Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine

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A B S T R A C T

A double-blind placebo-controlled crossover trial was used to determine the effects of topical ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, on the sensory disturbances in 20 patients with complex regional pain syndrome (CRPS). On two occasions separated by at least one week, sensory tests to light touch, pressure, punctate stimulation, light brushing and thermal stimuli were performed in the symptomatic and contralateral limb and on each side of the forehead before and 30 min after 10% ketamine cream was applied to the symptomatic or healthy limb. Venous blood for the plasma estimations of ketamine and norketamine was obtained 1 h after application of the creams. Ketamine applied to the symptomatic limb inhibited allodynia to light brushing and hyperalgesia to punctate stimulation. Systemic effects of the ketamine are unlikely to account for this as the plasma levels were below detectable limits. As touch thresholds were unchanged, NMDA receptors may contribute to the sensory disturbances in CRPS via actions at cutaneous nociceptors. Allodynia and hyperalgesia were detected in the ipsilateral forehead to a range of stimuli (brushing, pressure, punctate stimulation, cold, heat, and warmth). In several patients, ketamine treatment of the symptomatic limb inhibited allodynia to brushing the ipsilateral forehead, suggesting that the mechanism that mediates allodynia in the symptomatic limb contributed to allodynia at more remote sites. The present study shows promise for the use of topical ketamine as opposed to parenteral and oral forms which often result in undesirable side effects.

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1. Introduction

Complex regional pain syndrome (CRPS) can develop after apparently trivial injury and is often associated with widespread sensory disturbances [21,64,77]. Unfortunately, the treatment of neuropathic pain states, including CRPS, remains a significant challenge [19]. Moreover, many of the commonly used orally administered drugs can cause significant central side effects such as somnolence and cognitive impairment with loss of patient compliance [30,33]. A number of topical applications have been tried for neuropathic pain states, targeting peripheral receptor systems and pain mediators, but with mixed success [16,17,36,39–41,47,48,53,59,79,84,89,94,97].

Glutamatergic mechanisms are widely involved in excitatory neurotransmission, including nociception [7,68,88]. Of particular importance is the involvement of N-methyl-D-aspartate (NMDA) receptors in chronic pain states, including CRPS. As all major groups of glutamate receptor are found on nerve fibres in peripheral tissues [10], it would appear logical to attempt local peripheral block of NMDA receptors to reduce allodynia in CRPS. The general anaesthetic agent ketamine [18], and its major metabolite norketamine, have a significant non-competitive blocking action on NMDA receptors [1,24]. Subanaesthetic dosage of ketamine provides worthwhile analgesia both in acute, postoperative and chronic pain states [4]. Trials of the use of ketamine in the treatment of neuropathic pain states have largely revolved around its intravenous administration [2,3,5,11,25–27,29,34,37,42,49–51,54,69,71,80,82,93] but intramuscular [35] and subcutaneous infusions have also been tried [25,67,70]. Alternative routes of administration have included epidural [85], intrathecal [96], placement adjacent to the sympathetic chain [83], oral [15,31,75,91] and topical application [12,32,41,57,60,61,73,74,81,90]. Several randomised, double-blind, placebo-controlled studies have reported on the reduction of allodynia following intravenous administration of ketamine [7,25,28,29,65] but literature on the topical use of ketamine is particularly sparse, mostly comprising case studies. To our knowledge, only one group has reported the effects of topical ketamine on pain and hyperalgesia in a double-blind, placebo-controlled trial. In this study neither ketamine 1% nor amitriptyline 2%, either separately or combined, were effective in patients with neuropathic pain, possibly because drug concentrations were suboptimal [60].

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Topical administration aims to deposit drugs with localised activity in the outer layers of skin, thus minimizing systemic absorption and reducing unwanted central side effects [78]. For ketamine, these include vivid dreaming, dysphoria and alteration of cognition. The aim of the current study was to investigate the sensory effects of topical ketamine 10% in CRPS, particularly on allodynia. A double-blind placebo-controlled trial was used with simultaneous plasma estimations of ketamine and its principal metabolite. The sensory effects were investigated in the CRPS-affected limb and also in the forehead, to determine if the effects of ketamine were restricted to the site of application or whether topical ketamine also impeded the hemilateral sensory disturbances associated with CRPS [21].

