: recurring pain (all patients with recurring pain, either neuropathic, nociceptive, or both at one of the follow-ups), CRPS-relapse (all patients with a CRPS-relapse), and results of the statistical comparison of differences between the entire group and the subgroups (exact p-values)

	N	Entire Group 20	Subgroup: Recurring Pain from Initial Injury 9	Subgroup: CRPS-Relaspse 4
Age (years)	(Mean ± SD)	30.4 ± 10.7	30.7 ± 8.2	33.7 ± 11.9
	Range (min–max)	34 (14–38)	23 (19–42)	26 (20–46)
	P Value		0.95	0.58
Weight (kg)	(Mean ± SD)	68.4 ± 18.7	68.6 ± 15.9	68.7 ± 31.6
	Range (min–max)	67.3 (48.5–115.8)	49 (48.5–97.5)	66.0 (49.8–115.8)
	P Value		0.99	0.98
Height (cm)	(Mean ± SD)	167.6 ± 10.7	168.9 ± 12.6	168.0 ± 12.6

	Range (min–max)	42.0 (152–194)	42.0 (152–194)	29.0 (154–183)
	P Value		0.78	0.95
Duration of CRPS (months)	(Mean ± SD)	49.4 ± 25.6	49.7 ± 22.8	60.0 ± 19.6
	Range (min–max)	78 (6–84)	60 (24–84)	48 (36–84)
	P Value		1.0	0.59

CRPS = complex regional pain syndrome.

Table 3. Failed physiotherapy and pharmacotherapy: summarizes the individual patients' failed physiotherapeutic and pharmacotherapeutic approaches at baseline

Patient No.	Physiotherapy	Pharmacotherapy			
		NSAID	Antidepressants	Anticonvulsants	Spasmol
1	+	+	+		
2	+	+	+	+	+
3	+	+	+	+	+

4	+	+	+	+	+
5	+	+	+	+	+
6	+	+	+	+	+
7	+	+	+	+	+
8	+	+	+	+	+
9	+		+	+	+
10	+	+	+	+	+
11	+	+	+	+	+
12	+	+	+	+	+
13	+	+	+	+	+
14	+	+	+	+	
15	+		+	+	+
16	+		+	+	+
17	+	+	+	+	
18	+	+	+		+
19	+	+	+	+	+
20	+	+	+	+	+

The “+” indicates, which treatments have been performed and failed, defined as being without primary effect, or no lasting (>2 months) on pain relief.

NSAID = nonsteroidal anti-inflammatory drugs; DMSO =

dimethylsulfoxid containing ointment; IVRSB = intravenous regional sympathetic blockade.

Table 4. Failed Interventional therapies: summarizes for the individual patients' failed interventional treatments at baseline

Patient No.	Trigger-Point-Infiltrations	Nerve-Blocks		Sympathetic Blocks			
		Selective Nerve Blocks	Brachial Plexus Block	IVRSB	Intrapleural Block	Stellate Ganglion Blocks	G B
1		2	2	1		3	
2					2		
3					3		
4	>8	>4		2	2	>4	
5	>10	>2			>3		
6	>4	>4		2			
7		>6					
8		>8					
9	>4	>5	2	2	2	>6	
10	5	>6			2		
11	>4	>5		2	2	>6	
12	>6	>6			2	>4	

13	>8	>8	3	>5	1		
14	>8	>8		2	1	>6	
15	>6	>8			2	>6	
16	>4	>6	2			>4	
17	>10	>8	2			>8	
18	>6	>4		2		2	
19		3		1			
20	>8	>11		2			

The performed interventions, which had failed, are indicated by a number, indicating the frequency of failed interventions, or by a "+." Failure was defined as being without primary effect on pain, or no lasting effect (>2 months) on pain relief.
IVRSB = intravenous regional sympathetic blockade.

Pain Intensities and Pain relief

Pain Intensities

Pain intensities were analyzed for the entire group, as well as for the subgroup of patients with recurring initiating or maintaining pain (nociceptive or neuropathic, but without associated CRPS signs or symptoms) and the subgroup with relapsing CRPS (neuropathic pain and associated CRPS signs and symptoms).

At baseline, pain intensity of the entire group (N = 20), and of the subgroups with later recurring pain, and relapsing CRPS were NRS 8.9 ±

0.3, 8.8 ± 0.2, and 9.2 ± 0.2 (mean ± SD), respectively, and no statistically significant differences between the groups were detected.

Following ketamine treatment, a significant reduction of pain intensity was observed at 1 week and 1 month for the entire group (NRS 0.5 ± 0.8, and 0.6 ± 1.0), and the subgroup with recurring pain (1.4 ± 0.7, and 1.7 ± 1.1, N = 7) ($P < 0.001$). At 3 months, pain intensity was significantly ($P < 0.001$) reduced compared with baseline in the entire group (NRS 0.9 ± 1.6) and the subgroup with recurring pain (2.0 ± 0.9, N = 4). Three patients had a CRPS relapse, but had significantly reduced pain compared with baseline (NRS 3.8 ± 1.4, $P < 0.004$). Pain intensity at 6 months was significantly reduced for the entire group of patients (2.0 ± 2.4, $P < 0.001$), the subgroups with recurring pain (3.6 ± 2.0, $P < 0.001$, N = 6), and those with a CRPS relapse (4.6 ± 1.1, $P < 0.002$, N = 4). The results are summarized in Figure 2.

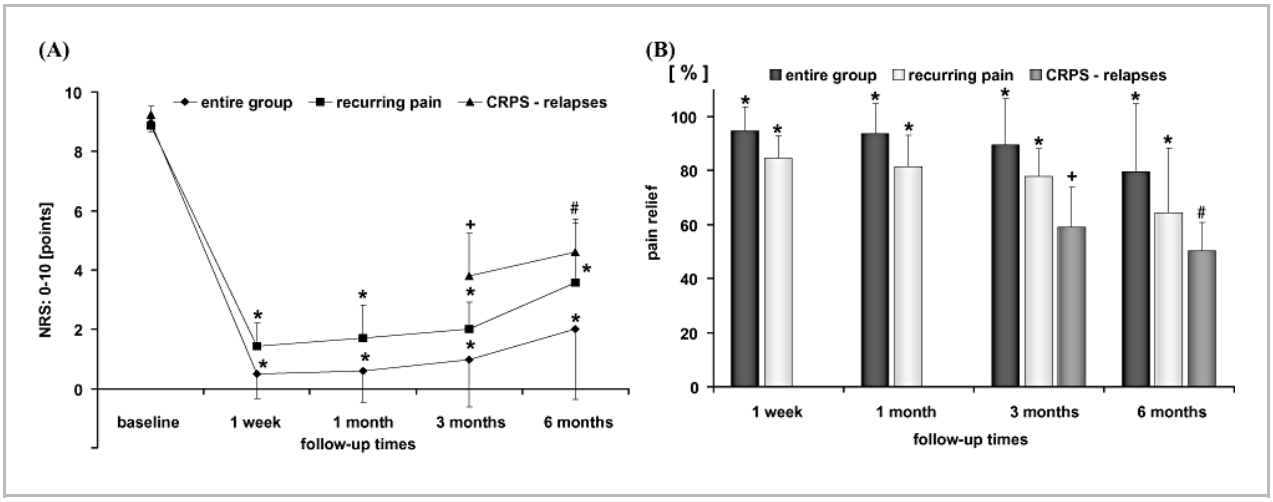

Figure 2

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The pain intensities (A) and the degree of pain relief (B) before and following the treatment. Part (A) shows the pain intensities (NRS: 0–10, data presented as mean ± SD) of the entire treatment group (N = 20) for baseline, at 1 week, and 1, 3, and 6 months following treatment and significant differences

compared with baseline (*$P < 0.001$), and the results of the subgroup analyses for patients with recurring pain (N = 7 at 1 week, and 1 month, N = 4 at 3, and N = 6 at 6 months) and significant differences compared with baseline, as well as results for the subgroup with relapsing CRPS (N = 3 at 3 months, N = 4 at 6 months) and significant differences compared with baseline (+$P < 0.004$; #$P < 0.0029$). Part (B) summarizes the percentage of pain relief following the treatment. Data are presented as means ± SD for the entire group and the subgroups with recurring pain, and relapsing pain, respectively. Significant degrees in the percentage of pain relief are indicated (*$P < 0.001$; +$P < 0.004$; #$P < 0.002$). NRS = Numeric Rating Scale; CRPS = complex regional pain syndrome.

