CLINICAL REPORT

A Novel Compound Analgesic Cream (Ketamine, Pentoxifylline, Clonidine, DMSO) for Complex Regional Pain Syndrome Patients

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■ **Abstract**

Background: Evidence suggests that complex regional pain syndrome (CRPS) is a manifestation of microvascular dysfunction. Topical combinations of α2-adrenergic receptor agonists or nitric oxide donors with phosphodiesterase or phosphatidic acid inhibitors formulated to treat microvascular dysfunction have been shown to reduce allodynia in a rat model of CRPS-I. Driven by these findings, we assessed the outcomes of CRPS patients treated with a compound analgesic cream (CAC) consisting of ketamine 10%, pentoxifylline 6%, clonidine 0.2%, and dimethyl sulfoxide 6% to 10%.
Methods: An audit was conducted on 13 CRPS patients who trialed the CAC. A detailed report was compiled for each patient which comprised baseline characteristics, including CRPS description, previous treatments, and pain scores (numerical pain rating scale; 0 to 10). Recorded outcomes consisted of pain scores, descriptive outcomes, and concurrent medications/treatments, for which basic analysis was performed to determine the effectiveness of the CAC. Case reports are presented for 3 patients with varying outcomes.
Results: Nine patients (69%) reported pain/symptom reduction (4.4 ± 2.1 vs. 6.3 ± 1.9) with use of the CAC. Six patients reported sustained benefits after 2 months of CAC use, and 2 patients reported complete resolution of pain/symptoms: one had early CRPS-I and the other received a partial CRPS diagnosis. An otherwise medication refractory and intolerant patient found partial benefit with the CAC.
Conclusions: These results demonstrate promise for this topical combination as a useful treatment in multimodal therapy for patients with CRPS, with the potential to resolve pain/symptoms in early CRPS patients. ■

Key Words: complex regional pain syndrome, topical analgesic, pentoxifylline, clonidine, ketamine, NO donor, dimethyl sulfoxide, nitric oxide complex regional pain syndrome

INTRODUCTION

Complex regional pain syndrome (CRPS) is a progressive multifactorial condition that usually develops in a limb following trauma or surgery.[1] The Budapest criteria for CRPS characterize the disorder according to symptoms of constant pain, allodynia, hyperalgesia, edema, abnormal sweating, abnormal changes in blood flow, skin color, skin temperature, and hair/nail growth, as well as motor disturbances.[1] In the absence of peripheral nerve injury, CRPS is type I, whereas CRPS-II denotes direct nerve injury.[2] A complete understanding of the underlying etiology of CRPS is lacking, although it is evident that CRPS invokes multiple pathological mechanisms, including vasoconstriction, deep muscle ischemia, free radical generation, peripheral nerve sensitization, and inflammation or production of pro-inflammatory cytokines in peripheral tissue and cerebrospinal fluid.[3]

Complex regional pain syndrome remains a difficult and frustrating condition to treat, and although a wide

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range of treatments have been documented in the literature, many have low clinical response rates.[2] In practice, a multimodal treatment regime is typically applied to achieve successful control or resolution of pain and symptoms, especially in the first 12 months after onset where the degree of chronicity of the symptoms may be less marked.[4,5] The regional nature of CRPS lends itself to incorporating regional treatment. The delivery of therapeutic agents to the subcutaneous tissues via skin absorption may enable the pathological mechanisms to be dampened or reversed. Topical analgesics have become popular agents in the multimodal treatment of CRPS. By administering analgesics topically, higher and more effective concentrations can be delivered locally to the affected site, while systemic concentrations remain low, thus minimizing side effects.[6] A range of topical compound analgesic creams (CACs) have been used for focal neuropathic pain conditions for a number of years[7–12]; however, there is no current consensus on what represents an optimal CAC for neuropathic pain, and many practitioners have derived their clinical practice from empirical observation.[13]

Ragavendran et al.[14] hypothesized that by combining agents aimed at correcting affected tissue functions, namely microvascular function, inflammation, and oxidative stress,[3,15–18] one could effectively reduce allodynia in CRPS. They tested topical combinations consisting of an α2-adrenergic (α2A) receptor agonist or nitric oxide (NO) donor with a phosphodiesterase (PDE) or phosphatidic acid (PA) inhibitor in a rat model of CRPS-I. Significantly reduced allodynia was observed with a combination of clonidine, pentoxifylline, and a NO donor (S-nitroso-N-acetylpenicillamine). Clonidine, an α2A receptor agonist, has been long used topically for nociceptive and neuropathic pain with its ability to inhibit inflammatory cytokines, modulate sensory neurons, and increase blood flow.[13,19–21] Pentoxifylline is a PDE4 inhibitor with various therapeutic effects, such as increasing blood flow[22,23] and inhibition of inflammatory cytokine production.[24,25] Various NO donors have previously been used to treat neuropathic pain.[26]