2. Materials and methods

2.1. Participants

Twenty sequential patients with features of CRPS (6 males, 14 females), attending a small private pain medicine centre, were studied. Each patient met the diagnostic criteria for CRPS [43] and the majority (17) met the more stringent criteria by Harden et al. [38]. Twelve had developed CRPS in an upper limb and eight in a lower limb. CRPS had developed after fractures (five patients), soft tissue injury, or sprain (six patients), surgery or needle insertion (three patients). Four patients had developed pain following infection, clotting, electric shock or anaphylactic reaction. In all, eighteen patients were classified CRPS Type 1 and two patients were classified CRPS Type 2 following direct injuries to an ulnar nerve. The pain had persisted for 2 months to 19.2 years (median duration 18 months). Sensory, autonomic and motor disturbances were reported by patients and noted during the initial physical examination (Table 1). The sensory disturbances to punctate stimulation and brushing in the symptomatic and healthy limbs were determined using the standard tests of sensation described below. The temperature of the first phalanx of each toe was determined in lower limb CRPS patients, whilst the equivalent was obtained in the fingers of patients with upper limb pain, using an infrared skin thermometer (Tempett IR Thermometer, Somedic Sales AB, Sweden) after the patient had rested quietly for at least 20 min in a room maintained at 20 ± 2 °C. The Murdoch University Human Research Ethics Committee approved the study and written informed consent was obtained from each participant.

2.2. Sensory testing

All assessments were performed by the same examiner (LK) on the most hyperalgesic dorsal aspect of the symptomatic limb (lateral or medial hand or foot), as determined at the initial examination. Testing was performed at only one site in each limb to limit the duration of testing and thus decrease any effects of fatigue. If hyperalgesia did not differ between the lateral and medial sites, the lateral site was selected. The equivalent site was tested in the contralateral limb. Sensory testing was also conducted on each side of the forehead to determine remote effects of the ketamine.

2.2.1. Light touch

Threshold to touch was estimated by using thin Von Frey filaments (Senselab Aesthesiometer, Somedic Sales AB, Sweden). With closed eyes, patients indicated the site of stimulation on the symptomatic or healthy limb, once a sensation was detected. The assessment started with mid-range filaments and thicker or thinner filaments were applied as required, until the detection threshold was established for each site. When detection was missed on at least two of three touches, this was determined to be at a level be-

low the threshold for light touch. The participants were required to make similar distinctions for each side of the forehead.

2.2.2. Pressure-pain thresholds

Pressure-pain thresholds (PPT) were assessed with a rounded-tip (1 cm diameter) spring-loaded algometer [22]. Force was applied to each limb in increments of 200 g to a maximum of 2.3 kg or until pain was reported. In the forehead, force was applied in 80 g increments on each side. Some patients did not perceive pain at 2.3 kg. For these participants, a value of 2.3 kg was recorded as the pressure-pain threshold.

2.2.3. Punctate stimulation

Sharpness was rated at each site in response to a single application of a firm nylon bristle (Filament 17, Senselab von Frey Aesthesiometer, Somedic Sales AB, Sweden), which was tolerated by all patients. Ratings were given on a scale from 0 (not sharp) to 10 (stabbing). Sufficient force was applied to bend the bristle for 1 s. Wind-up to punctuate stimulation was investigated with three repeated applications of the bristle at 1-s intervals. The sharpness from the final application was recorded.

2.2.4. Sensations evoked by light brushing

Light stroking with a small brush (3–4 strokes backward and forward) was rated at each site as a normal or abnormal sensation. When the brushing evoked an abnormal sensation, the participants gave a qualitative description of that sensation. The sensations with an element of pain (e.g., sharp, scratching, or uncomfortable sensations) were categorised as allodynia. Because of their disparate quality, the patients were not asked to rate the intensity of these sensations. Dull or numb sensations to brushing were also noted by two patients (Table 1) but were not regarded as allodynia.

2.2.5. Thermal thresholds

A thermal stimulator with a 2 cm diameter circular stimulating area operating on the Peltier principle was used to determine thermal thresholds. The contact probe was applied at a thermoneutral starting temperature of 32 °C. The probe temperature was increased or decreased at a rate of 0.5 °C/s to a maximum of 50 °C or a minimum of 5 °C. The following stimuli were presented sequentially: decreasing probe temperature until a cold sensation was detected; increasing probe temperature until a warm sensation was detected; decreasing probe temperature to the cold pain threshold; and increasing probe temperature to the heat pain threshold. For determination of cold and warm sensory thresholds, the subject was instructed to report as soon as a change of temperature was detected. For cold pain and heat pain thresholds, the subject was instructed to signal the first instance of pain. Some subjects did not detect the cold pain sensations at 5 °C; for these a value of 5 °C was assumed as the cold pain threshold. Similarly, a heat pain threshold of 50 °C was recorded for those who did not perceive heat pain at 50 °C. Stimulation was rotated between each site until all sites had been tested two to four times (two assessments were considered sufficient if differences between presentations were equal to or less than 0.2 °C). The average of the values for each sensation was considered to be the detection threshold for that sensation.

2.2.6. Topical ketamine and placebo

Absorption of topical agents can be influenced by vehicle composition [13]. Pluronic lecithin organogel (PLO), a microemulsion-based gel, was used in the composition of the cream to assist penetration of the stratum corneum of the skin. It is a stable compound that shows no harmful effects when applied for prolonged periods [20,46,95]. The racemic form of ketamine hydrochloride 10% in PLO was used in the ketamine cream (Professional Compounding

Table 1
Sensory, vasomotor/sudomotor and motor/trophic disturbances in CRPS patients.