Pain Relief

The calculated percentage of pain relief was significant following ketamine treatment at 1 week (mean ± SD: 94.5% ± 8.9, and at 1, 3, and 6 months (93.5% ± 11.1, 89.4% ± 17.0, 79.3% ±25.3) in the entire group of patients ($P < 0.001$). Analyses for the subgroup with recurring pain showed significant pain relief at 1 week (84.4% ±8.22, N = 7, $P < 0.001$), and 1, 3, and 6 months (81.4% ± 11.5, 77.8% ± 10.1, and 64.32% ±23.8, N = 7, 4, and 6, $P < 0.001$ in all), respectively.

Pain relief in the subgroup of CRPS patient with relapse was maintained at 3, and 6 months (59% ± 14.7, N = 3, $P < 0.004$, and 50.21% ±10.6, N = 4, $P < 0.002$). Figure 2 summarizes the results.

Movement Disorder

Upper Extremity

For statistical analyses, the separately assessed scores the impairment of

movement in the arm and hand of each side of the body was added to a total score for hands and arms. Thus, the minimal sum score was 0 (normal bilateral movement) and maximal 6 (total bilateral impairment). All patients (N = 20) showed impaired movement in the upper extremities.

At baseline a sum score of 3.2 ± 1.2 (mean ± SD) for movement in the arms, and 3.7 ± 1.2 for movement in the hands was documented (N = 20). At 1, 3, and 6 months, a significant ($P < 0.001$) reduction of the sum score was noted for the movement impairment in the arms (1.4 ± 0.83, 0.5 ± 0.8, and 0.4 ± 0.8), and hands (1.6 ± 0.8, 0.5 ± 0.9, and 0.5 ± 0.8), respectively.

Lower Extremity

Statistical analyses of scores for decreased movement in the lower extremities were based on the direct scores of the aforementioned 4-point-based numeric rating scale. Of the entire group, only those with a movement disorder in the lower extremity were included for statistical analyses. At baseline, patients with movement disorder of the lower extremity (N = 15) had a score of 2.3 ± 0.7 (mean ± SD). Following treatment, their impairment was significantly reduced at 1, 3, and 6 months (1.3 ± 0.9, 0.6 ± 0.7, and 0.6 ± 0.6; N = 15, $P < 0.001$). Figure 3 summarizes the results.

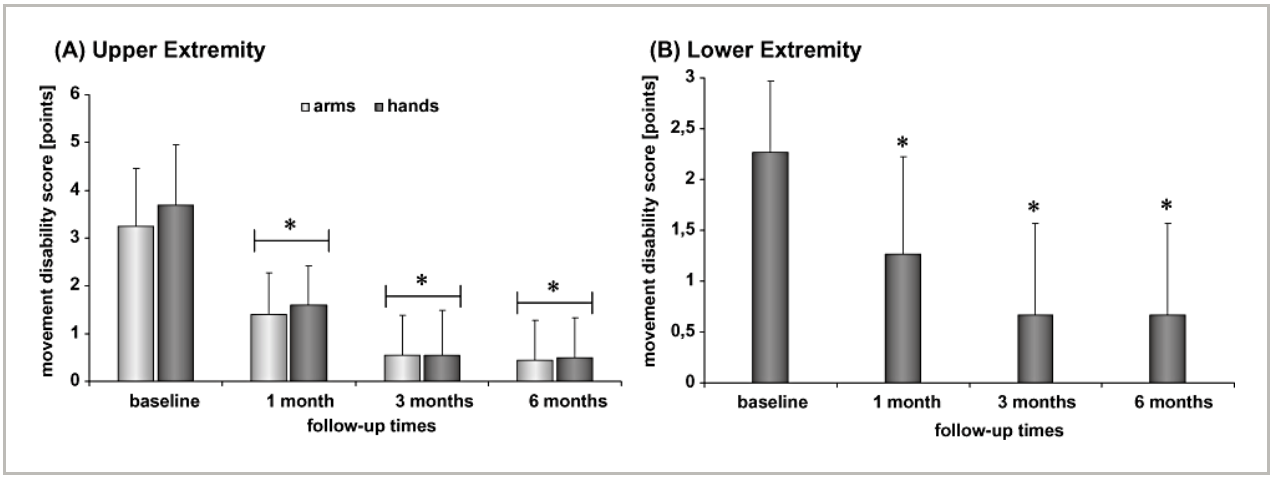

Figure 3

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The changes for the movement disability score (4-point rating scale: 0: normal movement, 3: total impairment) of the different assessment times. Data are presented as means ± SD for baseline, and the follow-ups at 1, 3, and 6 months. (A) Upper extremity: data show the results of a sum-score (movement disability scores of both body sides were added, thus a minimal score of 0 (normal bilateral movement), and 6 (total impaired bilateral movement) for impairment of movement in arms and hands, and significant differences compared with baseline (*$P < 0.001$). (B) Lower extremity: results and significant differences in the movement disability score for the lower extremity at baseline and the follow up assessments ($P < 0.001$).

Quality of Life

Activities of Daily Living

At baseline, the ability to independently accomplish activities of daily living was rated as severely impaired by seven, and as totally impaired by 13 patients, with a mean score of 2.35 ± 0.4 (mean ± SD) for the entire group. At 3 months, the impairment was rated as severe by one, as moderate by 12, and as not impaired by seven patients, with a mean score of 0.7 ± 0.6, and a significant difference compared with baseline ($P < 0.001$). At 6 months, there was a significant difference in the ability to perform activities of daily living compared with baseline. One patient rated total impairment, three severe impairment, six moderate impairment, and 10 patients no impairment for a mean score of 0.7 ± 0.9 ($P < 0.001$). Results are shown in Figure 4.

