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The use of ketamine in complex regional pain syndrome: possible mechanisms

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Complex regional pain syndrome is a neuropathic pain syndrome that is characterized by: severe pain beyond the area of injury; autonomic dysregulation; neurogenic edema; movement disorder; and atrophy and dystrophy. Ketamine is an open-channel NMDA blocker that only acts on those receptors whose Mg²⁺ block has been lifted. It is effective in the treatment of the syndrome when standard treatments have failed. Different protocols are utilized depending on the severity of illness. There have been no serious ketamine-induced complications from these protocols, owing to careful psychological screening and the liberal use of midazolam and lorazepam to counter any psychomimetic effects and clonidine to block possible 'Olney's' lesions.

KEYWORDS: clonidine • CRPS • immune modulation • ketamine • long-term depression • long-term potentiation • midazolam • NMDA receptor

Complex regional pain syndrome (CRPS) is most often caused by a fracture, soft-tissue injury or surgical procedure, although in a small group of patients no inciting cause can be identified [1,2]. CRPS is divided into type I, in which no nerve lesion is identified (reflex sympathetic dystrophy [RSD]), and CRPS type II, in which a specific nerve has been damaged (causalgia). Recent evidence suggest that CRPS I is a post-traumatic neuropathy due, in part, to the distal degeneration of A- δ and C-fiber small-diameter peripheral axons. However, this mechanism cannot account for the percentage of patients in whom no injury can be detected, or in those with an initiating CNS injury [3].

Factor analysis reveals that the signs and symptoms noted in CRPS patients cluster into four distinct subgroups: abnormalities in pain processing (allodynia, hyperalgesia and hyperpathia); temperature change and skin color; edema and sudomotor dysregulation; and motor dysfunction and trophic changes [4,5]. The current proposed diagnostic criteria require at least one symptom in each of the four factors and one sign in at least two of the four factors [6,7]. In general, early in the disease there is an inflammatory phase with prominent neurogenic edema, while later the pain spreads and autonomic, motor and trophic signs become more prominent [1]. CRPS has been demonstrated to be a systemic condition that involves both central and peripheral components of the pain matrix [8], as

well as having complex interactions between the immune and nervous system [9,10].

Epidemiology

The incidence of CRPS after injury is variable, which may be owing to the expertise of the examiners, the nature of the cohort studied and the time period in the course of the disease in which they were examined [11,12]. Bickerstaff and Kanis reported an incidence of CRPS in 28% shortly after Colles fracture that fell to 1–2% after 1 year, which is lower than that quoted in the literature [13]. Zyluk also reported that 87% of his patients resolved their CRPS at 1 year following radial fracture [14].

The incidence of CRPS is greater in females than males by approximately 4:1. A recent population-based study from The Netherlands reported an incidence of 40.4 females and 11.9 males per 100,000 person-years at risk [15]. An earlier population-based study from Olmsted County (MN, USA) had demonstrated an incidence of 8.57 females and 2.16 males per 100,000 person-years at risk [16]. The dramatic difference may represent the characteristics of the cohorts reported (primarily urban vs rural).

Overview of the pathophysiology of pain in CRPS

Complex regional pain syndrome most often follows fractures, injury to soft tissue, a nerve

injury or a surgical procedure [1]. Accumulating evidence supports a post-traumatic neuropathy of C- and A- δ fibers as its etiology, although this mechanism cannot account for the percentage of patients in whom no injury can be detected or who have suffered a CNS lesion [3].

A review of recent evidence supports the view that these lesions lead to maladaptive plasticity at all levels of the pain matrix, such that pain occurs spontaneously and is pathologically magnified by noxious and innocuous mechanical and thermal stimuli [17].