	Limb	Pain duration (months)	Sensory		Vasomotor/sudomotor				Motor/trophic				
			Hyperalgesia	Allodynia	Temp. sensation	ΔT (°C)	Dyschromia	Hyper-hidrosis	Tremor	Dystonia	Hair growth	Nail growth	Skin changes
1. F, 59	RU	24	Hyperalgesia	**Allodynia**	Cold	0.46	**Flushed**/cyanotic	**Sweats**	**Resting**	**Dystonia**		Fast	
2. F, 35	RU	19	**Hyperalgesia**	**Allodynia**	Hot/cold	0.40		**Sweats**	Intention		**More**	Fast	**Scaly**
3. F, 51	RL	125	**Hyperalgesia**	**Allodynia**	Hot/cold	−0.26	Flushed/**cyanotic**	Sweats			**Less**	Fast	**Scaly**
4. M, 45	LL	6	**Hyperalgesia**	**Allodynia**		0.18	**Cyanotic**	Sweats					
5. F, 54	LU	27	Hyperalgesia	**Allodynia**	Cold	−0.04		Sweats	Resting				**Pale**
6. M, 20	RL	2	**Hyperalgesia**	**Allodynia**	**Cold**	−1.34	**Flushed**/cyanotic	Sweats	**Resting**		**Less**	Fast	**Scaly**
7. F, 27	RL	17	Hyperalgesia	**Allodynia**	**Cold**	−2.96	**Flushed**/cyanotic		Resting				**Yellow**
8. F, 37	LL	3	**Hyperalgesia**	**Allodynia**	**Cold**	−3.82	**Pale**/flushed/cyanotic	Sweats	Resting			Slow	**Mottled**
9. F, 44	LU	26	**Hyperalgesia**	Allodynia	Cold	−0.36	**Pale**/flushed	**Sweats**				Fast	
10. M, 50	RU	230	**Hyperalgesia**	**Allodynia**	hot	−1.14	Flushed	Sweats	Resting		Less	**Dystrophy**	**Glossy**
11. M, 48	LU	23	Hyperalgesia	Allodynia	Cold	−0.37	**Flushed**		**Resting**			Fast/brittle	**Scaly**
12. F, 35	RU	10	**Hyperalgesia**	**Allodynia**	Cold	0.44	Flushed/cyanotic	Sweats	Resting		**Less**	Slow	**Glossy**
13. F, 38	RU	57	**Hyperalgesia**	**Allodynia**	Cold	0.04	**Flushed**/cyanotic	Sweats	Intention			Brittle	**Pigmented**
14. F, 20	LU	2	Hyperalgesia	**Allodynia**	Hot/cold	0.60	**Flushed**	Sweats	**Resting**	**Dystonia**			
15. M, 51	RU	129	**Hyperalgesia**	**Allodynia**	Cold	0.46	**Pale/flushed**	**Sweats**	**Resting**				**Cracks**
16. M, 23	LU	6	**Hyperalgesia**	**Allodynia**	Cold	−0.02	**Flushed**	Sweats	**Intention**		**More**	Fast	**Scaly**
17. F, 31	RU	13	**Hyperalgesia**	**Allodynia**	Hot/cold	0.36		Sweats	**Resting**				Pigmented
18. F, 51	RL	10	**Hyperalgesia**	**Allodynia**	**Hot**	1.00	**Flushed**	Sweats			**Less**	Fast	**Scaly**
19. F, 41	LU	118	Hyperalgesia	**Allodynia**	Hot	0.84	**Flushed**/cyanotic	Sweats	Resting			Slow, **brittle**	
20. F, 36	LL	11	**Hyperalgesia**	**Allodynia**	**Cold**	−3.00	**Flushed**/cyanotic			**Dystonia**			**Scaly**

Symptom history as reported by patients. Signs of disturbances noted during the initial physical examination are italicized in bold. *Limb* LU, left upper extremity; RU, right upper extremity; LL, left lower extremity; RL, right lower extremity. The *sensory disturbances* reported by patients included hyperalgesia, allodynia and numbness. Numbness was reported by all but two patients (Nos. 4 and 10). The sensory disturbances noted during an initial physical examination included hyperalgesia to punctuate stimulation with a firm bristle (a sharpness rating (0–10) of at least 2 higher in the affected than the unaffected limb indicated hyperalgesia) and allodynia to brushing the skin with a light brush (an uncomfortable or painful sensation indicated allodynia). Two patients reported a numb sensation to the brushing (Nos. 9 and 11). *Vasomotor and sudomotor disturbances* reported by patients were asymmetrical temperature sensations, dyschromia and hyperhidrosis. Patients reported whether they perceived their limb to be cold or hot. Four patients reported that the limb would at times appear cold and other times hot. ΔT, temperature asymmetry between the affected and unaffected limb as averaged for the first phalanx of each toe (lower limb patients) or each finger (upper limb patients). Negative values indicate that the affected limb was cooler than the unaffected limb. Swelling was reported by all patients. *A decreased range of movement* was observed and reported by all patients. Other *motor disturbances* reported by patients included weakness (all patients), tremor and dystonia. *Trophic changes* (hair, nails and skin) varied greatly between patients.

