

Review Article:

The Role of Ketamine in Treatment of Complex Regional Pain Syndrome: A review of current evidence

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Abstract

Complex regional pain syndrome (CRPS) remains one of the most challenging chronic pain condition. Various therapies have been attempted but with suboptimal clinical improvement. Central sensitization plays a major role in its pathogenesis which involves increased activity of N-methyl-D-aspartate (NMDA) receptors. Therefore, NMDA receptor antagonists, specifically ketamine, is a rationale option for treatment of CRPS. We performed a simple review of current evidence of literature focusing on efficacy and safety related to ketamine use in CRPS. Our aim is to provide published clinical evidence of efficacy of ketamine in treatment of CRPS to aid clinical decision-making. We searched PubMed for articles published after year 2000. After our literature search and careful filtering for relevant articles, we included 12 meta-analysis/systematic reviews, 4 randomized control trials, 4 open-label prospective trials, and 5 retrospective studies. In conclusion, our review suggests that ketamine is a promising treatment option for refractory CRPS patients, although the long-term efficacy is still in question. Ketamine appears to be safe and devoid of major adverse effects. Other aspects such as route of administration, duration of treatment, and optimal dose are less defined and needs further research. Finally, the numbers of high-quality studies are limited and further large, placebo-controlled, randomized trials are needed to evaluate the long-term efficacy and cost-effectiveness of ketamine therapy in CRPS.

Keywords: Complex regional pain syndrome; Reflex sympathetic dystrophy syndrome; Hyperalgesia; Allodynia; Treatment; N-methyl-D-aspartate receptor antagonists; Ketamine; Analgesic.

Abbreviations: CNS: Central Nervous System; CRPS: Complex Regional Pain Syndrome; IV: Intravenous; NMDA: N-methyl-D-Aspartate; RCT: Randomized Control Trials; SE: Standard Error; VAS: Visual Analog Scale.

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Introduction

Complex regional pain syndrome (CRPS), or reflex sympathetic dystrophy syndrome, is a rare severe chronic pain syndrome with a reported incidence rate of 5.46 to 26.2 per 100 000 persons [1,2]. Few treatments have proven effective, because of a poor understanding of the pathogenesis of the disorder [3]. Although first definitions were made more than 200 years ago, there is still no effective treatment options [4].

CRPS is defined as “a syndrome characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion” [5, 6]. It typically occurs in distal parts of an extremity after acute tissue trauma. A noxious event, or spinal cord or brain injury may also incite the disease. It is characterized by continuing neuropathic pain such as hyperalgesia (increased sensitivity to a painful stimuli) and allodynia (pain from an otherwise non-painful stimuli), intense burning pain, vasomotor and sudomotor instability (altered skin color and/or temperature, sweating, edema), trophic changes (hair, nail, skin), motor dysfunction (limited range of motion, weakness, tremor, dystonia) and patchy bone demineralization [3,4]. Two subtypes were defined as: CRPS type I (reflex sympathetic dystrophy) without major nerve damage, and CRPS type II (causalgia) with major nerve damage [6].

Pathogenesis

Pathogenesis of CRPS is multifactorial and not fully understood [7]. Classic inflammation, neurogenic inflammation [8], altered cutaneous innervation after injury [9,10], autonomic nerve system dysfunction [7], lower levels of circulating catecholamines [11], peripheral and central sensitization and maladaptive changes in pain perception at the level of central nervous system [3,12,13], were proposed mechanisms.

Genetic factors [14-16] and psychophysiological interactions [17, 18] were also blamed to contribute.

Central sensitization plays a major role in CRPS. It is defined as modulation and amplification of neural signaling within the central nervous system (CNS) [19]. In this phenomenon, there is a pathological enhancement in excitability of CNS neurons caused by increased membrane excitability, synaptic efficacy, or reduced inhibition. As a result, pain perception is no longer coupled to the intensity of peripheral stimuli. Pain can be generated by normal non-noxious stimuli to non-injured tissue or can be exaggerated and persists long after the noxious stimuli have disappeared [20]. Biochemically, normally sub-threshold sensory inputs can now activate the pathologic low-threshold pain receptors resulting in exaggerated response such as hyperalgesia and allodynia [3]. This extraordinary process is mediated by reduction of firing threshold in A-delta and C fibers, leading to ongoing release of neuropeptides and the excitatory amino acid glutamate from peripheral afferent terminals [9, 21-23]. This constant level of depolarization leads to blockade of magnesium ions on N-methyl-D-aspartate (NMDA) receptor, and activates it. Activation of NMDA receptor, causes the release of calcium, and acts along different pain pathways in the dorsal horn of the spinal cord and increase excitatory transmission. Despite the noxious stimulation is removed, pain signal transmission remains constant. Considering those mechanisms, NMDA receptors has a key role in central sensitization, and neuronal plasticity [20]. Thus NMDA receptor antagonists have a potential role in treatment of CRPS.