In 90% of patients, CRPS results from an injury that damages the terminal twigs of C- and A- δ fibers in soft tissue or bone [3,7,18,19]. Similar injury in rodents and human autopsy material support this hypothesis [20,21]. The distinction between inflammatory pain (which will resolve with healing of the inciting trauma) and neuropathic pain (from damage to peripheral or central components of the pain matrix) is blurred in these patients, as there are components of each at the site of injury. The clinical distinction between type I CRPS and type II CRPS is also not clear, as both demonstrate similar symptoms and signs. Following injury, inflammatory, nociceptive and immune processes evolve in parallel, which induces and maintains the syndrome [22–24]. Neurogenic inflammation is mediated at the site of injury by the activation of C-fibers that release substance P and calcitonin gene-related peptides, the consequence of which is erythema, increased temperature, protein extravasation and edema [25]. The injury-induced barrage is maintained by a microenvironment ('inflammatory soup') surrounding the C-fibers composed of cytokines, protons, prostaglandins, bradykinin, endothelin-1 and neuropeptides [26–29]. **Prostaglandin E2, serotonin, bradykinin, epinephrine, lipoxygenase, BDGF, adenosine and neurotrophin-3** induce peripheral nociceptive terminal-membrane sensitization. These compounds activate intracellular phosphokinase A and C that phosphorylate tetrodotoxin (TTX)-resistant sensory neuron-specific sodium channels (SNS), which lowers their activation threshold and increases their sodium current [30].

Recently, the phenomenon of 'hyperalgesic priming' of primary afferent nociceptors, in which an acute inflammatory insult triggers long-lasting hypersensitivity, has been described [31,32]. An important component of this afferent discharge is that from mechano-insensitive C-fibers, which appear to be critical for central sensitization of pain transmission neurons (PTNs) [33–35]. Central sensitization is the heightened excitability of nociceptive neurons at all levels of the central and peripheral pain matrix, and is thought to require a continuous nociceptive afferent barrage from the area of injury. It may also be induced by an early high-frequency discharge of mechano-heat-insensitive C-fibers, and later in its course may be maintained by an A β -fiber drive [4,17]. The second major mechanism leading to central sensitization and hyperexcitability of PTNs is the interaction between the immune system and the central and peripheral pain matrix, particularly at the level of the dorsal horn (DH) [36–38]. Central sensitization is characterized by: spread of pain in regional distributions beyond the site of injury and out of a nerve or root distribution; a lowered activation threshold of nociceptive neurons; evoked mechanical or thermal allodynia that is not stimulus bound and an increased

receptor field size of central and pain transition neurons [17,35,39,40]. CRPS may be an illness of maladaptive plasticity at all levels of the peripheral and central pain matrix – such that pain occurs spontaneously and is pathologically magnified by noxious and innocuous mechanical and thermal stimuli [17].

It is clear that, over time, the syndrome spreads and there are changes in the CNS control of autonomic, somatosensory and motor systems [8,17,24,41]. **Essential to the induction and maintenance of pain in the syndrome is the activation of the NMDA receptor.** This is an important mechanism for the central sensitization of PTNs and modulation of the immune system [17,42].

Neuroimmune interactions

Neuroinflammation and neuroimmune interactions may also lead to central sensitization [17]. Macrophages clear the cellular debris that occurs after injury and present antigens that activate lymphocytes, which release cytokines and chemokines that have pleiotropic effects on neurons, Schwann cells, DH ganglion (DHG) cells and satellite cells. Macrophage activation is an important component of Wallerian degeneration and immune activations in the injured nerve [36]. All animal models of neuropathic pain demonstrate DH glial cell activation following tissue or nerve injury [43]. Similar findings have been demonstrated in the seminal autopsy case of a long-standing CRPS patient [44]. Experimental studies suggest that microglial activation is most important in the initial phase of neuropathic pain, while astroglia activation is critical for its maintenance [9,10,45]. The signaling molecules demonstrated following glial activation include: ATP, CX3CL1 (fractalkine), CCL2 (monocyte chemoattractant protein-1), proinflammatory cytokines (TNF- α , IL-6, IL-1 β and SP) and glutamate [46–52]. Activated microglia and astrocytes secrete cytokines, chemokines, glutamate, nitric oxide, prostaglandins and ATP, which activate DH neurons and are a major component of the process that influences the induction and maintenance of neuropathic pain [9,10,17,18,46,53]. Experimental and clinical evidence has demonstrated the beneficial effects of ketamine treatment for CRPS pain (TABLE 1) [54–57]. This article will focus on aspects of the physiology and pharmacology of ketamine and its use in the treatment of CRPS.

