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Reduction of Allodynia in patients with Complex Regional Pain Syndrome:

A double-blind placebo-controlled trial of Topical Ketamine

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Abstract

This double-blind placebo-controlled crossover trial aimed to determine the effects of topical ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, on 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 minutes after 10% ketamine cream was applied to the symptomatic or healthy limb. Venous blood for plasma estimations of ketamine and norketamine was obtained one hour after application of the creams. Ketamine applied to the symptomatic limb inhibited allostynia to light brushing and hyperalgesia to punctate stimulation. Systemic effects of the ketamine are unlikely to account for this as plasma levels were below detectable limits. As touch thresholds were unchanged, NMDA receptors may contribute to 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, 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.
Introduction

Complex regional pain syndrome (CRPS) can develop after apparently trivial injury and is often associated with widespread sensory disturbances that can spread to other areas of the body [21, 64, 77]. Unfortunately, the treatment of neuropathic pain states, including CRPS, remains a significant challenge with an unmet need for specific and targeted therapies [19]. Moreover, many of the commonly used orally administered drugs, including the tricyclic antidepressant amitriptyline and anticonvulsant agents such as gabapentin and pregabalin, can cause significant central side effects such as somnolence and cognitive impairment with loss of patient compliance [30; 33].

Glutamatergic mechanisms are widely involved in excitatory neurotransmission in the central nervous system 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; 16; 17; 36; 39; 40; 41; 47; 48; 53; 59; 79; 84; 89; 94; 97], it would appear logical to attempt local peripheral block of NMDA receptors to reduce alldynia in CRPS. The general anaesthetic agent ketamine had been in use for several decades after its clinical introduction [18] before it, and its major metabolite, norketamine, were recognised to 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. A current topical review considers routes of administration and the minimum plasma levels required to alter pain thresholds [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
other parenteral routes have been tried including intramuscular [35] and subcutaneous infusions [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 investigated effects of topical ketamine on pain and hyperalgesia in a double-blind, placebo-controlled trial. Neither ketamine 1% nor amitriptyline 2%, either separately or combined, were effective in patients with neuropathic pain, possibly because drug concentrations were suboptimal [60].

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. 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].

Materials and Methods

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 (5 patients), soft tissue injury, nerve injury or sprain (8 patients), surgery or needle insertion (3 patients). Four patients had developed pain following infection, clotting, electric shock or anaphylactic reaction. The pain had persisted for 2 months to 19.2 years (median duration 15 months).

Sensory, autonomic and motor disturbances were reported by patients and noted during the initial physical examination (Table 1). The distribution and extent of sensory disturbances to punctate stimulation and brushing 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). The Murdoch University Human Research Ethics Committee approved the study and written informed consent was obtained from each participant.

**Sensory testing**

All procedures were carried out in a room maintained at 20 ± 2°C. All assessments were performed by the same examiner (LK) on the most hyperalgesic dorsal aspect of the symptomatic limb (lateral or medial site), 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.
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 below the threshold for light touch. Participants were required to make similar distinctions for each side of the forehead.

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 gm to a maximum of 2.3 kg or until pain was reported. In the forehead, force was applied in 80 gm 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.

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) on a scale from 0 (not sharp) to 10 (stabbing). Sufficient force was applied to bend the bristle for 1 second. Wind-up to punctuate stimulation was investigated with three repeated applications of the bristle at 1-second intervals. The sharpness from the final application was recorded.

Sensations evoked by light brushing. Light stroking with a small brush was rated at each site as a normal or abnormal sensation. When the brush was felt as an abnormal sensation, participants gave a qualitative description of that sensation.

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/sec 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 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.

*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 Centers of America, 9901 South Wilcrest, Houston, Texas, USA). The placebo contained the same PLO vehicle but without the addition of ketamine or any other active ingredient. The two creams were indistinguishable. 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 minimise any systemic effects but was usually enough to cover the area of testing as well as the neighbouring medial or lateral side of the limb.

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

**Assay of ketamine and norketamine by high performance liquid chromatography.** Plasma (1 ml) was spiked with ephedrine as an internal standard, alkalised with NaOH, and extracted with t-butyl methyl ether. The organic phase was back extracted into 0.05M HCl and aliquots of the HCl phase were injected onto the HPLC column. Separation was performed on a Merck Chromolith® Performance column (100 mm x 4.6 mm id) using a mobile phase of 6% v/v acetonitrile in 50 mM K₂HPO₄ adjusted to pH 2.5 with H₃PO₄. The mobile phase was pumped at 2.5 mL/min and analytes were detected by their UV absorbance at 210nm. 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 µg/L, 50 µg/L 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 µg/l and 0.7 µg/l for norketamine and ketamine, respectively.

**Trial Sequence.** Participants underwent two separate sensory assessments with application of the topical creams, separated by at least one 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 minutes 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.