Management

Aim of the treatment is to control pain followed by recovery of function. Patient education, psychosocial

and behavioral treatment are suggested for selected patients [24]. Physical and occupational therapy are considered as first line treatment modalities [4,25]. Motor dysfunction, such as weakness, tremor, contractures and decreased range of motion are frequent symptoms of CRPS and an early and aggressive physical therapy is aimed at improving function but without exacerbating autonomic dysfunction and pain. Unfortunately, allodynia in the affected limbs are obstacles to a successful physical rehabilitation [26]. Pharmacologic treatment of the syndrome consist of controlling inflammation and pain (Non-steroidal anti-inflammatory drugs, corticosteroids, free oxygen radicals), controlling osteoporosis (bisphosphonates, calcitonin), medications for neuropathic pain (anticonvulsants, antidepressants, gabapentin, ketamine), topical preparations (lidocaine, capsaicin), alpha adrenergic agonists and antagonist (phenoxybenzamine, prazosin, clonidine), opioids and recently intravenous immunoglobulin (ivIG)(4). Interventional treatment methods include nerve blocks, peripheral and central neuromodulation techniques, and surgery [27].

Ketamine (2,2 Chlorophenyl 2 methylaminocyclohexanone), was first introduced as a ‘dissociative anesthetic’ 50 years ago [28]. Since 1980 it is known that ketamine is predominantly a noncompetitive antagonist of NMDA receptor [29], and also targets nicotinic, muscarinic, monoaminergic, mu 2 opioid receptors. In addition, interaction with voltage gated calcium and sodium channels have been described. All of those may contribute, however NMDA receptor antagonism accounts for most of its effects [30]. Clinical uses of ketamine incudes induction of anesthesia in patients with hemodynamic instability and active asthmatic disease, sedation of uncooperative patients, especially children, sedation in emergency room, and sedation

for short painful procedures, and recently as an antidepressant(30). Finally ketamine is demonstrated to be useful in chronic pain conditions which involves central sensitization, for example post herpetic neuralgia, migraine, burns, fibromyalgia, neuropathies and CRPS [31].

There are few clinical guidelines for using ketamine in CRPS. Therefore, we performed a simple review of current evidence of the literature focusing on efficacy of ketamine in CRPS. We hope to provide high quality evidence to aid clinical decision-making.

Methods

Key words included “ketamine”, “N-methyl-D-Aspartate Antagonists”, “complex regional pain syndrome”, “treatment”. We based the review on work published after year 2000 from major pain, anesthesiology, surgical and rehabilitation journals where appropriate. The articles are individually screened by all authors for relevance to this review. We decided to include systematic reviews, meta-analysis, randomized control trials (RCT), observational prospective studies and case series reports. All results are screened for relevance and importance by all authors.

Results

Systematic Reviews and Meta-analysis

Our literature search yielded five systematic reviews, two meta-analysis, three most recent guidelines, and five simple reviews about ketamine treatment in CRPS patients (Table 1).

In a review by Xu et al. [32], authors recommended IV ketamine infusion could be used in selected patients with refractory CRPS. However, the authors noted two side effects. Firstly, they stated that, in case of prolonged and/or repeated infusion within a short period, increased risk of ketamine-induced liver injury