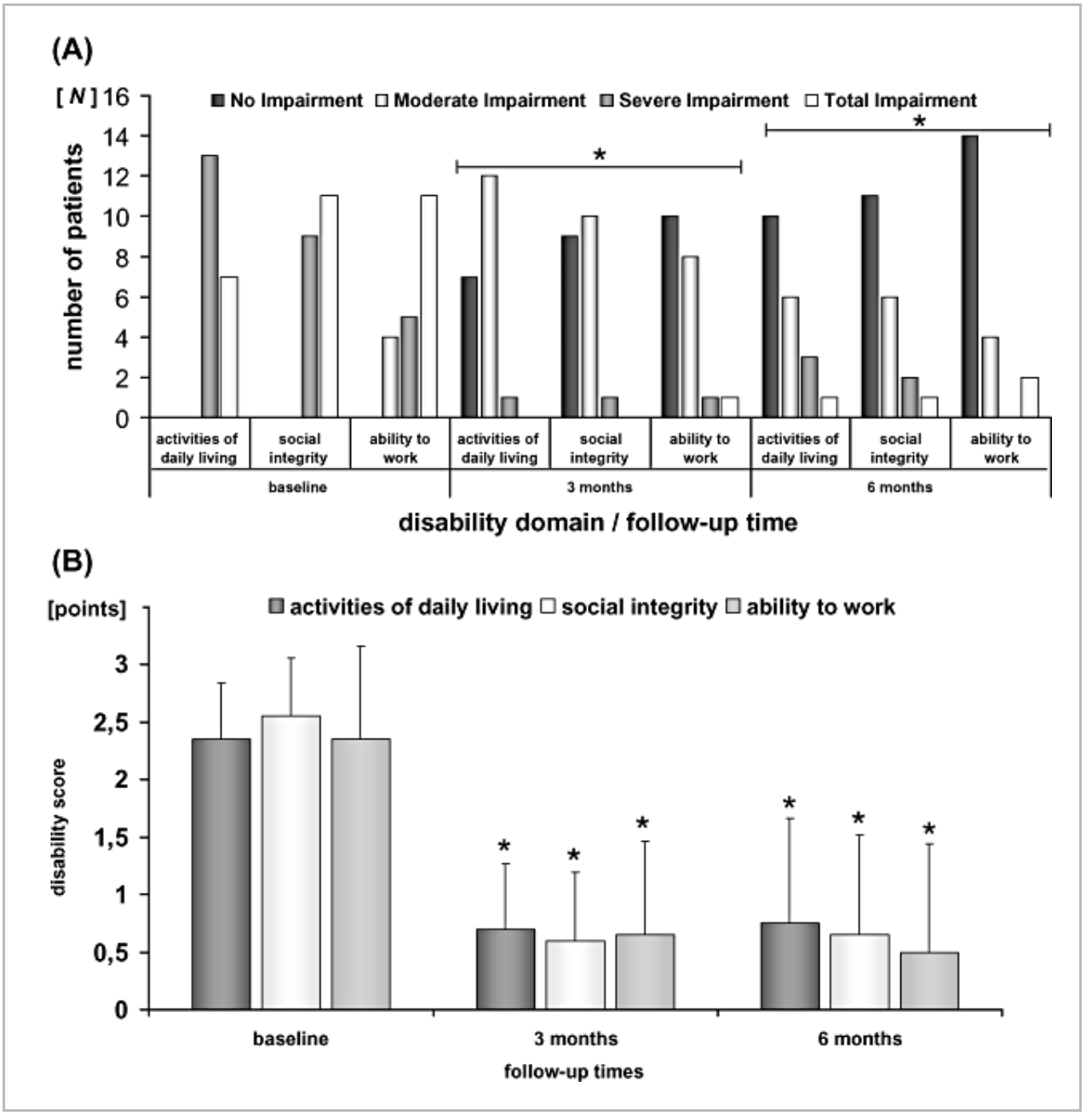

Figure 4

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The results for the assessments of quality of life: the impairment in activities of daily living, the impairment in social integration, and the ability to work. Patients rated their impairment on a 4-point rating scale (0: no impairment, 3: total impairment). Part (A) shows the absolute number (N) of patients in each category of impairment at baseline and the follow-ups, and significant differences compared with baseline (*$P < 0.001$). (B) Severity of impairment: the impairment scores

for the entire group for impairment of activities of daily living, social integration, and the ability to work at baseline, 3, and 6 months and significant differences compared with baseline (*$P < 0.001$).

Social Integration

The impairment in social integration prior to treatment was rated as complete by 11 patients and severe by nine. Their mean impairment score was 2.5 ± 0.5. At 3 months, their impairment was rated as severe by one, as moderate by 10, and nine were unimpaired. Their mean score of 0.6 ± 0.6, was significantly improved compared with their pretreatment baseline ($P < 0.001$). At 6 months, there was significant improvement in the group with one patient rating total impairment, two severe impairment, six moderate impairment, and 11 patients no impairment (mean score of 0.6 ± 0.8 ($P < 0.001$). Results are shown in Figure 4.

Ability to Work

The impairment in the ability to work prior to treatment was rated as complete by 11, severe by 5, and as moderate by four patients (mean impairment score of 2.3 ± 0.8). At 3 months, the impairment in ability to work was rated as complete and severe by one patient in each category, as moderate by eight, and as not impaired by 10 patients (mean score of 0.6 ± 0.8), which was significantly improved compared with their baseline ($P < 0.001$). At 6 months, there was significant improvement in the ability to work as only two patients in the cohort were unable to work, four had moderate impairment, and 14 patients had no impairment (mean score of 0.5 ± 0.9) ($P < 0.001$). Results are shown in Figure 4 and Table 5.

Table 5. Individual outcome following anesthetic ketamine: the individual patients' outcome for: pain response (data shown for the follow-ups at 1, 3, an 6 months), movement disorder (data shown for baseline, 3, 6

months; numbers given indicate: sum score movement disability in the arms (0: bilateral normal movement–6: bilateral total impairment)/sum score movement disability in the hands (0: bilateral normal movement–6: bilateral total impairment)/movement disability score for the lower extremities (0: normal walking–3: total impairment), and the impairment in the assessed aspects of quality of life: every day activities, social life activities, and working capacity

Patient No.	Pain			Movement Disorders			Activities of
	1 Month	3 Month	6 Month	Baseline	3 Months	6 Months	Baseline
1	FR	FR	FR	3/3/0	0/0/0	0/0/0	TI
2	FR	FR	FR	4/5/0	0/0/0	0/0/0	SI
3	RP	FR	FR	4/4/0	0/0/0	0/0/0	SI
4	RP	CRPS	CRPS	4/5/2	2/2/1	2/2/1	SI
5	FR	FR	RP	2/3/0	1/0/0	1/1/0	SI
6	FR	FR	FR	5/5/3	0/0/0	0/0/0	TI
7	RP	CRPS	CRPS	4/5/3	2/3/3	2/3/3	TI
8	FR	FR	RP	2/4/2	0/0/1	0/0/1	SI
9	FR	FR	FR	2/3/1	0/0/0	0/0/0	SI
10	RP	FR	FR	2/3/2	0/0/0	0/0/0	TI
11	RP	CRPS	CRPS	2/3/3	2/2/1	2/2/1	SI
12	RP	RP	RP	5/5/3	2/2/2	2/2/2	TI

13	RP	FR	FR	5/6/3	1/0/0	0/0/0	TI	M
14	FR	FR	RP	4/2/2	1/1/0	0/1/0	SI	M
15	FR	RP	RP	2/2/1	0/0/0	0/0/0	SI	M
16	FR	FR	FR	3/3/2	0/0/0	0/0/0	SI	N
17	FR	FR	FR	1/1/0	0/0/0	0/0/0	SI	M
18	RP	RP	CRPS	4/4/2	0/1/1	0/0/1	SI	M
19	FR	FR	FR	4/4/3	0/0/0	0/0/0	TI	N
20	FR	RP	RP	3/4/2	0/0/1	0/0/1	SI	N

FR = full remission; RP = recurring pain; CRPS = complex regional pain syndrome-relapse; NI = no impairment; MI = moderate impairment; SI = severe impairment; TI = total impairment.

Ketamine and Norketamine Plasma Concentrations

High-pressure liquid chromatography analysis of ketamine and norketamine plasma levels was in 18 patients. The sampling and analysis of two patients was incomplete, because of initial technical difficulties and therefore were not included in the analyses. Figure 5 summarizes the plasma concentrations for ketamine and norketamine.