**Statistical Approach**

Before the creams were applied, differences in pain and sensory thresholds between the symptomatic and healthy limbs were investigated with paired t-tests. Effects of ketamine on limb pain were investigated in Drug (ketamine versus placebo) x Side (symptomatic versus healthy side) x Pre-Post (the change from before to after the application of the creams) analyses of variance. The effect of most interest was the Drug x Side x Pre-Post interaction, as it tested whether ketamine applied to the symptomatic limb inhibited sensory disturbances in that limb. More generally, the Drug x Pre-Post interaction tested whether ketamine inhibited painful sensations locally when applied to either limb. Effects of ketamine on sensory disturbances in the forehead were investigated in similar analyses.

**Results**

**Effect of topical ketamine on sensory disturbances in the symptomatic limb**

Before the creams were applied, sensory disturbances in the symptomatic limb included allodynia to brushing and hyperalgesia to punctate stimulation and pressure
In addition, there was a non-significant trend for the touch threshold, assessed with von Frey hairs, to be greater in the symptomatic than healthy limb, and for the heat pain threshold to be lower in the symptomatic than healthy limb. In the group as a whole, cool, warmth and cold pain thresholds were similar in both limbs.

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 x Side x Pre-Post interaction, F(1,19) = 4.41, p = 0.049] (Figure 1). Ketamine also inhibited pain evoked by pricking the skin three times with a firm von Frey bristle [Drug x Pre-Post interaction, F(1,15) = 10.6, p = 0.005]; the inhibitory effect was greatest when ketamine was applied to the symptomatic limb (Figure 2). A similar trend was detected after the skin was pricked once [Drug x Pre-Post interaction, F(1,15) = 3.63, p = 0.076].

The pressure-pain threshold increased in the symptomatic limb after the ketamine cream was applied either to the symptomatic or healthy limb [Side x Pre-Post interaction, F(1,19) = 5.33, p = 0.032] (Figure 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-Post main effect F(1,18) = 4.56, p = 0.047]. However, the cool, cold-pain and heat-pain thresholds did not change.

**Effect of topical ketamine on 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, 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 asymptomatic 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 x Pre-Post interaction, F(1,19) = 4.75, p = 0.042]; the inhibitory effect was greatest when ketamine was applied to the symptomatic limb (Figure 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 °C 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 °C 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 °C to 39.1 ± 0.7 °C [Pre-Post main effect F(1,18) = 4.79, p = 0.042]. The other sensory thresholds remained unchanged.

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.

Discussion
The primary aim of this study was to determine whether topical ketamine inhibited sensory disturbances in the symptomatic 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 is 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, plasma levels of ketamine and its active metabolite, norketamine, were below the limits of detection after the creams were applied. 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]. For example, during inflammation, intraplantar injection of NMDA aggravated mechanical and thermal
hyperalgesia and boosted the excitability of nociceptive afferents in the inflamed rat paw [23]. Conversely, in an animal model of neuropathic pain involving spinal nerve ligation, an intraplantar injection of the non-competitive NMDA antagonist MK-801 into the ipsilateral hind paw shortly before or ten days after the ligation inhibited mechanical hyperalgesia, whereas injection of the same dose of MK-801 into the contralateral hind paw had no effect [45].

In animal models of inflammation, NMDA increases the excitability of thermal nociceptors [23]; thus, 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 peripheral NMDA receptors were not involved in mediating thermal hyperalgesia. Alternatively, NMDA receptor blockade after the topical ketamine treatment may have been 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.

Sensitivity to warmth decreased in both limbs when the creams were applied, and sensitivity to cool and warm sensations decreased in the forehead. Conversely, 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 were detected in plasma samples after the creams were applied. The pressure-pain threshold increased in the symptomatic limb irrespective of whether ketamine was applied to the symptomatic or healthy 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 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 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.
Conflicts of interest

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

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<table>
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<th>Limb</th>
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<th>Vasomotor/Sudomotor</th>
<th>Motor/trophic</th>
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<td>LL</td>
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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. Sensory disturbances reported by patients included hyperalgesia, allodynia and numbness. Numbness was reported by all but two patients (Nos. 4 and 10). 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 abnormal 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. Swelling was reported by all patients. ∆T, 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. 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, skin) varied greatly between patients.
Table 2
Sensory thresholds and allodynia in the symptomatic and healthy limbs before ketamine and placebo creams were applied to the symptomatic limb