Table 1. Evaluation of Meta-Analysis and Reviews of Ketamine For Complex Regional Pain Syndrome (CRPS)			
Study/Year	Study type	Results and Recommendations	
Xu J. et al./ 2016(32)	Systematic Review	<ul style="list-style-type: none"> • IV ketamine infusion could be used in selected patients with refractory CRPS • Increased risk of ketamine-induced liver injury • Mild to moderate psychotomimetic side effects 	
Connolly SB. et al./2015(31)	Systematic Review	<ul style="list-style-type: none"> • subanesthetic dose ketamine is a promising option • Toxicity • Not be considered as a first-line option 	
Azari P. et al./2012(23)	Systematic Review	<ul style="list-style-type: none"> • Ketamine demonstrated promising results for safe and efficient use in the treatment of CRPS • Not found enough evidence to recommend the use of ketamine in CRPS routinely 	
O'Connell NE. et al./2013(33)	Systematic Review	<ul style="list-style-type: none"> • Might be a promising option in the management of CRPS • Effects was not seen further than 4 to 11 weeks • Variety of side effects 	
Cossins L. et al./2013(34)	Systematic Review	<ul style="list-style-type: none"> • Moderate evidence for the role of low-dose IV ketamine administration in long-standing CRPS • Liver failure with prolonged or repeated treatment 	
Harden RN. et al./2013(4)	Guidelines	<ul style="list-style-type: none"> • NMDA receptor antagonists was suggested in patients who have significant allodynia-hyperalgesia • Effective doses likelihood toxicities have to be observed carefully 	
Goebel A. et al./2012(35)	Guidelines	<ul style="list-style-type: none"> • Moderate evidence for low-dose IV ketamine 	
Perez RS. et al 2010. (36)	Guidelines	<ul style="list-style-type: none"> • Moderate evidence, and only IV subanesthetic dose of ketamine administration reduces pain in CRPS-I 	
Goebel A. et al./2013(37)	Review	<ul style="list-style-type: none"> • Paucity of data in the long-term efficacy or safety information • Either hallucinations or inebriation were occurred 	
Collins S. et al./2010(38)	Review	<ul style="list-style-type: none"> • Significant effects in post amputation pain • No significant pain reduction in the CRPS 	
Dworkin RH. et al./2013(39)	Review	<ul style="list-style-type: none"> • Not recommended for neuropathic pain • Limited evidence of ketamine in long term benefits 	
Blonk MI. et al./2010(40)	Review	<ul style="list-style-type: none"> • Limited place as an additive therapy in CRPS 	
Kosharskyy B. et al./2013(41)	Review	<ul style="list-style-type: none"> • Ketamine could be only administered in an IV formulation • Low oral bioavailability, potential psychomimetic side effects, and lack of easily available formulation 	
Collins S. et al. 2010(38)	Meta-analysis	<ul style="list-style-type: none"> • No significant effect of IV ketamine in CRPS • Data was insufficient to draw a certain conclusion 	
Werthi MM. et al./2014(44)	Meta-analysis	<ul style="list-style-type: none"> • Bisphosphonates, NMDA analogs and vasodilators were the only agents showing better long-term pain reduction than the placebo 	

should be considered. Secondly, patients receiving ketamine might have experience mild to moderate psychotomimetic side effects during drug infusion.

Connolly et al. [31], suggested in their review that subanesthetic dose ketamine is a promising option. However, because of the insufficient evidence for the efficacy of ketamine for CRPS and likely toxicity, they stated that it couldn't be considered as a first-line option.

We found one systematic review [23] for the efficacy and safety of ketamine for CRPS patients. In this systematic review authors assessed 3 randomized

placebo-controlled trials, 7 observational studies, and 9 case reports, and finally ketamine demonstrated promising results for safe and efficient use in the treatment of CRPS however, the authors could not found a enough evidence to recommend the use of ketamine in CRPS routinely.

One Cochrane review evaluated the management of pain and disability in patients with CRPS [33], IV ketamine was found as relatively effective treatment option for CRPS. However, its effects was not seen further than 4 to 11 weeks post-treatment period, and it was related with a variety of side effects. Authors

Table 2. Evaluation of Randomized Controlled Trials and Observational Studies of Ketamine For Complex Regional Pain Syndrome (CRPS)		
Study/Year	Study type	Results and Recommendations
Sigtermans al./2009(42)	et Randomized placebo-controlled trial	<ul style="list-style-type: none"> • Ketamine was associated with a significant reduction of pain score compared with placebo over the 12-week study period • At 12th week no significant difference between the groups • Ketamine group did not show functional improvement despite pain relief
Schilder al./2013(45)	et Secondary analysis of a placebo-controlled study	<ul style="list-style-type: none"> • Ketamine resulted in significantly decreased pain up to 6 weeks after infusion but no improvement in motor function • No direct effect of ketamine on motor function
Schwartzmaet al./2009(43)	Randomized double-blind placebo controlled trial	<ul style="list-style-type: none"> • The ketamine group had a statistically significant reduction in various pain endpoints throughout the entire 3 months • The ketamine group had an improved quality of life although not statistically significant
Goldberg al./2005(48)	et Open label prospective study	<ul style="list-style-type: none"> • Significant reduction of pain throughout the duration of the study also with improved ability to initiate movement
Koffler al./2007(49)	et Open-label prospective study	<ul style="list-style-type: none"> • 5 day anesthetic ketamine infusion significantly reduced acute and overall pain at 6 weeks following treatment • Withdrawn from opioids or other pain medications • Ketamine had no adverse neurocognitive side effects, there was marked improvement in certain cognitive parameters
Keiferet al./2008(51)	Pilot open-label study	<ul style="list-style-type: none"> • Over the 10-day infusion period, there was no relief of pain intensities compared to baseline • No improvement in somatosensory parameters • Insignificant increase in mechanosensory detection threshold
Keifer al./2008(52)	et Open label	<ul style="list-style-type: none"> • <i>Complete pain relief was achieved in majority of patients at 6 months after treatment</i> • <i>Significant improvement in quality of life, and motor function.</i>
Finch al./2009(47)	et Double-blind placebo controlled crossover trial	<ul style="list-style-type: none"> • Topical ketamine treatment in affected limbs significantly decreased allodynia to light brushing and hyperalgesia to punctate stimulation • Peripheral NMDA receptors also are involved in CRPS