We conducted a retrospective review of patients who were prescribed a combination analgesic cream consisting of ketamine, clonidine, pentoxifylline, and dimethyl sulfoxide (DMSO). Ketamine has a history of efficacy in CACs for CRPS,[10–12,27] and topical ketamine, in particular, has been shown to reduce allodynia as well as hyperalgesia in CRPS patients; hence it was added to the combination. DMSO was chosen as the NO donor as it too has a long history of use in CACs for CRPS with positive results.[2,28,29] As a free radical scavenger, DMSO is theorized to combat oxygen radical overproduction resulting from excessive inflammation.[30] DMSO is also known to enhance topical drug penetration.[31] Furthermore, a case study by Kopsky and Hesselink[9] showed that a stepped-combination of topical amitriptyline, followed by ketamine and lastly DMSO, significantly reduced pain and improved quality of life in a patient treated for 5 months with no side effects.

METHODS

Patients

With approval from the Bellberry Human Research Ethics Committee (2014-07-378), a retrospective chart review was conducted on 13 patients presenting with CRPS at a multidisciplinary pain clinic who had trialed a CAC consisting of ketamine 10%, pentoxifylline 6%, clonidine 0.2%, DMSO 6% to 10%. The cream was to be applied 3 times daily. Patients were followed up in consultation as part of routine clinical practice. Patient consent for use of information for research and quality assurance programs was obtained.

Data Collection

A detailed report was made for each patient from the physician's charts consisting of demographic information, pain description, CRPS duration, previous medications, and procedures, pre-CAC pain scores, duration of CAC treatment, pain outcomes, and concurrent analgesic medications and/or treatments. Pain scores were self-reported; patients rated their average, best, and worst pain on a numerical pain rating scale (NPRS) of 0 to 10, where 0 denotes "having no pain" and 10 denotes "the worst pain imaginable".

Data Analysis and Case Reports

Analysis was primarily descriptive due to the nature of the data. Basic analysis (means, standard deviations, counts, and percentages) was performed within Microsoft® Office Excel (Redmond, WA, U.S.A.) where appropriate. Case reports were written for 3 patients with detailed follow-up records and varying, interesting outcomes.

Table 1. Summary of Baseline Characteristics of Complex Regional Pain Syndrome (CRPS) Patients Prior to Trialing the Compound Analgesic Cream (CAC)

Baseline Characteristics	*N*/Mean
Gender	
Male	3
Female	10
Age	46.6 ± 13.3
CPRS type	
I	11
II	0
Not otherwise specified	2
CRPS Region	
Upper limb	7
Lower limb	6
CPRS Duration	
≤ 1 year	7
> 1 year	6
Prior analgesic medications tried	
None	0
1	2
2	3
≥ 3	8
Pre-CAC NPRS	
Average	6.3 ± 1.9
Best	5.0 ± 2.6
Worst	8.8 ± 1.5

Data are presented as number of patients or means ± SD. *N* = 13.