Genetics

There is evidence that genetic factors may play a role in the pathophysiology of CRPS [58]. The disease may develop in approximately 10% of patients without a clear inciting event [11,59], which suggests etiologies other than trauma as causative of disease. There is some evidence that more severely affected patients are younger, which suggests a genetic susceptibility, and this has also been noted in other inflammatory conditions [60,61]. CRPS families with several affected members have been described, but no clear inheritance pattern is evident [62–65]. In the de Rooij study, familial CRPS patients had a lower age at onset, were more severely affected and had dystonia. This study also demonstrated no overall increased risk in CRPS siblings, although there was a possible association in siblings younger than 50 years of age [58]. There is strong evidence that HLA-B62 and HLA-DQ8 are associated with the subgroup of CRPS that have dystonia [58].

Table 1. Summary of clinical usage of ketamine for complex regional pain syndrome.

Study (year)	Sample Size	Design	Outcome measure	Controls	Dose	Duration	Follow-up	Results	Complications	Ref.
Webster <i>et al.</i> (2006)	13 patients: 8 M/5 F	Observational retrospective chart review	Pretreatment versus post-treatment pain	None	0.25 mg/kg max (0.12 mg/kg mean) continuous iv. outpatient infusion (home healthcare with infusion pump)	13.7 ± 0.5 days (1 patient: 8 weeks)	1 month	Reduced pain (85%) VAS: 7.7 (pre-) to 4.8 (post-treatment); p = 0.003	Confusion (2 out of 13), dizziness (3 out of 13), fatigue (4 out of 13) – none serious	[162]
Correll <i>et al.</i> (2004)	33 patients	Observational retrospective analysis	Pretreatment versus post-treatment pain	None	Titrated to 40 mg/h	One treatment of continuous iv. infusion for 5 days	3 years	Pain free: 54% for 3 months; 31% for 6 months/12 patients with repeated infusions: 100% relief; 58% for 1 year	Hallucinations (6 out of 33); dizziness, light-headedness and increased liver enzymes (4 out of 33)	[134]
Goldberg <i>et al.</i> (2005)	40 patients: 4 M/36 F	Open-label prospective	Pain reduction (spontaneous); mobility; objective component	None	40–80 mg over 4 h/session/day	Ten sessions: 4-h iv. outpatient infusion	3 and 6 months	Reduced 'worst' pain scores; increased mobility; decreased autonomic dysfunction	Hallucinations (none); dizziness and nausea (few); headaches (4 out of 40); restlessness (5 out of 40); increased heart rate (8 out of 40)	[139]
Kiefer <i>et al.</i> (2007)	1 patient: F aged 16 years	Compassionate care	Pain reduction (spontaneous); mobility; autonomic dysregulation	None	Anesthetic ketamine doses (3–5 mg/kg/h); midazolam (4 mg/kg/h)	5 days of coma intubation	1 year	Complete pain relief; normal mobility; no ANS symptoms	No lasting complications at 1 month; psychometric side effects resolved with midazolam	[131]
Becerra <i>et al.</i> (2009)	1 patient: F aged 22 years; CRPS type I and 1 month post-treatment CRPS(-)	Compassionate care: fMRI to compare pain state CRPS(+) and 1 month post-treatment CRPS(-)	Spontaneous pain, evoked (brush) pain; cold and heat pain: pre- and post-infusion	None	Anesthetic ketamine doses (7 mg/kg/h); midazolam (4 mg/kg/h)	5 days of coma intubation	1 month: fMRI post-treatment	Spontaneous and evoked pain reduction: 7–9 out of 10 (onset) to 0–1 out of 10 (1 month post-treatment); recovered state paralleled specific default networks in healthy volunteers	Weakness; psychomimetic effects (treated successfully in 2 weeks with Ativan®); nausea (3 weeks)	[57]

ANS: Autonomic nervous system; CRPS: Complex regional pain syndrome; F: Female; fMRI: Functional MRI; iv.: Intravenous; M: Male; Max: Maximum; PD: Pharmacodynamic; UTI: Urinary tract infection; VAS: Visual Analogue Scale.