Table 3. Evaluation of Retrospective studies of Ketamine For Complex Regional Pain Syndrome (CRPS)		
Study/Year	Study type	Results and Recommendations
Correll al./2004(53)	et Retrospective Study	<ul style="list-style-type: none"> • Immediate pain relief after the infusion was complete in 76% patients • After infusion therapy, 54% of patients were pain free for ≥ 3 months • 36% of patients required a second course of infusion, more impressive pain free duration, with 58% of these patients pain free ≥ 1 year
Webster al./2006(54)	et Retrospective Study	<ul style="list-style-type: none"> • 85% reported pain reduction during the period of infusion • Side effects were experienced by most patients (mild and consists of dizziness and fatigue)
Patil al./2012(55)	et Retrospective Study	<ul style="list-style-type: none"> • For CRPS patients, reduction in VAS score was 7.2, while for non-CRPS, the reduction was 5.1 which is statistically significant • Lack of long-term follow-up • 38% of the patients reported pain relief lasting more than 3 weeks and all reported improved exercise tolerance and increase energy
Polomano al./2013(56)	et Retrospective Study	<ul style="list-style-type: none"> • Significant reduction in "present pain intensity" and improvement in global pain relief • Not significant decrease in average opioid consumption up to 24 hours after therapy • Not specifically include CRPS patients
Russo al./2016(58)	et Retrospective Study	<ul style="list-style-type: none"> • Compound analgesic cream • 69% patients reported significant reduction in pain

concluded that ketamine, and most probably other NMDA receptor antagonists, might be a promising option in the management of CRPS [33].

In a systematic review evaluating 2 RCTs, Cossins et al. [34], indicated a moderate evidence for the role of low-dose IV ketamine administration in long-standing CRPS. Authors also stated that likelihood occurrence of liver failure with prolonged or repeated treatment should be taken into consideration.

this study use of NMDA receptor antagonists was suggested in patients who have significant allodynia-hyperalgesia. In the UK guidelines there is moderate evidence for low-dose IV ketamine [35]. Likewise, in the Dutch guidelines evidence for this treatment was stated as “moderate”, and only IV subanesthetic dose of ketamine administration reduces pain in CRPS-I [36].

Table 4. Route of administration and Dosage	
Study/Year	Intervention (dose and duration of infusion)
Patil et al./2012 (55)	<ul style="list-style-type: none"> 49 patients received ketamine infusion for a median of 38.3 minutes (range from 30 minutes - 8 hours) Mean total dose per infusion was 0.9 (± 0.4) mg/kg. Median duration between infusion was 233.7 days
Shirani et al./2008 (50)	<ul style="list-style-type: none"> IV ketamine 50 mg over 30 minutes followed by two more infusion 2 weeks apart
Webster et al./2006 (54)	<ul style="list-style-type: none"> Mean duration was 16.4 days (5-55 days) Mean dose 0.12 mg/kg/hr. (0.01 mg/kg/h - 0.25 mg/kg/h)
Carr et al./2004 (60)	<ul style="list-style-type: none"> 20 chronic pain patients (1 CRPS) 10% solution of ketamine hydrochloride (each spray contains 10 mg ketamine) During breakthrough pain, nasal spray self-administered (maximum of 5 sprays, 50 mg ketamine)
Goldberg et al./2005 (48)	<ul style="list-style-type: none"> Outpatient ketamine infusion Started with 40 mg over 4 hours, then up titrated to 80 mg over 4 hours over a 10 day period Clonidine (0.1 mg) and midazolam (2-4 mg) as adjuvant
Koffler et al./2007 (49)	<ul style="list-style-type: none"> Maintained plasma ketamine levels of 250-300 ug/dl for at least 4.5 days (medically induced coma)
Nama et al./2010 (59)	<ul style="list-style-type: none"> IV ketamine infusion started at 100 mcg/kg/h and continued for 19 hours
Kiefer et al./2008 (52)	<ul style="list-style-type: none"> Anesthesia induced by bolus IV ketamine (1-1.5 mg/kg) and midazolam (2.5-7.5 mg) Ketamine infusion over 5 days, starting at 3 mg/kg/h followed by gradual daily titration to final dose of 7 mg/kg/h. IV midazolam (0.15-0.4 mg/kg/h) to acquire adequate sedation; IV clonidine (0.20-0.85 mg/kg/h) to manage side effects of ketamine

Updated guidelines for the treatment of CRPS have been published by several authors. In most recent one by Harden et al [4], authors stated that ketamine was evaluated for neuropathic pain and for CRPS, however during the treatment at effective doses likelihood toxicities have to be observed carefully. In

In one of recent reviews that are reporting opposed views of ketamine use for CRPS, Goebel stated that there is a paucity of data in the long-term efficacy or safety information, and in the majority of the patients either hallucinations or inebriation were occurred transiently [37]. In a review by Collins et al. [38], apart

from significant effects in post amputation pain, there was no significant pain reduction in the CRPS patients who received IV ketamine.