RESULTS

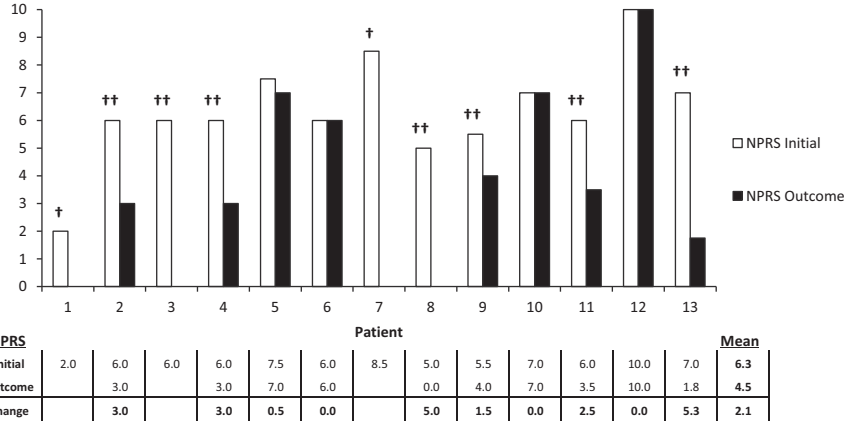
Patient Demographics

The study consisted of 3 males and 10 females, with a mean age of 46.6 (± 13.3). Eleven patients were diagnosed with CRPS type I, and 2 were diagnosed with CRPS "not otherwise specified", which was used to describe patients with some CRPS symptoms, but that do not completely satisfy the Budapest criteria for CRPS. These patients are at risk of converting to the complete syndrome. Seven patients had CRPS of the upper limb, and 6 had CRPS-I/"CRPS—not otherwise specified" of the lower limb. Duration of CRPS ranged from 1.5 months to 7 years (5 patients ≤ 6 months, 2 patients ≤ 1 year, 6 patients > 1 year). Mean NPRS initial was 6.3 (average), 5.0 (best), 8.8 (worst). A summary of patient characteristics and pretreatment information is presented in Table 1.

Treatment Outcomes

Nine patients (69%) reported pain reduction with CAC treatment (Figure 1). Seven of these patients reported major benefits; 6 of these were taking an additional opioid analgesic (3 with pregabalin and 2 with tapentadol) and 1 was taking prednisone (Table 2). Two patients reported resolution of pain or symptoms. One of these patients had early CRPS-I of the hand that had been present for only 6 weeks and was also taking prednisone + alendronate (patient #13), and the other was diagnosed with "CRPS—not otherwise specified" of the calf and experienced complete resolution of symptoms in combination with a thromboembolism-deterrent (TED) stocking and pregabalin (patient #8). Another patient reported elimination of surface hypersensitivity with CAC + pregabalin treatment (patient #4).

Ten patients had reported outcome pain scores (NPRS) relating to CAC treatment. The mean change in NPRS was −2.1 ± 2.0 (Figure 1), while the mean change in NPRS for the 6 patients that reported treatment benefits was −3.4 ± 1.5. The mean time between CAC commencement and follow-up for pain outcomes was 6.1 weeks (± 2.7). Four patients ceased use of the CAC due to 0 or minimal benefit, and 1 patient ceased use of the CAC following success of a dorsal root ganglion stimulation trial. Six patients reported sustained benefits in subsequent follow-ups of ≥ 2 months of CAC use. One patient reduced CAC use and found reduced benefit after 6 months.



NPRS														Mean
Initial	2.0	6.0	6.0	6.0	7.5	6.0	8.5	5.0	5.5	7.0	6.0	10.0	7.0	6.3
Outcome		3.0		3.0	7.0	6.0		0.0	4.0	7.0	3.5	10.0	1.8	4.5
Change		3.0		3.0	0.5	0.0		5.0	1.5	0.0	2.5	0.0	5.3	2.1

Figure 1. Average numerical pain rating scale (NPRS) scores: pre-compound analgesic cream (initial) and at follow-up (outcome). Outcome scores were not available/recorded for all patients (some outcomes were purely descriptive). (†Denotes partial benefit(s) reported; ††denotes major benefit(s) reported; mean follow-up time = 6.1 ± 2.7 weeks.)

Table 2. Summary of Compound Analgesic Cream (CAC) Outcomes

Outcomes	*N*/Mean
Follow-up time (weeks)	6.1 ± 2.7
Descriptive outcomes	
No benefit	5
Partial benefit	2
Major benefit	6
Outcome NPRS*	
Mean	4.5 ± 2.1
Mean change (all; *N* = 10)	2.1 ± 2.0
Mean change (benefit; *N* = 6)	3.4 ± 1.5
Concurrent analgesic medications	
0	3
1	8
2	0
≥ 3	2
Effective concurrent treatments†	
None/none tried	7
Analgesic medications	4
Sympathetic nerve blocks	2
Dorsal root ganglion stimulator	1
TED Stocking	1

*Mean change (all) = change in NPRS for all patients with recorded scores (*N* = 10), mean change (benefit) = change in NPRS for patients with positive outcomes (*N* = 6).
†Some patients found success with a combination of CAC and these treatments (ie, TED stocking + analgesic medications; DRGS + analgesic medications).

It is possible that a trend exists for a greater likelihood of patients with a CRPS duration of less than 1 year to report positive outcomes with use of the CAC (6/7 patients of < 1 year CRPS duration), as well as for patients with CRPS of the upper limb (6/7 patients with CRPS of the upper limb). Three of the 4 patients who reported no benefit had CRPS of the lower limb with a > 1-year CRPS duration.