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Study (year)	Sample Size	Design	Outcome measure	Controls	Dose	Duration	Follow-up	Results	Complications	Ref.
Finch <i>et al.</i> (2009)	20 patients	Double-blind placebo-controlled crossover trial	Effects of: light touch, pressure, punctate stimuli, light brushing and thermal stimuli	20 patients	10% ketamine cream, lightly applied	Acute treatment: 1 day	30 min after application	Inhibited dynamic mechano-allodynia and hyperalgesia to punctate stimuli; had distant effects	None	[128]
Sigtermans <i>et al.</i> (2009)	60 CRPS type I patients: 12 M/ 48 F	Double-blind randomized placebo-controlled parallel group	Spontaneous pain; ability to move limb; active range of motion; state temperatures; volumetric measurements; threshold for touch	12 subjects	Ketamine titrated to side effects: 22.2 mg/h/70 kg; at a mean rate of 30 mg/h/70 kg patient	4.2 days	3 months	Significant pain relief versus placebo until week 11 (independent of disease duration); no functional improvement nor change in other motor or sensory parameters	Mild psychomimetic side effects during infusion (93%); nausea (63%); vomiting (47%); headache (37%); liver function and blood pressure unaffected	[163]
Shirani <i>et al.</i> (2008)	1 patient: F aged 41 years	Compassionate care	Pain relief; edema reduction; autonomic dysregulation	None	50 mg iv. over 30 min	Three doses, 1 week apart	1 year	Pain free	Hypertension following first treatment – successfully resolved with labetalol and hydralazine	[132]
Kiefer <i>et al.</i> (2008)	20 patients	Open-label Phase II trial	Pain relief; movement disorder effects; quality of life; ability to work	None	Anesthetic dose titration of ketamine (7 mg/kg/h); midazolam (4 mg/kg/h)	5 days of coma with intubation	1, 3, 6 months and 10 years	Complete remission at 1 month in all patients and 17 at 6 months; quality of life, ability to work, associated movement disorder significantly improved in 1 patient. 10 of 20 patients were pain and medication free with full life at 10 years post-treatment	2 weeks: acute hallucination and taste in general. 1 month: respiratory infection (2 out of 20); UTI (2 out of 20); hallucination (5 out of 20); ataxia (15 out of 20); weakness, metallic taste, weight loss (20 out of 20); cognitive impairment (0 out of 20)	[140]

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Study (year)	Sample Size	Design	Outcome measure	Controls	Dose	Duration	Follow-up	Results	Complications	Ref.
Schwartzman et al. (2009)	19 patients: 1 M/18 F	Double-blind randomized placebo-controlled	Affective/discriminative parameters (McGill short-form); dynamic allodynia; joint pain; deep muscle pain; activity watch; severity of pain in most affected area	10	Ketamine: 0.35 mg/kg/h; 0.1 mg clonidine and 2 mg of midazolam at the beginning and end of procedure	4-h infusion for ten doses	3 months	Reduction of spontaneous pain ($p < 0.05$); decrease in affective component of McGill short form, mechano-allodynia and spontaneous burning pain; activity increase by watch for 1 month post-treatment	Treatment group (9). Nausea (4 out of 9); headaches (4 out of 9); dysphoria (4 out of 9). No psychomimetic effects	[54]
Dahan et al. (2011)	60 patients: treatment group – 22 F/8 M; placebo – 26 F/4 M	Randomized; 60 CRPS patients – 30 patients received ketamine and 30 received placebo	PD and PD parameters; pain relief	30 patients	S-ketamine infused from 5 to 20 mg/h	100-h infusion: mean ketamine dose given over 4.2 days was 1568 + 601 mg	3 months	Plasma concentration of ketamine and its metabolites decreased rapidly after termination of infusion. 50 days of significant pain relief	None	[117]

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Earlier studies also suggested a significant association between CRPS and HLA-DQ1, HLA-DR6 and HLA-DR13 [65–68].

Structure & function of the NMDA receptor

NMDA receptors are heteromeric complexes formed by four subunits derived from three related gene families: *NR1*, *NR2* and *NR3* [69]. Glutamate and glycine-responsive NMDA receptors are formed by two NR1 subunits that contain a glycine binding site and one or more of the four NR2 NMDA subunits (NR2A–D). The NR2 domain contains the glutamate binding site [70]. The multiple receptor isoforms are formed by splicing of NR1 transcripts and differential expression of NR2 subunits [71]. Each isoform has a different developmental evolution, distinct brain distribution and functional properties. Each subunit has a modular design that is a functional unit [69,71,72].