Moreover, in a review by International Association for the Study of Pain-Neuropathic Pain Special Interest Group use of ketamine for neuropathic pain was not recommended, stating the limited evidence of ketamine in long term benefits [39]. There is a lack of knowledge in the use of oral ketamine; therefore it has a limited place as an additive therapy in CRPS [40]. Finally, in another review, authors stated that, even though ketamine is the most effective and well-studied NMDA receptor antagonist, it could be only administered in an IV formulation. Additionally, most important disadvantages of ketamine administration were emphasized as follows: Low oral bioavailability, potential psychomimetic side effects, and lack of any easily available formulation [41].

Collins et al. [38], performed a meta-analysis assessing two studies [42,43]. Both revealed significant heterogeneity and did not indicate a significant effect of IV ketamine on the pain management in CRPS. Authors concluded that based on current evidence the data was insufficient to draw a certain conclusion about its efficacy on neuropathic pain and no significant pain relief could be achieved for ketamine IV in CRPS. The authors indicated additional RCTs requirement to evaluate the role of NMDA receptor antagonists in CRPS [38].

In a “network” meta-analysis by Wertli et al. [44], a comprehensive comparison of currently available treatment in CRPS 1 was made which include NMDA analogs, calcitonin, bisphosphonate, vasodilators, anticonvulsive and radical scavenger. Although most medications showed some efficacy on short-term period, bisphosphonates, NMDA analogs and vasodilators were the only agents showing better long-term pain reduction than the placebo.

Randomized Control Trials

Although there is logic to use ketamine for CRPS due to its blockade of NMDA receptors, it is important to realize there has been very few objective evidence from RCTs to confirm this belief. Our literature search yielded three randomized, placebo-controlled trials and included all of these in our review [42,43,45] (Table 2). These trials evaluated the efficacy of ketamine in refractory CRPS patients who have failed other forms of therapy.

Sigtermans et al. [42], studied the effects of low-dose ketamine on pain scores in a randomized placebo-controlled parallel-group trial. Sixty long-standing CRPS-1 patients (median duration 7 years) were randomized to either receive low-dose ketamine (n=30) or placebo (n=30) for 4.2 days and were followed weekly for a total of 12 weeks. Ketamine was associated with a significant reduction of numerical rating scale pain score compared with placebo ($p < 0.001$) over the 12-week study period. The lowest pain score was observed 1 week after ketamine infusion (ketamine 2.68 ± 0.51 , placebo 5.45 ± 0.48). Accordingly, 20 subjects who were initially in the placebo group received ketamine after unblinding and also had a similar reduction in pain scores. However, at 12th week, the significance of pain reduction between the two groups was lost. Ketamine group did not show functional improvement despite pain relief, which the authors attributed to insufficient dose and duration of treatment. Other parameters, including sensibility, temperature, and volumetric measurements of affected limbs also did not show any significant difference. In a secondary analysis of Sigtermans' RCT, Schilder et al. [45], evaluated the time-dependent relationship of pain and motor function in 29 CRPS patients. Movement parameters (velocity, frequency, amplitude, and number of arrests) were assessed at baseline and weeks 1, 3, 6, and 12 after

infusion. Ketamine resulted in significantly decreased pain up to 6 weeks after infusion but no improvement in motor function. But the study revealed a significant inverse relationship with pain and motor function irrespective of whether the subject received ketamine or placebo. The authors found no direct effect of ketamine on motor function. However, it highlighted that pain reduction may improve motor function via a not yet determined mechanism.