Case 1 (Patient No. 4)

A 47-year-old male patient presented to the clinic with CRPS-I of the upper limb. He experienced a traumatic injury 4 months prior in which the fifth finger was amputated and the fourth finger partially severed. He had since been left with persistent pain over the stump of the fifth and fourth fingers with occasional phantom pain, and pain on the third finger with movement. He was taking oxycodone 5 mg at night without benefit. The pain was described as alternating between burning, shooting or dull, and when severe, radiating to the elbow or shoulder. The fourth finger had significant swelling and both fourth and fifth were warm, abnormal sweating and positive for brush allodynia and punctate mechanical hyperalgesia.

He was prescribed pregabalin 75 mg bid to titrate slowly to 300 mg bid for the neuropathic component of his pain, vitamin C 500 mg qid, which aids in prevention of CRPS spread, and the CAC to apply tid. After 3 weeks on this regimen, the patient reported 50% to 70% reduction in pain and elimination of surface hypersensitivity. A further 6 weeks later, the patient reported 50% reduction of pain, except for on the fourth and fifth fingers. The physician suspected direct peripheral nerve injury related to the initial surgical repair, which would explain neuropathic pain independent of the CRPS pain. In attempt to alleviate the remaining pain, the patient underwent a series of stellate ganglion blocks with similar success, followed by a pulsed radiofrequency neurotomy of the digital nerves 7 weeks later without improvement. At this point, he was had discontinued the CAC and was only taking pregabalin at night. The patient has since been awaiting reoperation of the fingers by an orthopedic surgeon.

Case 2 (Patient No. 7)

A 60-year-old female patient with preexisting CRPS-I of the right upper limb returned to the clinic with ongoing pain following a carpal tunnel release and ulnar nerve release. The pain was present in the wrist, radiating outwards to the fingers and elbow with activity. She had brush allodynia, punctate mechanical hyperalgesia, and a positive pinch rolling test. She was taking 2 tablets of paracetamol 665 mg tid for her pain. She was also suffering from anxiety and depression with pain induced insomnia. For these indications, she was prescribed agomelatine 25 mg to take at night and the cream, to apply 3 times a day. The patient failed to commence the CAC immediately, and in the meantime trialed several psychotropic medications, including amitriptyline 12.5 mg and mirtazapine 30 mg, with intolerable side effects and severe uncontrolled pain. A trial of tapentadol 100 mg titrated to 250 mg did not improve pain and caused minor side effects.

After trialing the CAC for 6 weeks, the patient reported partial benefit, after which she was directed to discontinue use in order to ascertain the degree of its provided benefit. The patient was then trialed on a combination of duloxetine 30 mg daily and sodium valproate 200 mg bid and, once again, experienced severe side effects and hence ceased this combination. At a later consultation, the patient reported a pain flare and was prescribed prednisone in combination with orphenadrine 100 mg as a skeletal muscle relaxant. She found no benefit from the prednisone and experienced side effects on the orphenadrine and hence ceased these medications. After approximately 5 months of initially trialing the CAC, the patient recommenced use of it and

found that it helped focal pain on the elbow. This partial benefit was continuing at a follow-up another 3 months later. In this time, she had also trialed gabapentin 300 mg at night and alprazolam without benefit. The patient is since under consideration for further surgery or a trial of spinal cord stimulation.

Case 3 (Patient No. 8)

A 43-year-old female patient presented to the clinic with right distal leg pain following a fall injury 5 months prior. The injury resulted in a large hematoma that was resolved with evacuation and drainage. She had been left with persistent stabbing pains, numbness, pressure induced allodynia, and rapid hair growth over the lateral aspect of the calf. There was subtle edema and hemosiderin deposit present. No burning pain, brush allodynia or color, temperature, sweating, or swelling changes were present. Ultrasound showed minor heterogeneity of the subcutaneous fat. She was diagnosed with neuropathic pain, possibly CRPS, due to peripheral nerve injury and was therefore diagnosed with "CRPS—not otherwise specified". She was not taking any medication at the time of consultation; co-codamol and ibuprofen had provided only partial benefit in the past.

As a strategy to avoid potential full CRPS development, she was trialed on the CAC, to apply 3 times a day, along with a TED stocking for the edema, and pregabalin 75 mg bid, titrating slowly to 300 mg bid. The patient was seen 8 weeks later and reported complete elimination of the stabbing pain. The patient reported minor numbness over the previously painful area and occasional deep pressure induced pain.