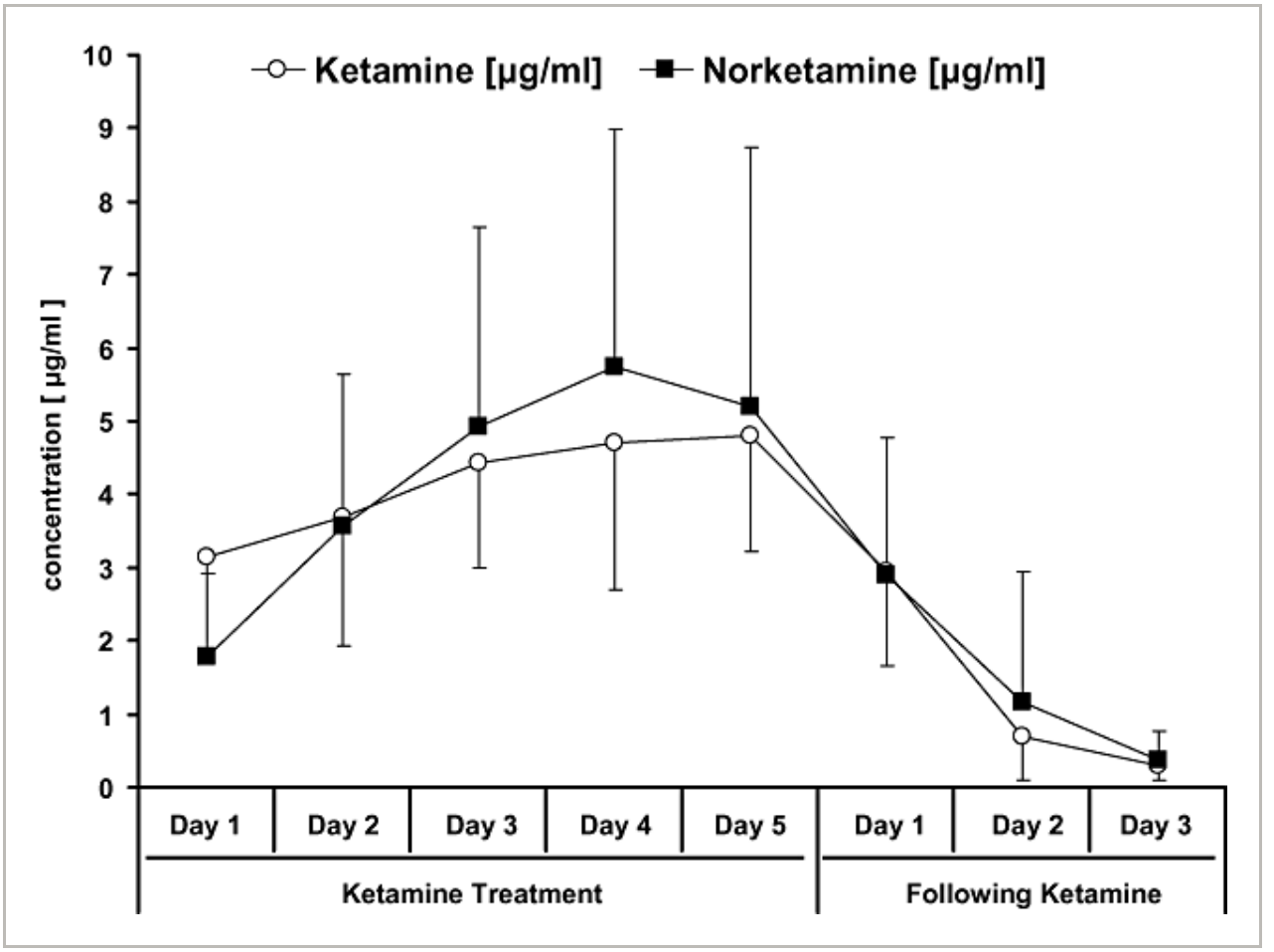

Figure 5

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Ketamine and norketamine plasma concentrations. Summarizes by the HPLC determined plasma concentrations for racemic ketamine and the primary active metabolite norketamine (µg/mL) over the five treatment days with anesthetic days and subsiding in the three consecutive days after anesthetic ketamine treatment. HPLC = high-pressure liquid chromatography.

Side Effects

Ketamine-Specific Side Effects

Psychotropic Ketamine Side Effects

Psychotropic side effects that included anxiety, dysphoria, nightmares, and difficulties with sleep were observed in the majority of patients upon emergence from ketamine anesthesia. The intensity of these ketamine-specific side effects was most severe in the initial days following emergence from anesthesia and resembled an acute withdrawal. These symptoms were successfully treated with small doses of clonidine and/or benzodiazepines. The psychotropic side effects faded within the first week following treatment in the majority of patients. However, five patients reported difficulties with sleeping and recurring nightmares for a month following treatment. Muscular weakness was reported in all patients for as long as 4–6 weeks following treatment.

Adverse Treatment Effects

Infectious Complications

No major or life threatening complications were observed. The majority of complications were infections associated with the intensive care nature of treatment. Seven patients had respiratory infections, tracheobronchitis in five, and pneumonia in two patients. Fever was observed early (within 24–48 hours) following the initiation of anesthetic doses of ketamine, with concomitant leucocytosis (12,000–16,000/μL) and elevation of the CRP (6–25 mg/dL). Culture of tracheal secretions revealed *S. aureus* (methycillin sensible *S. aureus*, N = 6), *Klebsiella pneumoniae* (N = 2), and *Proteus mirabilis* (N = 1), as the pathogens in these cases. Lower urinary tract infections were seen in six patients, and urine cultures revealed enterococcus species (*E. faecium*, *E. faecalis*), and *E. coli* as the pathogens. These infectious complications were successfully treated with antibiogram-guided antibiotic therapy.

Laboratory Evaluation

During treatment, transient rises in liver enzymes, CPK and CKMB were observed. Blood tests prior to the start of therapy revealed elevated liver

enzymes (γ-GT: 20–60 U/L in five patients, and GOT: 20–38 U/L in five patients), all of whom had been taking combinations of analgesics, antidepressants, and seizure medications. Under anesthesia, elevations of liver enzymes were noted in 16 patients for γ-GT (range: 30–94 U/L), GOT (range 30–98 U/L), and GPT (20–94 U/L), the maximal elevations occurred on days 5–6 of treatment. Elevations in CPK (range: 20–800 U/L) were observed in 16 patients, all of whom had normal ratios for CPK/CKMB which where below 10%. Both the elevation of liver enzymes and CPK decreased following treatment and returned to reference values within 10–14 days.

Discussion

This open-label study suggests an impressive effect of anesthetic ketamine in advanced and refractory CRPS patients. Pain scores were significantly improved and long-term complete pain relief was observed in 50% of patients. Patients that suffered recurring pain alone and recurring pain in conjunction with a CRPS relapse also maintained significant relief during the course of the study. In addition, there was significant improvement of the movement disorder, ability to perform activities of daily living, and the ability to work in concert with the decrement in pain. However, the dramatic nature of the intervention would be expected to cause a strong placebo response and the nonrandomized uncontrolled design of this study leave its results suggestive but unproven.

There are many possible mechanisms that underlie the marked and long-lasting effects of anesthetic ketamine in these severely affected CRPS patients. Because this is an open-label phase II study with lack of controls, the results may not be completely attributable to ketamine. Anesthetic doses of ketamine have not been studied in the therapy of chronic pain states. Existing evidence for the efficacy of ketamine in chronic pain disorders was obtained by utilizing low subanesthetic dose protocols

primarily for neuropathic pain states other than CRPS. The first data on the beneficial effects of ketamine for CRPS were obtained from case reports and small case series 23-26, 28. In these studies, subanesthetic ketamine was administered via systemic, epidural or topical routes and provided dramatic relief from pain and associated CRPS symptoms in some patients. However, these studies differ in the routes of ketamine administration, dosage, treatment time, patient clinical profiles, and the duration of observation following treatment. The main limitations in determining the benefit of ketamine in these studies are sample size, lack of a control population and standardization of the treatment and measurement protocols. Long-term pain relief for 8 months was observed following a 10-day course of epidural ketamine (0.25 μg/kg/h) in a patient with lower extremity CRPS 23. Harbut utilized continuous subanesthetic ketamine for 6 days in a patient that had suffered 9 years of CRPS and achieved pain relief for 5 months 28. Recently, a larger-scale retrospective case series described long-term relief from pain following continuous low-dose ketamine 27. In this series, the best response to ketamine was observed in patients with early CRPS whose symptoms and signs were well localized to the distal aspects of one extremity. In a subgroup of refractory CRPS patients, we recently showed subanesthetic continuous S(+)-ketamine (500 mg/day) administered over 10 days (exceeding the equianalgesic ketamine dosages used by Correll) was ineffective in relieving pain or attenuating severe thermal and mechanical allodynia 29. To our knowledge, there are no randomized controlled trials on the efficacy of ketamine in the treatment of CRPS.