In 2009, Schwartzman et al. [43], evaluated the effect of outpatient ketamine infusion in patients with intractable CRPS. In this randomized double-blind placebo controlled trial, originally 40 subjects (20 in each group) were randomized to receive either ketamine (0.35 mg/kg/h, with maximum dose of 25 mg/h over a 4-h period for 10 days) or normal saline. The study was stopped early with 19 subjects (placebo: 10, ketamine: 9) and enough statistical power. Patients were followed up to 3 months after infusion. Results revealed the ketamine group had a statistically significant reduction ($p < 0.05$) in various pain endpoints throughout the entire 3 months of the trial, including short form McGill pain questionnaire and weekly pain questionnaires. When assessed with American Chronic Pain Association quality of life questionnaire, the ketamine group had an improved quality of life although not statistically significant. Interestingly, the same author experimented with anesthetic dose of ketamine on pain parameter and brain changes. The subject received ketamine (max dose 7mg/kg/h) for five days under general anesthesia. The patient reported significant improvement in spontaneous and evoked pain scores that lasted up to 12 months. Functional magnetic resonance imaging before and after infusion revealed changes in the cerebral cortex toward a normal pattern [46].

Finch et al. [47], evaluated the sensory effects of topical ketamine in CRPS. In this double-blind

placebo controlled crossover trial, twenty CRPS patients received 10% ketamine cream or placebo once per week for two weeks. Subjects had allodynia to brushing and hyperalgesia to punctate stimulation and pressure. The results showed that topical ketamine did not reduce pain in the symptomatic limb with average pain score of 4.9 on a scale of 0-10. However, ketamine treatment in affected limbs significantly decreased allodynia to light brushing ($p = 0.049$) and hyperalgesia to punctate (skin pricking) stimulation ($p=0.005$). The authors also tested for plasma levels of ketamine and norketamine, which were undetectable. This finding provides important insight into pathophysiology of CRPS. Allodynia and hyperalgesia were thought to be mediated by upregulated excitability of nociceptive neurons in the spinal cord (“central sensitization”)(3). This study showed that peripheral NMDA receptors also are involved in CRPS, which affords a new opportunity for targeted intervention without systemic effects of ketamine.

Open-label Prospective Studies

We found seven open-label prospective studies that evaluated the efficacy of ketamine in CRPS (Table 2). We have excluded two studies because the assessment was limited to the period of ketamine infusion and did not include outcomes after the intervention to help us ascertain whether ketamine had any effect on short- or long-term outcomes. But you put 4 open label here, not five??

In an early open label, prospective study, Goldberg et al [48] sought to evaluate the efficacy of outpatient ketamine infusion on CRPS. 40 patients with long-standing or rapidly spreading CRPS (type 1 and 2) received 4-hour ketamine infusions (start at 40 mg, titrated to final dose 80 mg) daily for 10 days. The study concluded there was significant reduction of pain throughout the duration of the study also with

improved ability to initiate movement. 25 of 40 patients (62%) had significant (70%) reduction of “worst” pain lasting up to 6 weeks after treatment while 8 (20%) had similar pain relief lasting up to 12 weeks.

Koffler et al. [49], in an open-label prospective study in 2007, aimed to evaluate effect of anesthetic ketamine on neurocognitive function in refractory CRPS I patients. Nine subjects with generalized hyperalgesia, motor dysfunction and severely functional impairment received ketamine (3-7 mg/kg/h) for 5 days. The study concluded that a 5 day anesthetic ketamine infusion significantly reduced acute and overall pain at 6 weeks following treatment in CRPS I. Worth noting is that all patients were withdrawn from opioids or other pain medications at 6 weeks. In contrast to the concern of ketamine’s inhibition on learning and memory function, the comparison of baseline and 6-weeks cognitive assessment showed no change in ability to learn and form new memory. Not only did ketamine had no adverse neurocognitive side effects, there was marked improvement in certain cognitive parameters, including brief attention and processing speed, likely from pain reduction and/or sparing of narcotic pain medications. This has important implications as many CRPS patients have pain-related executive function and memory impairments.

The observation that high doses of ketamine [50] but not low doses [51] are effective in resolution of pain in severe refractory CRPS led to the interest of experimenting anesthetic doses of ketamine. In a pilot study Kiefer et al. evaluated the effect of S(+)-ketamine on pain. S(+)-ketamine was selected because of its increased NMDA receptor and twice the analgesic potency compared to its standard racemic form. 4 refractory CRPS patients received ketamine infusion titrated (50 mg/day to 500 mg/day) over 10 days