Centers of America, 9901 South Wilcrest, Houston, TX, USA). The placebo contained the same PLO vehicle but without the addition of ketamine or any other active ingredient. The two creams were physically indistinguishable to patients and experimenters alike. A subgroup of patients ($N = 5$) attempted to identify the active cream following the trial but did so at a rate no better than chance. The 10% concentration of ketamine was chosen on the basis of pilot tests. For each patient, the active and placebo creams were randomly labelled A or B by the compounding pharmacist. Throughout the trial, access to the randomisation codes was available only to the pharmacist. One of the investigators (LK) applied 0.5 ml of either A or B cream to the symptomatic limb while 0.5 ml of the other cream was applied to the healthy limb. The amount of cream was restricted to minimize any systemic effects but was usually enough to cover the area of testing on the dorsum of the hand or foot as well as the neighbouring medial or lateral side of the appendage.

2.2.7. Blood samples

Venous blood was drawn 1 h after the application of both topical agents for the first 10 patients during their initial trial. The blood was centrifuged for 10 min and the plasma was subsequently stored at −20 °C until it was analysed for concentrations of ketamine and its main metabolite, norketamine [8].

2.2.8. Assay of ketamine and norketamine by high performance liquid chromatography

Plasma (1 ml) was spiked with ephedrine as an internal standard, alkalinised with NaOH, and extracted with t-butyl methyl ether. The organic phase was back extracted into 0.05 M HCl and aliquots of the HCl phase were injected onto the HPLC column. The separation was performed on a Merck Chromolith® Perfor-

mance column (100 mm × 4.6 mm i.d.) using a mobile phase of 6% (v/v) acetonitrile in 50 mM K_2HPO_4 adjusted to pH 2.5 with H_3PO_4. The mobile phase was pumped at 2.5 ml/min and analytes were detected by their UV absorbance at 210 nm. The calibration curves ranging from 1–20 µg/l were linear for both norketamine and ketamine. Intra-day ($n = 5$) and inter-day ($n = 25$) relative standard deviations for both ketamine and norketamine, measured at 5, 50 and 200 µg/l ranged between 14.3% and 4.2%. The limit of quantitation was 1 µg/l for both analytes. The limits of detection were 0.5 and 0.7 µg/l for norketamine and ketamine, respectively.

2.2.9. Trial sequence

The participants underwent two separate sensory assessments with the application of the topical creams, separated by at least 1 week (median 1 week, range 7 days to 23 days) to allow for the metabolic removal of any active ingredients from the skin. The sensory assessments were performed before and 30 min after the application of the topical creams. This timing was determined after pilot testing. To rule out systematic effects of testing, the order of the assessments was randomised between participants. However, the order of the assessments was kept constant within each participant to ensure that the active and placebo conditions were identical.

2.3. Statistical approach

Although some of the score distributions did not fit a normal bell-shaped curve, logarithmic transformations did not necessarily improve the score distribution significantly and generally did not strengthen statistical effects. Therefore, where appropriate, a non-parametric statistical approach was employed. Before the creams were applied, differences in pain and sensory thresholds

between the symptomatic and healthy limbs were investigated with Wilcoxon's matched-pairs signed-ranks test. As analysis of variance generally is robust to violations of normality, the effects of ketamine on limb pain were investigated in Drug (ketamine versus placebo) × Side (symptomatic versus healthy side) × Pre-Post (the change from before to after the application of the creams) analyses of variance. The effect of most interest was the Drug × Side × Pre-Post interaction, as it tested whether ketamine applied to the symptomatic limb inhibited the sensory disturbances in that limb. More generally, the Drug × Pre-Post interaction tested whether ketamine inhibited painful sensations locally when applied to either limb. Wilcoxon's test was employed to investigate significant interactions. For clarity, the effects of ketamine on the sensory disturbances in the forehead were investigated in separate analyses. The association between the sensory disturbances in the symptomatic limb and the ipsilateral forehead was investigated with Spearman's correlation coefficient.

3. Results

3.1. Effect of topical ketamine on the sensory disturbances in the symptomatic limb

Before the creams were applied, the sensory disturbances in the symptomatic limb included allodynia to brushing and hyperalgesia to punctate stimulation and pressure (Table 2). In addition, the touch threshold, assessed with von Frey hairs, was greater in the symptomatic than healthy limb.