Complex regional pain syndrome is generally thought to be a subset of neuropathic pain 2, 4. Although as noted above, inflammatory components are often predominant in early stages 40, 41, the exact pathophysiology is unknown but strides have been made in the understanding of possible mechanisms that underlie the generation and maintenance of this possible neuropathic pain 8, 17. A critical role for

NMDA-receptors that contribute to central sensitization in chronic neuropathic pain is well established 16, 17. Consequently, the efficacy of several NMDA-receptor antagonists has been investigated in various neuropathic pain conditions. In human and animal studies, ketamine was shown to have a dose-dependent effect on neuropathic pain features, such as secondary hyperalgesia, allodynia, long-term potentiation, and wind-up 42-46. Several clinical trials in neuropathic pain conditions have confirmed beneficial effects of ketamine in the therapy of chronic pain. In a randomized controlled trial of postherpetic neuralgia, iv ketamine significantly reduced pain, allodynia, and hyperpathia 47. Similarly, intravenous ketamine has been shown to produce significant pain relief and reduction of wind-up pain in a randomized controlled trial of chronic phantom pain 48. A randomized trial of intramuscular ketamine provided 24 hours of significant pain relief in patients with facial neuralgia 49. Several trials have noted long-term affects of ketamine that outlast its pharmacological profile 18-20, 49. In addition, animal and clinical studies have demonstrated that the efficacy of ketamine is dose-dependent 19, 43, 44, 50. As the incidence and degree of ketamine side effects also depends on dosage, most trials in pain medicine have been performed with low doses 14. This trial of anesthetic dosage of ketamine in refractory CRPS, as well as the first patient treated on a compassionate care basis 51 demonstrated long-term significant pain relief that outlasts its pharmacological profile.

Many aspects of the pathophysiology of CRPS remain unclear. Recently, CRPS has been posited to be a disease of the CNS 7. The molecular mechanisms underlying CRPS are hindered by lack of an exact animal model that is completely valid for this complex clinical entity 52. Its characteristic signs and symptoms may occur as a consequence of dysregulated efferent central control of several systems (i.e., somatosensory, motor, and sympathetic) and appears to be maintained from a peripheral sensitizing afferent nociceptive barrage. The molecular

mechanisms responsible for inducing and maintaining these lasting and self-maintaining neuroplastic changes in CRPS are not known but there is evidence for NMDA-receptor mediated neuronal plasticity and facilitation of central pain processing [8]. Another potential mechanism underlying the syndrome is injury induced activation of central microglia that secrete inflammatory cytokines which activate central pain projecting neurons [53]. The relative importance of mechanisms for central sensitization mediated by the NMDA-receptor and subsequent calcium cascades or effects of inflammatory cytokines on pain transmission neurons or both in concert is not known [17], [21]. Recent evidence in a rat model of neuropathic pain demonstrated a comparable long-term suppression of allodynia by ketamine that outlasted the duration of its NMDA blockade [50]. Thus, down-regulation of central sensitization mediated by NMDA-receptor blockade might explain in part long-term effects of ketamine in neuropathic pain.

Other relevant mechanisms mediated by ketamine that contribute to pain relief in these patients must be considered. These include potential modulation of peripheral NMDA- and non-NMDA-receptors. Ketamine inhibits peripheral glutamate receptors which play a role in both peripheral and subsequent central sensitization [54]. In addition, ketamine interacts with various receptors involved in nociception that include AMPA and kainate glutamate receptors, voltage-dependent ion channels, sodium and L-type calcium channels, opioid receptors (μ-, κ-, and δ-opioid receptors), $GABA_A$-receptors, and nicotinic and muscarinic acetylcholine receptors [15]. Ketamine induced inhibition of nitric-oxide synthase might also contribute to its analgesic effects [15]. As noted above, proinflammatory mediators are known to play an essential role in the processes of peripheral and central sensitization [55]. Ketamine induces a profound inhibition of proinflammatory cytokines and other inflammatory mediators, both in experimental and clinical studies [15], [22]. A recent study demonstrated significant increases in proinflammatory cytokines in the

cerebrospinal fluid of CRPS patients, which suggests a potential role of neuroimmune activation in CRPS [56]. The anti-inflammatory effects of ketamine administered in anesthetic doses may also play a role in its effects on these patients. Alternatively or in addition to ketamine, midazolam and clonidine may also contribute to the effectiveness of this treatment. Clonidine, a central α_2-adrenergic agonist, has analgesic properties [57]. Its analgesic potency is weak but has effect when administered by epidural, intrathecal or a transdermal route. Although the analgesic effects of intravenous clonidine are controversial, a synergistic interaction with ketamine in our patients is possible [57]. Another synergistic effect of this treatment may be due to midazolam, a short-acting $GABA_A$ agonist. In the course of central sensitization, GABA-ergic inhibitory transmission is depressed by NMDA-dependent mechanisms which leads to prolonged depression of inhibitory transmission and thus potentiation of central pain projecting neuron hyperexcitability [17, 58]. The large doses of midazolam administered during treatment would be expected to enhance GABA-ergic induced inhibition during this treatment while its role as an analgesic is unclear [17, 58]. The possible contributions of the placebo effect and or resetting of pain processing mechanisms due to 5 days of anesthesia in the beneficial effects of this treatment are unknown.

A most relevant concern of this invasive procedure is patient safety. Modern intensive care medicine standards achieve a high level of patient safety. Ketamine has been safely used for over 30 years in clinical anesthesia and also in intensive care. However, a potential concern is NMDAR-antagonist induced neurotoxicity that has been demonstrated in animal experimental work in the developing and adult rat brain [59]. Neurotoxic effects are prevented by administration of clonidine and $GABA_A$-agonists [60, 61]. To the best of our knowledge, neurotoxicity of ketamine to date has not been demonstrated in humans [62]. Initial studies investigating ketamine sedation in brain injured patients in the intensive

care setting were not associated with significant morbidity or mortality [63], [64]. However, these studies were not powered for a valid assessment of safety. The reported duration of ketamine sedation (6.1 ± 3.2 days) and the dosage of ketamine (maximal dose: 94 ± 23 µg/kg/min) are comparable to our study (5 days of sedation; maximal dose: ~84 µg/kg/min) [63].

Nonetheless, it must be emphasized that this protocol is associated with serious risks. The major complications observed in this study were respiratory and urinary tract infections, representing typical infections in intensive care. Although, in this series, infections resolved under antibiotic treatment, it must be emphasized that infectious complications still represent the main source of morbidity and mortality in modern intensive care medicine. Transient ketamine-specific psychotropic side effects occurred on emergence from ketamine anesthesia and were successfully controlled by benzodiazepines and clonidine. There were no long-term psychiatric or cognitive impairments in any patient [65]. Moderate muscle weakness persisted for a month to 6 weeks.

In addition to all of the limitations inherent in a nonrandomized uncontrolled trial, there are several other limitations of this study: 1) the movement disorder, social integration, activities of daily living and ability to work measures were subjective and have not been validated in CRPS patient; 2) the CRPS patient population studied is not representative of that seen in most pain centers as it is drawn from the entire USA; 3) the mechanism of the spread of other validated factors of CRPS from the area of original injury is not known. The severity of this clinical component in these patients is unusual and may represent or be a consequence of the role of central glia pathophysiology in chronic pain states, central sensitization, functional reorganization of pain processing systems or dysfunction of descending pain control mechanisms. The area of primary CRPS may be maintaining a more generalized pain state.