according to side effects. Surprisingly, over the 10-day infusion period, there was no relief of pain intensities (average, peak and least pain) compared to baseline. Additionally, there was no improvement in somatosensory parameters (measured by quantitative sensory testing). After infusion, there was a small but insignificant increase in mechanosensory detection threshold, while heat detection-pain thresholds were unchanged. However, none had clinically relevant side effects. Subsequently, in an open-label phase II trial of 20 patients with severe or spreading CRPS, Keifer et al [52] evaluated the efficacy of anesthetic dose of ketamine on pain and functionality. Subjects were induced general anesthesia with a bolus of ketamine and midazolam and followed by a maintenance ketamine infusion for 5 days (start at 3mg/kg/h and up titrated to maximum dose 7mg/kg/h). Midazolam was co-administered to minimize ketamine’s hallucinogenic effects. Ketamine resulted in a significant pain reduction at 1, 3, and 6 months after infusion ($93.5 \pm 11.1\%$, $89.4 \pm 17.0\%$, $79.3 \pm 25.3\%$; $P < 0.001$). Complete remission of CRPS was achieved in all patients (100%) at 1 month, 17 (85%) at 3 months, and 16 (80%) at 6 months. Of those who had a CRPS relapse (4 patients), significant pain relief was still achieved at 3 and 6 months ($59.0 \pm 14.7\%$, $P < 0.004$; $50.2 \pm 10.6\%$, $P < 0.002$). Additionally, there was significant improvement in quality of life, ability to work and motor function at 6 months after treatment.

Retrospective Studies

We found five retrospective studies (Table 3). Four studies evaluated the efficacy and safety of subanesthetic ketamine infusion on CRPS while one study evaluated efficacy of a ketamine-containing analgesic cream on CRPS.

In a retrospective study by Correll et al. [53], a chart

review was performed on 33 CRPS (type I and II) patients with lower limbs involvement who received subaneshetic ketamine infusions. The duration of infusion therapy was from 2- 5 days. There was immediate pain relief after the infusion was complete in 25 of 33 (76%) patients, while 6 of 33 (18%) had partial relief and no relief in 2 of 33 (6%) patients. Using Kaplan-Meier analysis was used to estimate the duration of pain relief. After infusion therapy, 54% of patients were pain free for ≥ 3 months and 31% were pain free for ≥ 6 months. A portion of patients (12 of 33) required a second course of infusion, which had an even more impressive pain free duration, with 58% of 12 patients pain free ≥ 1 year and 33% pain free for >3 years.

Webster et al. [54] conducted a retrospective study to evaluate efficacy of prolonged ketamine infusions in severe neuropathic pain at an outpatient pain clinic. In this study 8 of 13 patients (62%) had CRPS and were refractory to standard treatments. The duration of therapy was average 16.4 days (minimum 5 days; maximum of 55 days). The mean dose was 0.12mg/kg/hr (minimum 0.01mg/kg/hr; maximum dose was 0.25 mg/kg/hr). 11 of 13 patients (85%) reported pain reduction during the period of infusion. Although not statistically significant, 7 of 13 patients (54%) reported pain improvement 1 month after in infusion. Side effects were experienced by most patients, but they were mild and consists of dizziness and fatigue.

Similarly, in a large 5-year retrospective study of 49 refractory chronic pain patients, Patil et al. [55], evaluated the efficacy of ketamine infusion on pain outcomes. 18 of 49 (37%) had CRPS. Duration of infusion ranged from 30 minutes to 8 hours. Infusions were routinely repeated every 3-4 weeks. The mean dose per infusion was 0.9 (± 0.4) mg/kg. While all patients had a significant visual analog score of 5.9

(standard error [SE] 0.35). There was an even more impressive reduction in visual analog score for CRPS patients. For CRPS patients, reduction in Visual Analog Scale (VAS) score was 7.2 (SE 0.51, $P < 0.001$), while for non-CRPS, the reduction was 5.1 (SE 0.40, $P < 0.001$) which is statistically significant. This study was limited by lack of long-term follow-up. 11 (38%) of the 29 followed up patients reported pain relief lasting more than 3 weeks and all reported improved exercise tolerance and increase energy.

Another retrospective study by Polomano et al. [56] the effect of low-dose ketamine was evaluated in patients who suffer neuropathic pain from major limb injuries sustained in combat. 19 patients with neuropathic pain who failed conventional multimodal analgesia received a 3-day IV infusion of ketamine at 120mg/kg/h. There was a significant reduction in “present pain intensity” and improvement in global pain relief. There was a decrease, while not significant, in average opioid consumption up to 24 hours after therapy. Although this study did not clearly specify the diagnosis of its subjects and did not specifically include CRPS patients, whether the results can be translated to CRPS patients is debatable. But in light of neuropathic nature of CRPS [57], the results of this study have important implications in CRPS.

In a recent retrospective study by Russo et al. [58], the efficacy of a compound analgesic cream containing 10% ketamine, clonidine, pentoxifylline, and dimethyl sulfoxide. A chart review was performed on 13 CRPS patients. After 6 weeks of use, 9 (69%) patients reported significant reduction in pain. 7 patients reported major benefits and 2 patients reported a complete resolution of pain symptoms.