The pain in the symptomatic limb averaged $4.9 + 0.5$ on a 0–10 scale (moderately painful), and did not change after the application of the ketamine cream or placebo. Nor did the touch threshold change significantly. Nevertheless, the ketamine cream inhibited allodynia to lightly brushing the symptomatic limb [Drug × Side × Pre-Post interaction, $F(1, 19) = 4.41$, $p = 0.049$] (Fig. 1). Ketamine also inhibited pain evoked by pricking the skin three times with a firm von Frey bristle [Drug × Pre-Post interaction, $F(1, 15) = 10.6$, $p = 0.005$]. The inhibitory effect was greatest when ketamine was applied to the symptomatic limb, but ketamine applied to the healthy limb also inhibited pin-prick sensations slightly in that limb (Fig. 2). The results were similar after the skin was pricked once [Drug × Pre-Post interaction, $F(1, 15) = 3.63$, $p = 0.076$].

The pressure-pain threshold increased in the symptomatic limb after ketamine or placebo cream was applied to the symptomatic limb [Side × Pre-Post interaction, $F(1, 19) = 5.33$, $p = 0.032$] (Fig. 3), and the warmth threshold increased in both limbs when the creams were applied [from $36.1 + 0.9 °C$ to $37.2 + 0.9 °C$, Pre-
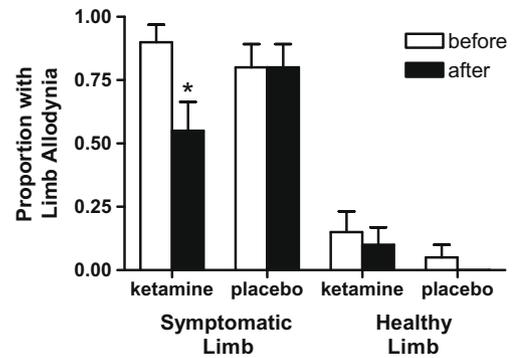

Fig. 1. Proportion of patients with allodynia (±SE) to lightly brushing the symptomatic and healthy limbs before and after the application of 10% ketamine cream and placebo. Allodynia in the symptomatic limb decreased significantly after the ketamine cream was applied (∗$p < 0.01$, Wilcoxon's test).

Post main effect $F(1, 18) = 4.56$, $p = 0.047$]. However, the cool, cold–pain and heat–pain thresholds did not change.

3.2. Effect of topical ketamine on the sensory disturbances in the forehead

Allodynia to brushing and hyperalgesia to punctate stimulation, pressure, cold and heat were detected on the symptomatic side of the forehead before the creams were applied to the limbs (Table 3). In addition, sensitivity to warmth was greater on the symptomatic side of the forehead than on the non-symptomatic side. As shown in Table 4, the sensory disturbances in the forehead were associated with heightened tactile sensitivity in the symptomatic limb, and with hyperalgesia to punctate and thermal stimuli.

In two patients, hypoesthetic sensations were evoked by lightly brushing the symptomatic limb but not the healthy limb, both before and after the ketamine and placebo creams were applied. In one of these patients, brushing the forehead also evoked a similar sensation on the symptomatic side before ketamine was applied to the symptomatic limb; this sensation persisted after the cream was applied. In the other 18 patients, brushing the limbs and forehead provoked either a normal sensation or allodynia. The ketamine cream inhibited allodynia to lightly brushing the forehead [Drug × Pre-Post interaction, $F(1, 19) = 4.75$, $p = 0.042$]. The inhibitory effect was greater when ketamine than placebo was applied to the symptomatic limb (Fig. 4).

Sensitivity to cool and warm sensations decreased slightly on both sides of the forehead after the creams were applied. In particular, the cool detection threshold decreased from $29.7 + 0.3$ to $29.1 + 0.5 °C$ [Pre-Post main effect $F(1, 18) = 4.52$, $p = 0.048$], whereas the warmth detection threshold increased from $34.9 + 0.5$ to $35.3 + 0.5 °C$ [Pre-Post main effect $F(1, 18) = 5.22$, $p = 0.035$]. Conversely, the heat pain threshold decreased from $39.7 + 0.6$ to $39.1 + 0.7 °C$ [Pre-Post main effect $F(1, 18) = 4.79$, $p = 0.042$]. The other sensory thresholds remained unchanged.

3.3. Detection threshold for ketamine and norketamine

Neither ketamine nor norketamine could be detected in any of the plasma samples from the first 10 patients assessed in the trial. Therefore, assays were discontinued for the remainder of the study. The threshold for detection was 0.7 μg/l for ketamine and 0.5 μg/l for norketamine.