The extracellular component (amino terminal) contains a modulatory domain and a ligand-binding domain [73]. The NR1 subunit binds the coagonist glycine, while the NR2 subunit binds glutamate. Both binding sites need to be occupied to achieve full channel activation [74]. The agonist-binding molecule is linked to a three-membrane segment and re-entrant loop [73]. The membrane domain is a component of the receptor channel pore and is pivotal for its high unitary conductance, calcium permeability and voltage-dependant magnesium block [75,76]. The cytoplasmic domains of the subunits contain residues that are dually modified by protein kinases and phosphatases and interact with structural adapter and scaffolding proteins to modify the functional characteristics of PTNs [17,77–81].

The NMDA receptor is also modulated by both BDNF endogenous and exogenous compounds (serine, zinc, polyamines and BDNFs) that alter PTN excitability and are clinically relevant [82–86]. In addition, NMDA receptor function is regulated by reduction and oxidation – such that reductants enhance NMDA currents and oxidants reduce channel activity [87]. Protons inhibit NMDA response by decreasing channel opening frequency, but do not change conductance or dwell time [78]. Further regulation of the NMDA receptor is effected by cyclin-dependent kinase 5, which controls its surface expression and degradation [88,89].

The unique qualities of the NMDA receptor that may be critical for its role in CRPS are: its ligand-gated and voltage-dependent activation; its requirement of coactivation by two ligands; its activity dependence that induces neural plasticity; its complex activation and regulation; and its pleiotropic actions that lead to central sensitization of PTNs at all levels of the pain matrix. The exact role of the NMDA receptor in CRPS is not known. It appears to be a central receptor that induces calcium-regulated molecular cascades that change cell excitability, but it also has important functions in immune modulation.

The role of the NMDA receptor in central sensitization

Synaptic facilitation (long-term potentiation [LTP]) of PTNs is a major mechanism that leads to the mechanical and thermal allodynia, hyperalgesia and hyperpathia that are characteristic of CRPS patients [90]. This is effected by presynaptic increases in synthesis and release of neurotransmitters, modulators and the calcium channel density, as well as structural enlargement of dendrites that lead to LTP [91–94]. LTP type III requires both gene transcription and protein synthesis and is the most persistent form of LTP. It is dependent on both NMDA and L-type voltage-gated sources of calcium currents [95]. The increase in intracellular calcium activates extracellular-regulated kinase II (ERKII p42 MAPK), which is selectively involved in NMDA-induced receptor LTP and may be important in severe long-standing CRPS, as well as other neuropathic pains. If ERK activation is suppressed, DH hyperexcitability, as well as the induction and maintenance of LTP, is blocked [96,97]. Postsynaptic mechanisms of LTP include increased phosphorylation of NMDA subunits, increased synthesis of ion channels and modification of scaffold proteins [79–81,98–100]. The NR2B receptor subunit appears to be of particular importance in the development of central sensitization [101–103].

Central sensitization can also be induced by interactions between the nervous and immune systems that result in the activation of glial cells [17,43,104,105]. The NMDA receptor is involved in both the modification of immune function and the central role of monocyte/macrophage passage through the endothelial cell barrier [106]. In this location, they differentiate into fully functional microglia at the involved segmental level and may induce hypersensitivity of PTNs, which induces and maintains chronic pain [107,108]. Increased inflammatory cytokines have been found in the cerebrospinal fluid of CRPS patients, and widespread activation of both astrocytes and microglia was demonstrated in the spinal cord autopsy material from a long-standing refractory CRPS patient [44,109]. The safe inhibition of the NMDA receptor has proven to decrease neuropathic pain experimentally and in patients with CRPS, which is the rationale for its use in this condition [110].