Route of Administration and Dosage

Different formulations of ketamine exist, but ketamine as a treatment for CRPS has been restricted to

intravenous, topical, oral and intranasal. There is no consensus regarding the most effective route of administration because there is no study yet to compare efficacy of different formulations (Table 4). Most studies evaluated efficacy of intravenous ketamine. The duration varies from 30 min to 10 days [48,50,55] but has been shown to be safe for as long as 8 weeks [54]. The dose varies from 100µg/kg/h [59] to 7mg/kg/h [52]. Low-dose ketamine has shown to be an effective analgesia but its effectiveness is not long lasting, especially in patients with severe CRPS [51].

Other routes of administration are less studied. In a study by Carr et al, intranasal ketamine's efficacy was evaluated in treatment of breakthrough pain in chronic pain. In this randomized, double-blinded placebo-controlled trial, 20 patients (1 CRPS patient), intranasal ketamine and not placebo was shown to significantly reduce breakthrough pain level with onset within 10 min and with relief lasting up to 1 hour. In contrast to placebo group, no patients in ketamine group required their usual rescue medications ($P = 0.0135$) [60].

Adverse events

The most common side effects with ketamine are psychotomimetic and appear to be dose-dependent. These include agitation, hallucinations, anxiety, and euphoria. Most studies have used benzodiazepines (including midazolam and lorazepam) to counter these effects with good results. In the study by Kiefer et al., where patients received anesthetic ketamine (7mg/kg/hr) for 5 days, a co-infusion of midazolam (0.15-0.04 mg/kg/h) negated any agitation during ketamine infusion. Ketamine related side effects were observed immediately after termination of ketamine but were mostly mild and controlled with low dose clonidine or benzodiazepines [52]. In a case study by Nama et al, adjunct dexmedetomidine (selective α_2 -

adrenergic receptor agonist similar to clonidine) was combined with subanesthetic ketamine infusion with in a female refractory CRPS patient to manage the ketamine related side effects. Pain relief was observed at 1 hour after start of infusion (100 µg/kg/h). A single 8 µg dose of dexmedetomidine was given 6 hours into the ketamine infusion which augmented the analgesia. The patient reported complete pain resolution and with no side effects. The authors theorized that dexmedetomidine both improved pain relief via a synergistic effect with ketamine and minimized side effects by its alpha-2 agonism and ketamine sparing properties. Another potential and fortunately rare side effect of ketamine is hepatotoxicity, especially with prolonged infusions and high doses [61]. In the study by Kiefer et al. [52], where anesthetic ketamine were infused for 10 days, mild elevation of liver enzymes were noted in majority of patient (16/20) but normalized within 10-14 days after infusion without intervention. Rare cases of transient blindness have also been reported [62].

Discussion

Since the first documentation of CRPS, its pathophysiology remains unclear and many medications of various mechanisms have been tried but with little progress. There is no cure for CRPS and many patients have suboptimal pain even after aggressive therapy. Ketamine appears to be an attractive and rational option due to its NMDA receptor antagonism and the role NMDA receptors play in central sensitization.

Our review attempts to provide some sense of our current knowledge of ketamine in CRPS treatment. Existing systemic reviews and Cochrane review consistently concluded that evidence for routine ketamine use in CRPS is moderate and of low quality. To our knowledge, only 3 RTCs were conducted. Most studies were limited by small sample size and

non-standardized in their methodology (use of different CRPS diagnostic criteria, dosage, duration of infusion and follow-up). Although considered as the most rigorous way of determining cause-effect relation and in this case, ketamine's effect on CRPS related outcomes. The small size and heterogeneity of only a handful of RCTs limits its generalizability. However, we do recognize CRPS is a relatively rare condition and large RCTs will be a difficult task. In the future, larger randomized trials should aim to conclusively examine the long-term efficacy and its impact on quality of life. Furthermore, more studies are necessary to individualize the optimal dose and duration of ketamine treatment based on duration and severity of disease.

Clinicians should also consider the practicality of ketamine infusions. Most insurance do not cover the financial cost of ketamine treatment and patients have to bear the full cost. Given the limited short-term benefits of ketamine and need for repeated sessions, this may translate to significant financial and psychosocial burden on CRPS patients. Our review suggests that subanesthetic ketamine infusion is moderately effective in alleviating pain and improve motor function, at least in the short-term. In light of limited effective therapeutic options, even the short-term relief (weeks to months) is arguably worth pursuing. Preliminary evidence show promising results at anesthetic doses and perhaps suggesting a dose-dependent effect of ketamine on clinical outcome. Ketamine appears to be effective and devoid of major side effects in the setting of proper monitoring and use of adjuvants to manage psychotomimetic effects. Finally, the numbers of high-quality studies are limited and further large, randomized trials are needed to evaluate the efficacy and cost-effectiveness of ketamine therapy in CRPS.

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