4. Discussion

The primary aim of this study was to determine whether topical ketamine inhibited the sensory disturbances in the symptomatic

Table 2
Sensory thresholds and allodynia in the symptomatic and healthy limbs before ketamine and placebo creams were applied to the symptomatic limb.

|	Mean ± SE		Wilcoxon's Z
	Symptomatic	Healthy	
Touch (von Frey units)	10.3 ± 0.9	8.8 ± 0.4	1.99[*]
Pressure (grams)	321 ± 82	1101 ± 116	3.92[***]
Brushing (% with allodynia)	85%	10%	3.04[**]
Sharpness (one application)	5.0 ± 0.7	3.5 ± 0.4	1.92
Sharpness (three applications)	5.7 ± 0.7	3.7 ± 0.4	2.20[*]
Cool threshold (°C)	26.2 ± 1.4	27.9 ± 0.9	1.09
Warmth threshold (°C)	36.6 ± 1.5	36.2 ± 0.6	0.04
Cold-pain threshold (°C)	19.0 ± 2.3	16.0 ± 1.5	1.33
Heat-pain threshold (°C)	39.9 ± 0.9	41.7 ± 0.6	1.91

[*] $p < 0.05$.
[**] $p < 0.01$.
[***] $p < 0.001$.
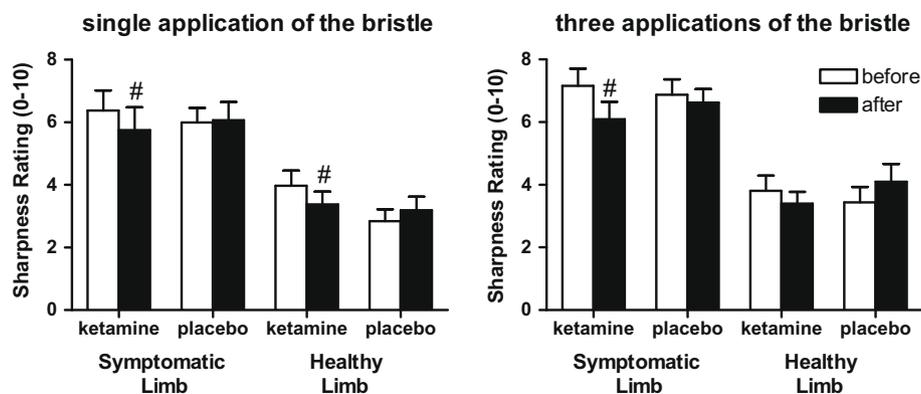
Fig. 2. Sharpness ratings (±SE) to punctate stimulation with a firm von Frey bristle before and after the application of 10% ketamine cream and placebo to the symptomatic and healthy limbs of patients who reported that the bristle induced a sharp sensation in the symptomatic limb (i.e., the rating was greater than 0 before the cream was applied). When the bristle was applied three times at intervals of approximately 1 s ($N = 16$), sharpness ratings decreased after the ketamine cream was applied to the symptomatic limb ($^{\#}p < 0.1$, Wilcoxon's test). Sharpness ratings to a single application of the bristle ($N = 16$) also decreased after the ketamine cream was applied to the healthy limb ($^{\#}p < 0.1$, Wilcoxon's test).

limb of patients with CRPS. We found evidence of this for allodynia and punctate hyperalgesia. The effect was greatest in the symptomatic limb, but ketamine applied to the healthy limb also slightly inhibited sharp sensations in that limb. This appeared to involve a local mechanism because ketamine applied to the healthy limb had no effect on allodynia or punctate hyperalgesia in the symptomatic limb.

Allodynia to brushing the skin and punctate hyperalgesia to sharp stimulation are mediated by sensitized spinal nociceptive and wide dynamic range neurons that receive input from nociceptive A-delta fibres and non-nociceptive A-beta fibres [55,56]. However, our findings suggest that a peripheral mechanism involving NMDA receptors also contributed to these sensory disturbances in our CRPS patients. This mechanism appeared to involve nociceptors because touch thresholds remained unchanged after the topical ketamine treatment. It did not seem to entail a systemic mechanism, because ketamine applied to the healthy limb was ineffective. Moreover, the plasma levels of ketamine and its active metabolite, norketamine, were below the limits of detection after the creams were applied. The plasma levels of ketamine above 150 µg/l have previously been shown to cause pain threshold elevation [9,92]. In our study the threshold for detection of ketamine was substantially lower, at 0.7 µg/l.

NMDA and related ionotropic glutamate receptors are present on peripheral primary afferent neurons in the hairy and glabrous skin of rats [44] and in the hairy skin of humans [52]. These glutamate receptor populations are up-regulated in inflamed human skin [86] and appear to be involved in sensitizing primary afferent nociceptors during inflammation and tissue injury [6,23,45]. As NMDA increases the excitability of thermal nociceptors in animal models of inflammation, [23], we expected that the NMDA antagonist ketamine would inhibit thermal hyperalgesia in our CRPS patients. However, the cold-pain and heat-pain thresholds remained unchanged, implying that NMDA receptor blockade after the topical ketamine treatment was insufficient to decrease the activity of thermal nociceptors within the timeframe of the experiment. A higher concentration of ketamine and a longer delay before testing (to permit greater entry of ketamine into the skin) could be employed to investigate this possibility.