A complete double blind placebo controlled randomized clinical trial would be logistically and ethically at least difficult, but its realization represents a major challenge of future work to possibly confirm the observed effect.

Conclusion

This phase II open-label study utilizing anesthetic doses of ketamine with midazolam and clonidine suggests possible effectiveness for severe CRPS patients that have failed all available standard therapies. A definitive, large multicenter randomized controlled trial is needed to confirm these results.

Acknowledgments

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Appendix

Table 6. Appendix 1: The validated criterion factors for CRPS and their location in the 20 patients of this study (Harden RN, Bruehl SP. Diagnostic Critera: The statistical derivation of the four criterion factors. In: Wilson P, Stanton-Hicks M, Harden N, eds. CRPS: Current Diagnosis and Therapy. Seattle, WA: IASP Press; 2005:45–58). Baseline pain expressed on a numeric rating scale (NRS: endpoints: 0: no pain and 10 most severe pain imaginable)

Demographics	Triggering Injury Site of Primary CRPS	Abnormalities in Pain Processing Factor 1	Skin Color and Temperature Changes Factor 2	Factor and Sudom Change Factor
No. 1 16 yo female CRPS 8 months Baseline Pain NRS 9 ASA Class I	Strain injury right right hand, wrist; brachial plexus traction injury	All brachial plexus distributions right, V1-V3 facial distributions Hyperalgesia to pinprick; spontaneous burning pain; evoked shooting pain; mechanical allodynia (dynamic and static); thermal allodynia to cold	Temperature asymmetry: increased right arm and face > left; erythematous right arm and face; fluctuating erythema right arm and face, to lesser degree left side of the face	Massive the enti edema shoulde hyperhi greater than lef

	Clinical criterion factors that were positive in a contiguous distribution	Positive in upper trunk left brachial plexus and left facial distribution (hyperalgesia to pinprick; mechanical dynamic and static allodynia; cold allodynia)		
No. 2 26 yo female CRPS 12 months Baseline Pain NRS 9 ASA Class I	Right brachial plexus traction injury	All brachial plexus distributions, V1-V3 facial distributions bilaterally Hyperalgesia to pinprick; spontaneous burning pain; evoked shooting pain; mechanical allodynia (dynamic and static); thermal allodynia to cold	Temperature asymmetry: increased right arm and face > left; erythematous right arm and face; fluctuating erythema right arm and face	Edema and fac hyperhi greater than lef

	Clinical criterion factors that were positive in a mirror distribution	Positive in upper trunk left brachial plexus distribution (hyperalgesia to pinprick; mechanical dynamic and static allodynia; cold allodynia)		
No. 3 25 yo male CRPS 24 months Baseline Pain NRS 9 ASA Class II	Right brachial plexus; Hodgkin's disease; compression of the brachial plexus by lymphoma	Right brachial plexus; V1-V3 Hyperalgesia to pinprick; spontaneous burning pain; evoked lancinating and tingling pain; deep ache; mechanical allodynia (dynamic and static); joint pain (small joints of the fingers); thermal allodynia to cold	Temperature asymmetry: increased in the right arm and face > the left arm and face; erythematous entire right arm and face; no fluctuation of erythema in right arm and face	Severe face; m edema arm an hyperhi bilatera arms ar edema arm an

	Clinical criterion factors that were positive in the left arm and hand	Hyperalgesia to pinprick; mechanical dynamic and static allodynia; cold allodynia; less severe spontaneous burning pain; less severe evoked lancinating pain	Normal temperature arm and face; slight erythema of the left ear; static color change of the ear (eryrhema)	
No. 4 46 yo female CRPS 60 months Baseline Pain NRS 9.5 ASA Class II	Right brachial plexus traction injury	Hyperalgesia to pinprick right face, arm, anterior chest and total leg; spontaneous burning pain, deep ache entire right side of the body; severe right L5-S1 distribution lancinating pain;	Temperature asymmetry; right arm and face > than left (higher); erythema of the right arm and face; normal skin color of the left arm and	Constar the righ and fac hyperhi arm an constar right fa sympto tightnes

		mechanical, dynamic and static allodynia of entire right side of the body; thermal allodynia to both cold and heat; cold allodynia spread six inches to either side of the stimulus (tuning fork)	face; fluctuating color change of the right arm and face	
	Clinical criterion factors that were positive in other than primary areas of involvement right arm Clinical criterion factors that were positive in other than primary areas of	Tactile mechanical dynamic and static allodynia (upper and lower trunk, brachial plexus distributions on the left); hyperalgesia to pinprick (upper	Minimal hyperhidrosis of left arm; normal temperature of left arm	Minima (rarely) arm

	involvement right leg	and lower trunk brachial plexus distributions); cold allodynia (upper and lower trunk); left arm Mechanoallodynia (static and dynamic) of the right upper leg in regional distribution		
	Additional features Severe non-fluctuating venous distention in hand and forearm veins; L4-L5; L5-S1 radicular motor and sensory changes on the left side; erythematous ear on the right; upper trunk of brachial plexus; lower trunk brachial plexus			
No. 5 29 yo female CRPS 30 months Baseline Pain	Right brachial plexus (electrical injury; tear of the labrum of the glenoid fossa of the humerus)	Severe hyperalgesia to pinprick regional distribution of the right upper	Higher temperature right upper extremity than left upper	Edema upper e face; hy of right extremi

NRS 8.5 ASA Class II		extremity; spontaneous burning pain; lightening-like pain right upper extremity; mechanical dynamic and static allodynia; cold allodynia; deep muscle sensitization to pressure of right upper extremity in regional distribution	extremity; erythema of entire right upper extremity; left trapezius ridge had color change; erythema static in affected areas	stiff righ
	Clinical criterion factors that were positive in contiguous areas	Mechanoallodynia, (static and dynamic) of the right face Allodynia and hyperalgesia to pinprick in the same distribution; spontaneous burning pain in the face and thigh	Increased temperature face V1-V3, and regionally in the upper thigh; erythema of the face; no fluctuation of erythema of the face	Edema hiperhi right fa distribu compla narrowi palpebr from ec
	Additional features Pain in bioccipital tendon; severe Tinel			

	signs with compression of the supraradicular fossa, pronator canal, Arcade of Frohse and carpal tunnel; anterior shoulder instability; touch on the arm spread to the face			
No. 6 46 yo female CRPS 72 months Baseline Pain NRS 8.5 ASA Class III	Crush injury of the right ankle and foot; operative osteosynthesis of the right foot	Hyperalgesia to pinprick of right lower extremity, burning pain most severe at the site of the original foot surgery; joint pain right foot; lightening-like pains right foot and leg	Colder right leg to the knee than left; erythema of the right lower extremity	Edema extremi stiffnes decreas from sw foot an hyperhi right lo hyperhi edema leg to th vasomo sudomo V1-V3 ri

	Clinical criterion factors that were positive in contiguous ipsilateral extremities (leg and upper extremity), face and mirror foot distribution	Right contiguous leg, upper extremity and face); hyperalgesia to pin prick; spontaneous burning, lancinating and deep pain; mechanical, dynamic and static allodynia; deep muscle sensitization; cold allodynia (right face > left arm)	Increased temperature of the right face; decreased temperature of the right upper extremity and right lower extremity	Hyperh cyanosi and upp
	Additional features Severe tenderness in area of surgical scar; spread of stimulus (pinprick and cold) from the right foot to the right face; V2,edema and hyperhidrosis of right face, most severe; spontaneous burning pain			
No. 7	Trauma to the lower	Hyperalgesia right	Right leg	Edema