DISCUSSION

This retrospective case series documents the outcomes of a novel CAC for treatment of CRPS patients within a clinic setting. A translational medicine strategy was implemented by taking the results of the Ragavendran study, together with the medical literature on effective topical CRPS/neuropathic pain treatments, and safely delivering them to patients with CRPS via a combination analgesic cream. In the Ragavendran study,[14] CRPS model rats were treated with various topical combinations of an α2A receptor agonist or NO donor with a PDE or PA inhibitor, a combination which may hypothetically improve microvascular function. They observed reduced allodynia with all topical combinations tested; one of these consisted of the α2A receptor agonist clonidine with the PDE inhibitor pentoxifylline. We selected these 2 topical analgesics, based on their positive findings, and combined them with DMSO, as the NO donor and a topical drug penetration enhancer,[31] and ketamine, both of which have demonstrated efficacy in treating CRPS,[2] for trial in patients with CRPS presenting at the pain clinic. Individual drug concentrations are chosen to reflect optimal therapeutic concentration while remaining under the concentration limit. The maximum concentration available in the base cream is typically 20% to 25%.

The CAC was trialed on 13 patients with CRPS-I and 2 with a "CRPS—not otherwise specified" diagnosis, which possibly represents a pre-CRPS state. The majority of patients (69%) reported pain relief, whether by pain score or descriptive comment, with 54% of patients reporting major benefits. The change in NPRS score was -2.1 ± 2.0 for all patients and -3.4 ± 1.5 for patients with positive outcomes reported. These scores are not wholly indicative of the CAC pain outcomes, however, as patients who reported pain relief descriptively could not be included in the analysis. For instance, patient #3 reported descriptively that pain had reduced down to background levels. All patients who reported major benefits were using the CAC in combination with an opioid analgesic, or in one case, with prednisone. One of these patients reported elimination of surface hypersensitivity and 2 patients reported resolution of CRPS pain or symptoms, both with relatively short-lived CRPS-I/CRPS "not otherwise specified". These 2 cases suggest that the CAC may be useful in resolving CRPS in its early stages, thus highlighting the importance of early diagnosis and implementing appropriate treatment as soon as possible.

It is possible that a trend exists for a higher success rate in patients with CRPS duration of less than 1 year. Six of the 7 patients with CRPS preexisting for less than 1 year reported positive outcomes/pain reduction. It is also possible that the likelihood for successful outcomes is greater in patients with CRPS of the upper limb; 6 of 7 patients with CRPS of the upper limb reported positive outcomes/pain reduction. Three of the 4 patients who reported no benefit had CRPS of the lower limb, preexisting for more than 1 year.

None of the patients included in this case series reported CAC-related side effects, although one patient, who was excluded from the study due to a lack of reported outcomes, incurred a rash and ceased use of the CAC. Theoretically, topical treatments should be better tolerated as systemic drug concentrations are kept to a minimum and are hypothetically more suitable for a

disorder such as CRPS as higher, and hence, more effective concentrations of drugs can be received at the site. We treated one patient who was not tolerant to multiple oral medications and although complete pain relief was unable to be achieved with the CAC alone, some benefit was attained.

No single topical agent has demonstrated a robust response to CRPS-related pain. It was hypothesized that the agents that had shown efficacy in the animal model used by Ragavendran et al., used in a combination cream, might yield effective pain control. The outcomes of this investigation support a useful role for the CAC in multimodal treatment regimens for patients with CRPS. Multimodal treatment regimens are especially appropriate for CRPS as a multifactorial disorder. Pain signaling pathways may be targeted by traditional analgesic medications such as opioids, while CACs, such as the one tested in this study, are designed to target multiple etiological factors in attempt to primarily resolve CRPS symptoms. The combinations tested by Ragavendran et al.[14] aimed to correct microvascular function and were shown to reduce allodynia in a rat model. For the current CAC, DMSO was used as the NO donor, a free radical scavenger with a strong history in treatment of CRPS that is widely used in the Netherlands to treat CRPS-I.[2,16,28–30] Free radical scavengers are theorized to play a part in correcting excessive inflammation by eradicating toxic oxygen free radicals.[30] Topical ketamine was also added, having been shown to reduce allodynia as well as hyperalgesia in CRPS patients.[32]

These results support the topical combination of ketamine, pentoxifylline, clonidine, and DMSO as potentially useful in treatment regimens for patients with CRPS. Over 50% of patients reported pain reduction and benefits with use of the CAC. In addition, the CAC has demonstrated the potential to resolve CRPS symptoms and even effectuate the resolution of a "pre-CRPS" diagnosis or CRPS of an early stage, highlighting the importance of recognizing this progressive syndrome in its early stages and implementing appropriate treatments immediately. We propose that this CAC is worthy of further investigation in the form of a prospective trial.

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