The sensitivity to warmth decreased in both limbs when the creams were applied, and the sensitivity to cool and warm sensations decreased in the forehead. Conversely, the sensitivity to heat pain increased on both sides of the forehead after the ketamine cream was applied to either limb. These changes are more likely to reflect a reduction in perceptual acuity due to fatigue or effects of repeated testing than a systemic effect of ketamine, because neither ketamine nor norketamine was detected in the plasma samples after the creams were applied. The pressure-pain threshold increased in the symptomatic limb irrespective of whether ketamine cream or placebo was applied to the symptomatic limb, possibly for similar reasons.

CRPS is associated with hemisensory disturbances that extend to the face [21,76,77,87]. Rommel et al. [77] reported that sensory impairment to light touch, heat-pain, cool and warmth extended hemilaterally to the face in 30% of patients, whereas facial sensation was symmetrical in patients with sensory impairment limited to the affected limb. Although hypoalgesia in the symptomatic limb was associated with hypoalgesia on the symptomatic side of the forehead in a few of our patients, in most cases allodynia to brushing and hyperalgesia to pressure, punctate stimulation, cold and heat were detected on the symptomatic side of the forehead. In addition, this site was generally more sensitive to warmth than contralaterally. In a previous study of the sensory disturbances in CRPS, we detected hyperalgesia to deep pressure on the symptomatic side of the forehead in the majority of patients; in addition, hyperalgesia to punctate stimulation extended ipsilaterally to the forehead in patients with punctate hyperalgesia in the symptomatic limb [21]. For unknown reasons, a greater range of sensory modalities was disrupted on the symptomatic side of the forehead in the present cohort of patients; this might have been a sampling
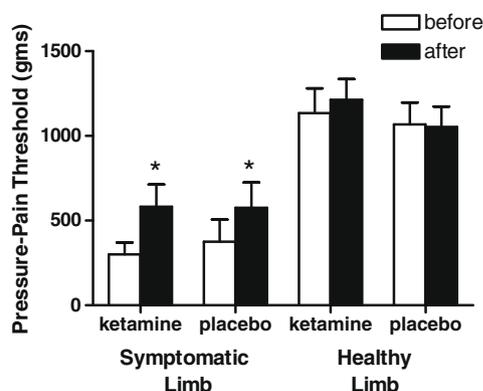

Fig. 3. Pressure-pain thresholds (±SE) in the symptomatic and healthy limbs before and after the application of 10% ketamine cream and placebo. The pressure-pain threshold increased in the symptomatic limb after the ketamine cream was applied either to the symptomatic or healthy limb ($^{*}p < 0.05$, Wilcoxon's test).

Table 3
Sensory thresholds and allodynia in the forehead ipsilateral and contralateral to the symptomatic limb before ketamine and placebo creams were applied to the symptomatic limb.

	Mean ± SE		Wilcoxon's Z
	Ipsilateral side	Contralateral side	
Touch (von Frey units)	5.0 ± 0.7	4.6 ± 0.6	0.49
Pressure (grams)	398 ± 44	524 ± 33	3.38[***]
Brushing (% with allodynia)	60%	5%	3.40[***]
Sharpness (one application)	5.1 ± 0.5	3.7 ± 0.5	2.07[*]
Sharpness (three applications)	4.9 ± 0.5	3.9 ± 0.5	1.94
Cool threshold (°C)	30.3 ± 0.2	29.5 ± 0.5	1.69
Warmth threshold (°C)	34.4 ± 0.4	35.8 ± 0.6	2.66[**]
Cold-pain threshold (°C)	24.7 ± 1.3	22.5 ± 1.3	2.98[**]
Heat-pain threshold (°C)	38.7 ± 0.7	40.8 ± 0.6	2.70[**]

[*] $p < 0.05$.
[**] $p < 0.01$.
[***] $p < 0.001$.

effect or possibly was due to greater precision of measurement as measures were averaged across two sessions in the present study. In general, hyperalgesia in the symptomatic limb was associated with hyperalgesia on the symptomatic side of the forehead, implying mediation by a similar mechanism (e.g., sensitization of spinal or supraspinal nociceptive neurons or disruption of central pain modulating processes).

Curiously, in a few patients ketamine cream applied to the symptomatic limb inhibited allodynia to lightly brushing the forehead. As this was a double-blind placebo-controlled trial and the effect was limited to allodynia, we are confident that this was not due to expectancy or social desirability biases. Clearly, the finding needs to be confirmed in a larger sample of patients. However, it is tempting to speculate that the mechanism that mediated allodynia in the symptomatic limb also contributed to allodynia at more remote sites. For example, disruption of central pain modulating processes might not only increase the excitability of sensitized spinal nociceptors but might also sensitize supraspinal nociceptive neurons that receive convergent hemilateral input (e.g., in the thalamus or somatosensory cortex). Cortical processing of input from the symptomatic limb is disrupted in CRPS [58,62,63,72], with heightened cortical responses to noxious stimuli and shrinkage of representation of the symptomatic limb in the somatosensory cortex. This cortical reorganization might account for referred pain in CRPS [66], and might also explain why a reduction of allodynia in the symptomatic limb after the topical ketamine treatment was sometimes accompanied by a reduction of allodynia on the symptomatic side of the forehead.