Pharmacokinetics & pharmacodynamics of ketamine

Ketamine is a racemic mixture (50:50) of its enantiomers (*R*)- and (*S*)-ketamine that have significantly different pharmacodynamic properties. (*S*)-ketamine is the more potent analgesic, while its psychomimetic properties appear to be related to (*R*)-ketamine [111,112]. Ketamine is primarily metabolized by *N*-demethylation to (*S*)- and (*R*)-norketamine [113]. The

(*S*)-norketamine has been demonstrated to have an eightfold greater affinity for the NMDA receptor, as demonstrated in a rat cortical wedge preparation [114]. Pharmacodynamic and kinetics studies of single administrations of the racemic mixture of the drug have demonstrated a higher clearance rate and volume of (*S*)-ketamine than (*R*)-ketamine, which produces a higher plasma concentration of (*R*)-ketamine [115,116]. The same relative enantiomer selectivity has also been demonstrated for norketamine, in addition to which (*S*)-norketamine is thought to produce the antinociceptive effect.

The pharmacokinetic and pharmacodynamic properties of ketamine have recently been investigated with regards to CRPS [117]. A total of 30 patients were age- and gender-matched to normal subjects. The patients underwent a 100-h infusion of ketamine titrated from 5 mg/h (per 70 kg) to a maximum dose of 30 mg/h (per 70 kg) in accordance with unacceptable side effects (psychomimetic or agitation/hallucinations) and treatment response. Pain scores were obtained three times a day (numerical rating scale 0 = no pain; 10 = unbearable pain) during the infusion. Venous blood samples were obtained and (*S*)-ketamine and (*S*)-norketamine were measured. No motor side effects occurred during the procedure. The infusion rate at the end of the treatment period was 20 ± 4 mg/h (per 70 kg). The mean total ketamine dose administered over 4.2 days was 1568 ± 601 mg (range 533–2637 mg). The maximum (*S*)-ketamine and (*S*)-norketamine concentrations achieved were 248 ± 91 ng/ml and 280 ± 112 ng/ml, respectively. Utilizing a three-compartment model, 36% of ketamine was metabolized to norketamine and both (*S*)-ketamine and (*S*)-norketamine concentrations rapidly declined at the end of the infusion.

A similar study conducted over 5 days in 16 CRPS patients, in which ketamine was titrated from 10 to 40 mg/h and maintained over 5 days at this dosage, utilized enantiomer-selective liquid chromatography/mass spectroscopy and determined that: ketamine and norketamine concentrations stabilized 5 h after the start of the infusion; (*R*)-ketamine clearance was significantly lower than (*S*)-ketamine, which resulted in a higher steady-state concentration for this (*R*)-enantiomer; the first-order elimination of (*S*)-ketamine was significantly greater than that of the (*R*)-enantiomer [118].

These pharmacokinetic profiles of (*R*)- and (*S*)-ketamine were obtained from a linear one-compartment model. The concentrations of ketamine peaked at 250 ng/ml for days 1–3. A prior Japanese study found no clearance differences between ketamine and norketamine, which was ascribed to large interindividual and ethnic differences in the microsomal CYP2B6 system that is pivotal to ketamine metabolism [113].

In the Dahan *et al.* study, 24 of the 30 CRPS patients had an analgesic effect from the ketamine infusion, while 25 of the 30 control patients did not (TABLE 1) [117]. There was a tendency towards improvement in patients with shorter disease duration. The treatment effect (decline of numerical rating scale [NRS] lasting >1 week) was 67%, while the placebo response was 23%. The failure of ketamine treatment in approximately 30% of patients was hypothesized to occur: from a dosing effect (greater concentration of drug may be required in some patients); from

a duration of treatment effect (longer treatment may be more effective); from a metabolic effect (degradation of drug); from treatment of nonspecific pain rather than CRPS; and from genetic differences in the NMDA receptor.

The Goldberg *et al.* studies revealed that although ketamine and norketamine plasma concentrations reach steady-state quickly, pain relief increased over time [118,119]. No statistical differences between the ten responders and the six nonresponders were found with regard to ketamine clearance and first-order elimination rate of norketamine. This suggests that ketamine and norketamine may not be responsible for all of the drug's antinociceptive effect. Hydroxylated, dehydration metabolites or other compounds may also be important in this role. No significant complications occurred during this study. The effective concentrations of (*S*)-ketamine and (*S*)-norketamine for pain relief were similar to those of the Sigtermans *et al.* study [55].