<table>
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<th></th>
<th>Symptomatic</th>
<th>Healthy</th>
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<tbody>
<tr>
<td>Touch (von Frey units)</td>
<td>10.3 ± 0.9</td>
<td>8.8 ± 0.4</td>
<td>0.054</td>
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<tr>
<td>Pressure (grams)</td>
<td>321 ± 82</td>
<td>1101 ± 116</td>
<td>&lt;0.001</td>
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<td>Brushing (% with allodynia)</td>
<td>85%</td>
<td>10%</td>
<td>&lt;0.001</td>
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<td>Sharpness (one application)</td>
<td>5.0 ± 0.7</td>
<td>3.5 ± 0.4</td>
<td>0.072</td>
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<tr>
<td>Sharpness (three applications)</td>
<td>5.7 ± 0.7</td>
<td>3.7 ± 0.4</td>
<td>0.015</td>
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<td>Cool threshold (°C)</td>
<td>26.2 ± 1.4</td>
<td>27.9 ± 0.9</td>
<td>0.328</td>
</tr>
<tr>
<td>Warmth threshold (°C)</td>
<td>36.6 ± 1.5</td>
<td>36.2 ± 0.6</td>
<td>0.847</td>
</tr>
<tr>
<td>Cold-pain threshold (°C)</td>
<td>19.0 ± 2.3</td>
<td>16.0 ± 1.5</td>
<td>0.164</td>
</tr>
<tr>
<td>Heat-pain threshold (°C)</td>
<td>39.9 ± 0.9</td>
<td>41.7 ± 0.6</td>
<td>0.071</td>
</tr>
</tbody>
</table>
Table 3

Sensory thresholds and allodynia on each side of the forehead before ketamine and placebo creams were applied to the symptomatic limb

<table>
<thead>
<tr>
<th></th>
<th>Mean ± S.E.</th>
<th>Other Side</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptomatic Side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Touch (von Frey units)</td>
<td>5.0 ± 0.7</td>
<td>4.6 ± 0.6</td>
<td>0.561</td>
</tr>
<tr>
<td>Pressure (grams)</td>
<td>398 ± 44</td>
<td>524 ± 33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Brushing (% with allodynia)</td>
<td>60%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sharpness (one application)</td>
<td>5.1 ± 0.5</td>
<td>3.7 ± 0.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Sharpness (three applications)</td>
<td>4.9 ± 0.5</td>
<td>3.9 ± 0.5</td>
<td>0.037</td>
</tr>
<tr>
<td>Cool threshold (°C)</td>
<td>30.3 ± 0.2</td>
<td>29.5 ± 0.5</td>
<td>0.073</td>
</tr>
<tr>
<td>Warmth threshold (°C)</td>
<td>34.4 ± 0.4</td>
<td>35.8 ± 0.6</td>
<td>0.020</td>
</tr>
<tr>
<td>Cold-pain threshold (°C)</td>
<td>24.7 ± 1.3</td>
<td>22.5 ± 1.3</td>
<td>0.017</td>
</tr>
<tr>
<td>Heat-pain threshold (°C)</td>
<td>38.7 ± 0.7</td>
<td>40.8 ± 0.6</td>
<td>0.007</td>
</tr>
</tbody>
</table>
Table 4

Association (Pearson’s correlation coefficient) between sensory disturbances in the symptomatic limb and asymmetry of sensations in the forehead

<table>
<thead>
<tr>
<th>Ipsilateral side of the forehead</th>
<th>Sensations in the symptomatic limb (compared with the healthy limb)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Loss of touch</td>
</tr>
<tr>
<td>Loss of touch</td>
<td>.275</td>
</tr>
<tr>
<td>Pressure hyperalgesia</td>
<td>-.467*</td>
</tr>
<tr>
<td>Allodynia to brushing</td>
<td>-.377</td>
</tr>
<tr>
<td>Sharp – 1 rating</td>
<td>-.533*</td>
</tr>
<tr>
<td>Sharp – 3 rating</td>
<td>-.388</td>
</tr>
<tr>
<td>Reduced cool sensitivity</td>
<td>.040</td>
</tr>
<tr>
<td>Reduced warm sensitivity</td>
<td>-.258</td>
</tr>
<tr>
<td>Cold hyperalgesia</td>
<td>-.350</td>
</tr>
<tr>
<td>Heat hyperalgesia</td>
<td>-.526*</td>
</tr>
</tbody>
</table>

* p<0.05; ** p<0.01; *** p<0.001
**Figure legends**

**Figure 1.** Proportion of patients with allodynia (± S.E.) 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).

**Figure 2.** Sharpness ratings (± S.E.) 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 second (N = 16), sharpness ratings decreased after the ketamine cream was applied to the symptomatic limb (* p<0.05). Sharpness ratings to a single application of the bristle (N = 16) also decreased after the ketamine cream was applied to the healthy limb (# p ≤ 0.06).

**Figure 3.** Pressure-pain thresholds (± S.E.) 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).

**Figure 4.** Proportion of patients with allodynia (± S.E.) to lightly brushing the symptomatic and non-symptomatic sides of the forehead before and after the application of 10% ketamine cream and placebo to the symptomatic limb. Allodynia on the symptomatic side of the forehead decreased after the ketamine cream was applied to the symptomatic limb (# p = 0.083) but did not change after the placebo cream was applied to the symptomatic limb.
Figure 2
Figure 4

Proportion with Forehead Allodynia

ketamine  placebo  ketamine  placebo

Symptomatic Limb  Healthy Limb

# before  after