The strengths of this study include the double-blind placebo-controlled crossover design, confirmation that ketamine did not enter the bloodstream in detectable concentrations, and the psychophysical assessment of multiple sensory modalities. However, as only one concentration of ketamine was employed, only a single dose was administered, and effects of ketamine were assessed at only one time point, further controlled studies are needed to determine whether the therapeutic effects of ketamine in CRPS are limited to dynamic allodynia and punctate hyperalgesia or also include other forms of hyperalgesia.

Parenteral and oral forms of ketamine have shown some promise for treating the burning pain and exquisite skin hypersensitivity of CRPS and other chronic pain states associated with nerve injury [42]. However, administration by these routes is limited by central side effects such as hallucinations and nightmares. Frequent abuse of ketamine can even cause long-term memory impairment [14]. In open studies of topical ketamine, therapeutic effects appeared to strengthen with repeated applications [12,32,61,74,90]. As topical ketamine is simple and inexpensive to use, and systemic absorption appears to be minimal, further exploration of the therapeutic potential of topical NMDA blockers in CRPS would be welcome.

In conclusion, topical ketamine does not lead to pain reduction in patients with CRPS but does cause a reduction in allodynia, a most unpleasant aspect of this condition. Future treatment protocols could be expanded, to use topical ketamine for patients who manifest allodynia, as an adjunct to sensory-motor retraining programs and other more traditional forms of treatment.

5. Conflicts of interest

None of the authors has a conflict of interest with the contents of this paper.

Table 4
Association (Spearman's rank-order correlation coefficient) between the sensory disturbances in the symptomatic limb and the asymmetry of sensations in the forehead.

| Ipsilateral versus contralateral side of the forehead	Sensations in the symptomatic limb (compared with the healthy limb)								
	Loss of touch	Pressure hyperalgesia	Allodynia to brushing	Sharp – 1 rating	Sharp – 3 rating	Reduced cool sensitivity	Reduced warm sensitivity	Cold hyperalgesia	Heat hyperalgesia
Loss of touch	0.286	0.006	0.029	−0.052	−0.073	−0.187	−0.224	0.118	−0.043
Pressure hyperalgesia	−0.483[*]	0.206	0.220	0.710[***]	0.751[***]	0.447	0.351	0.593[**]	0.408
Allodynia to brushing	−0.390	0.167	0.094	0.278	0.329	0.244	0.313	0.420	0.379
Sharp – 1 rating	−0.669[***]	0.258	−0.021	0.643[**]	0.584[**]	0.616[**]	0.631[**]	0.744[***]	0.707[***]
Sharp – 3 rating	−0.574[*]	0.147	0.085	0.482[*]	0.409	0.614[**]	0.718[***]	0.808[***]	0.745[***]
Reduced cool sensitivity	−0.107	0.037	0.114	−0.030	−0.033	0.240	0.191	0.311	0.426
Reduced warm sensitivity	−0.312	0.294	0.043	0.254	0.272	0.395	0.426	0.242	0.337
Cold hyperalgesia	−0.349	0.363	0.363	0.521[*]	0.530[*]	0.284	0.239	0.679[***]	0.681[***]
Heat hyperalgesia	−0.608[**]	0.336	0.108	0.467[*]	0.451	0.595[**]	0.642[**]	0.660[***]	0.672[**]

[*] $p < 0.05$.
[**] $p < 0.01$.
[***] $p < 0.001$.
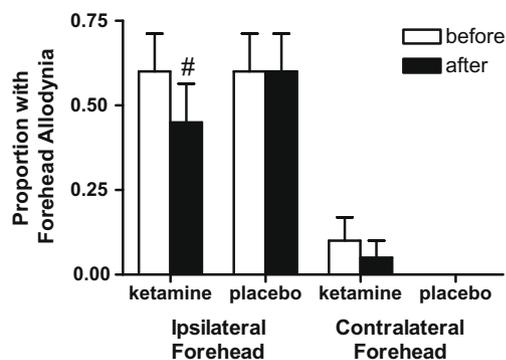
Fig. 4. Proportion of patients with allodynia (±SE) to lightly brushing the forehead ipsilateral or contralateral to the symptomatic limb before and after the application of 10% ketamine cream or placebo to the symptomatic limb. Allodynia on the ipsilateral side of the forehead decreased after the ketamine cream was applied to the symptomatic limb ($^\#p < 0.1$, Wilcoxon's test) but did not change after the placebo cream was applied to the symptomatic limb.

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