The use of ketamine for the treatment of CRPS

Ketamine is currently the most potent clinically available NMDA antagonist and has a well-established role in the treatment of acute and chronic pain [120,121]. Its use in surgical procedures may reduce 'wind-up' and punctate hyperalgesia. At the higher intraoperative doses used in major abdominal surgery it reduces the area of wound hyperalgesia and decreases the initiation and maintenance of chronic pain [122–124]. It has only been utilized in the treatment of CRPS relatively recently [54,55,125–140].

Analysis of double-blind randomized controlled trials in the treatment of CRPS

There is little evidence that the usual treatments for moderate-to-severe CRPS are effective. These include opioids, antidepressants, antiepileptics and sympathetic blockade [141–143]. Minimal relief has been achieved with dimethylsulfoxide cream, *N*-acetylcysteine and physiotherapy [144,145]. Spinal cord stimulation is difficult to use in generalized disease, but has been demonstrated to be effective for pain relief and vasomotor dysregulation; however, its efficacy decreases over time [146].

Several open-label case studies utilizing ketamine by infusion were successful in reducing pain in CRPS and cancer patients without severe side effects (TABLE 1) [126,131,132,134,139,140,147].

Finch and colleagues utilized a double-blind placebo-controlled crossover trial to determine the effects of topical ketamine on sensory abnormalities in 20 patients with CRPS (TABLE 1) [128]. Sensory tests evaluated the effects of light touch, pressure, punctate, brushing and temperature. A 10% ketamine cream was applied to the affected and unaffected extremities and the concomitant plasma concentration of ketamine and norketamine were obtained. Ketamine decreased dynamic allodynia and hyperalgesia to punctate stimuli in the affected arm. Mechano-allodynia and hyperalgesia were also noted in the ipsilateral forehead of affected patients, which was also decreased in some patients.

The authors concluded that since touch thresholds were unattenuated, and ketamine levels were not detectable in venous blood, the ketamine effect was at the level of cutaneous NMDA receptors. The decrease of allodynia at a remote site (forehead)

suggested that the mechanism that mediates allodynia segmentally may also contribute to allodynia at distant sites. Experimental support for this concept is presented in a recent report that demonstrated that the thalamus may be involved in widespread allodynia from a segmental lesion [148]. This mode of therapy needs to be evaluated in refractory patients with more generalized and long-standing disease.

The double-blind, randomized, placebo-controlled, parallel-group trial of 60 CRPS patients led by Sigtermans used a 4.2-day continuous infusion of low-dose ketamine, increased in a step-wise fashion that was titrated to pain relief [56]. Patients were evaluated for 12 weeks following the infusion. The median duration of disease in these patients was 7.4 (0.1–31.9) years. At the final titration time the ketamine dose was 22.2 ± 2.0 mg/h. Pain scores were significantly decreased for 10 weeks. These results differ from ketamine effects on acute experimental pain and EEG slowing, which is directly correlated with its plasma concentration and stops at the end of the infusion [55,149]. The mechanism hypothesized for this differential effect was long-term desensitization of the NMDA receptor. Even though substantial pain relief was obtained, patients demonstrated no functional improvement. This observation suggested that more profound effects could be related to the length of the infusion. It also underscores the need for physical therapy and psychiatric support for patients who have been socially isolated and unable to work for several years. The authors also noted that the ketamine effect was not related to length of disease. Only two patients dropped out of the trial owing to psychomimetic side effects, while 90% of patients reported hallucinations that were mild-to-moderate. Midazolam was used as an active placebo to dampen these psychomimetic complications [54,140]. A great strength of the study is that a placebo arm was utilized in a hospital inpatient setting.