28 yo female CRPS 60 months Baseline Pain NRS 9.5 ASA Class III	back and right leg	lower extremity to pinprick; severe spontaneous burning pain of right lower extremity (regional distribution); deep knee joint pain; pain at the injury site of the right lower back; mechanical, dynamic and static allodynia right leg; cold allodynia right lower extremity	slightly colder than left leg; both colder than normal; fluctuating erythema of the right lower extremity	(severe) hyperhi leg > lef fluctuat (compo patient wheelch
	Clinical criterion factors that were positive in contiguous areas of the ipsilateral extremity, face and contralateral leg	Ipsilateral arm hyperalgesia to pinprick; dynamic and static mechanoallodynia; cold and hot allodynia; joint pain; deep muscle allodynia to	Right upper extremity warmer than left upper extremity; erythematous right arm and hand; varied with pain,	Modera the righ hyperhi compar upper e nonvary edema extremi Edema

		pressure; spontaneous burning pain, lightening-like pain; tingling pain Face right side (V1-V3) hyperalgesia to pinprick; dynamic and static mechano allodynia; cold allodynia	movement and emotional stress Warmer than the left face (particularly V2); erythematous cheek and right ear; non-varying erythema	upper e hyperhi upper e constar the face
	Additional features Tinel signs very positive at supraclavicular fossa, Arcade of Frohse, pronator canal and carpal tunnel bilaterally; stimulus spread from arm to face right side; leg to face right side	Mirror distribution of left leg hyperalgesia to pinprick; dynamic and static mechano allodynia; cold allodynia (equal throughout the leg)	Cooler than right leg; minimal erythema compared to right leg; color change varied with emotional stress and cold	Edema > distall (compo being w bound); edema; hyperhi right sic

No. 8 42 yo female CRPS 30 months Baseline Pain NRS8.5 ASA Class II	Cruciate ligament tear; tibial plate fracture of the right knee	Hyperalgesia of the right knee and leg in a regional distribution; dynamic and static mechanoallodynia of the skin; deep sensitization of the quadriceps muscle; spontaneous burning pain of the knee that was continuous; evoked lightening-like pain and deep ache with weight bearing	Temperature asymmetry (warmer) than left knee; erythema of right knee; livedo reticularis and dusky cyanosis; increased erythema with exercise and heat of the right knee area and upper leg	Edema area; m of the ri leg; swe asymm left kne variable exercise and wal
	Clinical criterion factors that were positive in ipsilateral arm and face as well as in a mirror distribution Additional features Positive Tinel signs in the upper extremities	Ipsilateral right arm; ipsi- lateral face; mirror left leg, hyperalgesia and allodynia (static and dynamic)		V1-V3 e hyperhi face

	of the supraclavicular fossa; C2-C3 exit foramina; Arcade of Frohse; pronator canal, cubital and carpal tunnel; stimulus applied to R knee (pinprick) at times felt in the R or L face.			
No. 9 22 yo female CRPS 72 months Baseline Pain NRS 9 ASA Class II	Tendon rupture digit IV; operative repair in the right hand	Hyperalgesia to pinprick of right upper extremity; dynamic and static mechanoallodynia of the entire right upper extremity but more severe in the lateral hand; spontaneous deep ache and burning lancinating pain of the right hand and right upper extremity	Temperature asymmetry, primarily warmer of right versus left hand; erythema of right hand; color change varied from erythema to dusky cyanosis; livedo reticularis of right upper extremity most severe in the medial forearm	Edema (all finge asymm left upp most se hand; n right ha

	Clinical criterion factors that were positive in the ipsilateral upper and lower extremity; ipsilateral face and contralateral hand	Ipsilateral arm and leg; ipsilateral face (V1-V3) spontaneous burning pain, hyperalgesia to pin prick	Ipsilateral arm and leg; ipsilateral face (V1-V3) hyperhidrosis and warmer; contra lateral hand (much less degree than R hand)	Ipsilater leg; ipsi (V1-V3) and ede lateral h less deg right ha
	Additional features Positive Tinel signs in supraclavicular fossa, Arcade of Frohse, pronator canal, cubital tunnel right > left; spread of pinprick from the hand to the face and arm			
No. 10 19 yo female CRPS 60	Fracture of metatarsal V of the right foot	Hyperalgesia to pinprick of the right leg and right	Temperature asymmetry right foot	Edema right > l sweatin

months Baseline Pain NRS 9 ASA Class II		foot at area of injury (most) severe; dynamic and static mechano-allodynia of the right foot; cold allodynia of the right foot; spontaneous burning pain of the foot; most severe pain at the area of the original fracture; evoked lancinating pain and deep ache with walking; occasional spontaneous squeezing pain of the right foot and leg	colder than left; fluctuates with occasional right foot warmer than left; color change with erythema alternating with dusky cyanosis of right foot > left foot; heat and cold evoked erythema or cyanosis respectively	right > l positior increas always > left fo
	Clinical criterion factors that were positive in the ipsilateral face and extremities	Left leg; right arm; right face (V1-V3) spontaneous pain and mechanoallodynia (static and dynamic)	Left leg; right face (V1-V3) usually erythematous but alternating blanched	Left leg; (V1-V3) and usu and cya

	Additional features Positive Tinel signs bilaterally supraclavicular fossa, Arcade of Frohse, pronator canal, foramina exit areas C2–C3; spread of pinprick, hyperalgesia and cold stimulus to the entire right sidefrom a stimulus to right foot.			
No. 11 20 yo female CRPS 36 months Baseline Pain NRS 9 ASA Class II	Trauma to right shoulder and right arm (blunt trauma from falling object)	Hyperalgesia to pinprick right upper extremity; dynamic and static mechanoallodynia of right upper extremity; cold and warm allodynia of right upper extremity; spontaneous burning pain; deep ache; evoked lancinating pain; painful tingling of entire right upper extremity; spontaneous pain	Temperature asymmetry right > left upper extremity; erythema of right > left upper extremity; variable color change with emotional stress, exercise and cold	Edema upper e hyperhi left upp pitting e of forea

	worse right brachial plexus distributions	
Clinical criterion factors that were positive in the ipsilateral face, leg and contralateral arm	Spontaneous pain in ipsilateral face (V1-V3 3); ipsilateral leg; contralateral upper extremity both in a regional distribution; dynamic and static mechanoallodynia in the same distributions	Edema hyperhi of ipsila ipsilater extremi primari
Additional features Positive Tinel signs in the supraclavicular fossa; exit foramina of C2-CVasomotor and		

	Sudomotor/Edema Changes, CVasomotor and Sudomotor/Edema Changes-C4; pronator canal, cubital and carpal tunnel; dystrophic punched out skin ulcers; brown papular skin lesions of right upper extremity			
No. 12 35 yo female CRPS 72 months Baseline Pain NRS 9 ASA Class III	Trauma to right shoulder and right arm	Hyperalgesia to pinprick of the entire upper extremity; dynamic and static mechanoallodynia entire right upper extremity; cold allodynia right upper extremity; allodynia to deep somatic pressure; painful joint movement (both small and large joints of right upper extremity)	Temperature asymmetry; right upper extremity colder than left; cyanotic, bluish, livedo reticularis right > left upper extremity	Edema extremi forearm hyperhi hand ar variatio due to c and har

	Clinical criterion factors that were positive in right face and leg and left arm Additional features Positive Tinel signs bilaterally supraclavicular fossa, pronator canal, cubital and carpal tunnels; spread of pinprick and cold stimulus contiguously from area of application (12–14 inches).		Erythema and increased temperature of V1-V3 of right face	Edema hyperhi right fac
No. 13 38 yo female CRPS 24 months Baseline Pain NRS 9 ASA Class III	Crush injury digit III right hand, postoperative wound infection and amputation of the digit	Hyperalgesia to pinprick of the entire R hand and arm, site of amputation scar most severe; dynamic and static mechanoallodynia of the entire R arm; deep somatic sensitization and allodynia of	Temperature asymmetry right hand colder than left; dusky cyanosis of the right hand > left; livedo reticularis right forearm > left; color	Edema > left ha hyperhi right up extremi swelling increase and dep

			forearm and upper arm musculature; joint pain in the hand with movement	change right hand variable with emotional stress, cold and exercise	
	Clinical criterion factors that were positive in right face and right leg; left arm Additional features Positive Tinel signs bilaterally in supra clavicular fossa; Arcade of Frohse, pronator canal, cubital tunnel and carpal tunnel; spread of cold stimulus approximately 12 inches from the hand up the arm; spread of pinprick from the R			Right face (V1-V3) erythematous, warmer than leg	Edema hypergi face, rig left arm

	hand to the ipsilateral face on the R			
No. 14 19 yo male CRPS 84 months Baseline Pain NRS 9 ASA Class II	Sprain injury of the right hand	Hyperalgesia to pinprick over the entire right upper quadrant; spontaneous burning pain in right brachial plexus distributions; chronic deep somatic aching pain; evoked paroxysmal pain in right brachial plexus distributions; mechanical, dynamic and static tactile allodynia of the brachial plexus distributions and V1-V3	Temperature asymmetry, the right hand and arm warmer than the left; erythema of the right arm and face to a greater degree than the left; erythema increased with provocative maneuvers of stress and cold	Edemat and fac hyperhi arm an tightnes tissues forearm swollen severe e
	Clinical criterion factors in other area of CRPS involvementAdditional features Spreading pain from a		Right face (V1-V3) erythematous	Edema dorsum forearm the left

	cold stimulus 6–7 inches from site of application right side; spreading pain from pinprick stimulus fromthe arm to the face			
No. 15 36 yo female CRPS 60 months Baseline Pain NRS 9 ASA Class II	Paravenous IV line infiltration of the left forearm	Hyperalgesia to pinprick over the entire left upper extremity; spontaneous burning pain over the entire left upper quadrant including neck, face, arm and chest (abdomen spared); mechanical tactile dynamic and static allodynia over the left upper quadrant and face; triceps, forearm muscles; cold allodynia over the left upper quadrant including the neck and face; small and large	Temperature asymmetry left upper quadrant > than right; redness of the left upper extremity and face (primarily V2-V3); erythema increased with provoking factors of stress	Edema arm and hyperhi face, ar edema areas va emotion positior

		joint pain with movement		
	Clinical criterion factors in other area of CRPS involvement	Right upper trunk brachial plexus; left leg (mechanical and thermal allodynia); right arm, hyperalgesia to pinprick and mechanoallodynia (static and mechanic)		
	Additional features Positive Tinel signs at supraclavicular fossa, pronator canal, cubital tunnel and Arcade of Frohse; spreading pain from cold stimulus and pinprick from the left hand to face			
No. 16 25 yo female CRPS 25 months	Arnold Chiari repair operation; traction of the brachial plexus left shoulder	Hyperalgesia to pinprick over the entire left upper quadrant;	Temperature asymmetry left arm, face and hand	Edema arm; sw asymm hyperhi

Baseline Pain NRS 9 ASA Class II		spontaneous burning and lancinating pain left brachial plexus distributions; evoked tingling pain with movement; mechanical, dynamic and static allodynia in brachial plexus distributions	warmer than right; erythema left arm and face; color change always present became more evident with cold and emotional stress	L arm a extremi always evoked degree depend
	Clinical criterion factors in other areas of CRPS involvement Additional features Positive Tinel signs at supraclavicular fossa, neurovascular bundle, Arcade of Frohse and pronator canal; cold allodynia and pinprick stimulus spread from the hand to the shoulder and face		Left face (V1-V3) erythematous and warmer	Left fac edemat slight h
No. 17 48 yo female CRPS 72	Extension/distention trauma of the right hand	Hyperalgesia to pinprick of the right arm in a	Temperature asymmetry, right arm	Edema sweatin right > l

months Baseline Pain NRS 8.5 ASA Class II		regional distribution; spontaneous burning pain, deep ache, tingling of right arm; evoked lancinating pain with movement; dynamic and static mechanoallodynia of the right arm; deep somatic sensitization of right arm; small joint pain of the right hand; cold allodynia of the right arm	warmer than the left; minimal erythema of the right hand; color change increased with use, dependency and temperature change	minima (increas with de use
	Clinical criterion factors in other areas of CRPS involvement Additional features Positive Tinel signs supra and infraclavicular fossa; neurovascular bundle, pronator canal;		Right face (V1-V3) erythematous and warmer and upper thigh of the right leg warmer than left	Right fa edemat slight h

	spread of pinprick stimulus from the right hand to the right arm and face (V2)			
No. 18 41 yo female CRPS 84 months Baseline Pain NRS 9 ASA Class II	Motor vehicle accident; extension/flexion injury of the brachial plexus on the right	Hyperalgesia to pinprick right arm in a regional distribution; spontaneous burning pain; deep somatic pain; joint pain of the right hand; evoked tingling and hand pain with movement; dynamic and static mechano allodynia of all brachial plexus distributions of the right upper extremity; cold allodynia and heat allodynia right arm and hand > than the shoulder	Temperature asymmetry right arm colder than left; erythema of right arm and hand; color change varies throughout the day; at times spontaneously and at other times by emotional stress; movement and temperature change	Swelling > ventra hand; sv arm and hyperhi than lef extremi increase use
	Clinical criterion factors in other areas of CRPS involvement	Right face (V1-V3) hyperalgesia and mechanoallodynia	Warmer and erythematous right face	Right fa edemat hyperhi

		(dynamic and static)		
	Additional features Spreading pain from pinprick and cold stimuli from the hand to entire extremity and to contralateral face; positive Tinel signs supra and infraclavicular fossa, neurovascular bundle, Arcade of Frohse, pronator canal, cubital tunnel left > right arm			
No. 19 14 yo female CRPS 7 months Baseline Pain NRS 9 ASA Class III	Brown recluse spider bite of the inner right thigh	Hyperalgesia to pinprick of the entire right leg in a regional distribution; most severe surrounding the area of the spider bite; spontaneous burning pain of the entire thigh; severe burning in the six inches surrounding the	Temperature asymmetry right leg warmer than the left; erythematous right leg; fluctuating color change due to activity, cold and emotional stress	Edema leg (thig leg); hyp of right constar

	envenomation site; deep somatic pain; joint pain at the knee; tactile and dynamic mechano allodynia of the right leg; cold allodynia most severe six inches surrounding the site of envenomation but affecting the entire thigh; deep somatic sensitization of all muscles of the thigh	
Clinical criterion factors in areas other than primary CRPS region	Right face; right arm; right leg spontaneous pain, mechanoallodynia (Static and dynamic) and thermoallodynia to cold stimuli	Right face; right arm; right leg erythematous
Additional features Positive Tinel sign of the sciatic nerve in the		

	right sciatic notch; posterior popliteal positive Tinel sign on the right; abnormal spreading pain from cold or pinprick stimuli up the entire leg if the patient receives the stimulus near the site of the original injury			
No. 20 33 yo female CRPS 63 months Baseline Pain NRS 9 ASA Class II	Tibial torsion fracture; osteosynthesis operation, left lower leg	Hyperalgesia to pinprick left knee and lower leg; spontaneous burning pain, deep ache of muscles and joints; provoked lancinating pain with movement or weight bearing; mechanical and thermal allodynia left leg	Temperature asymmetry; left leg colder than right; slight erythema of the left foot; fluctuation of color change with movement and weight bearing of left foot	Edema extremi knee (m the foot asymm leg > th hyperhi fluctuat with exe and em

Criterion factors in other than primary area of CRPS Additional features Spreading pain from cold stimuli from foot to the knee; and from pinprick stimuli from the foot to the left face	Left face (V1-V3), left arm; right leg spontaneous pain, mechanoallodynia (static and dynamic) and thermoallodynia to cold stimuli	Left face (V1-V3); right leg erythematous; cyanotic buish right leg

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