The single randomized placebo-controlled outpatient double-blind study (nine patients; ten controls) utilizing a maximum of 0.35 mg/kg/h that did not exceed 100 mg over a 4-h infusion period, delivered in ten consecutive sessions (4 h/day \times 5 days; weekend off; 4 h/day for the next 5 days), was successful. It reduced the affective component of pain (McGill Pain Questionnaire) by 50% for 3 months. Pain in the most affected area, spontaneous burning pain, mechano-dynamic and static allodynia and overall pain responded at a statistically significant level ($p < 0.05$) (TABLE 1) [54]. Spontaneous pain was significantly reduced for 1 month. Activity watch scores were significantly decreased and demonstrated fewer spontaneous awakenings and lower daytime pain scores. None of the subjects in the placebo group had significant improvement in any sensory parameter. All other parameters of discriminative pain queried, which included overall pain, deep muscle pain, joint pain (large and small joints) and cold allodynia, as well as quality of life issues, did not reach statistical significance but tended toward improvement. Surprisingly, there was no significant difference between patients with a shorter or longer duration of illness (0.8–4.2 vs 6.8–20 years) in any pain parameter. However, the Dahan *et al.* study suggested that patients with a shorter length of illness had a better response to treatment [117]. This was similar to Sigtermans'

4.2-day infusion trial and correlated with a recent study of the natural history of 580 CRPS patients whose signs and symptoms were evaluated by regression analysis. Their pain scores on multiple pain parameters changed little after 1 year [1]. The strengths of the study were the use of an active placebo control and an objective measurement of sleep quality, awakenings and activity by actigraphy (activity watch data). The latter measurements help to minimize retrospective bias of self-reported data, in which there is a tendency to report peak and most recent symptoms [150,151]. Four of the nine subjects in the ketamine arm of the study and two of the ten patients in the placebo arm complained of headache, tiredness or dysphoria. None reported hallucinations, delusions or out-of-body experiences. The concomitant use of midazolam and clonidine may have controlled the psychomimetic effects of ketamine.

Ketamine coma

Those patients with severe long-standing or generalized CRPS who have failed all standard therapies, as well as the 5-day inpatient or 10-day outpatient protocol, are candidates for anesthetic dosage treatment [140]. This is a combination of ketamine and midazolam in conjunction with a daily dose of 0.1 mg of clonidine. Ketamine analgesic potency and duration of clinical effect are dose dependent [121]. The first 20 patients treated with anesthetic doses of ketamine, 7 mg/kg/h and 0.15–0.4 mg/kg/h of midazolam over 5 days, have been reported in detail (TABLE 1) [140].

Complete remission from CRPS was seen in all patients at 1 month, in 17 out of 20 at 3 months and in 16 out of 20 at 6 months. Ten of the original 20 patients have remained completely pain free from 5 to 11 years. These patients have returned to a normal life in all spheres and are taking no pain medication.

On the first day of ketamine anesthesia, patients start to mobilize neurogenic edema fluid. On the third day, venous tone returns to the affected extremity. This is manifest by the normal fluctuation of venous diameter during the day (venous motion). On emergence from anesthesia, many patients examine their formerly painful extremity and test movements. Most patients have difficulty speaking for a few hours and all are slightly confused and ataxic. As noted above, approximately 50% of severe long-standing generalized patients do not have a complete remission for more than a year. Their CRPS may be maintained from neuroimmune or other mechanisms [38]. The major complications seen in approximately 20% of patients were urinary and pulmonary infections that are typical in intensive care medicine. Transient ketamine-specific psychotropic effects occur on emergence from the anesthesia and are successfully treated with benzodiazepines. All patients lose approximately 10 pounds during treatment. Muscle weakness persists in some patients (mild degree) for 4–6 weeks. Some patients have an alteration of taste that lasts for approximately 1 month (metallic taste). A few patients are slightly ataxic for 1–2 weeks. Detailed psychological testing at 6 weeks following coma therapy assessed in nine patients revealed no adverse cognitive effects [152]. No long-term psychiatric impairments have been seen in any of these 20 patients.

The use of ketamine as adjunctive or combination therapy

Successful use of ketamine as adjunctive therapy for CRPS types I and II has also been recently reported. Three patients who had suffered gunshot wounds and developed severe pain, mechano- and thermal-allodynia gained pain relief from sympathectomy. The addition of 0.5 mg/kg of ketamine to their sympathetic blocks relieved their allodynia [130]. A patient suffering from refractory CRPS type I was treated with a 19-h infusion of ketamine and dexmedetomidine (an α -2 agonist similar to clonidine) with complete success. The combined usage of these drugs decreased the dose of ketamine necessary for effective analgesia [133]. Another patient with severe refractory CRPS type I was treated successfully with a continuous sciatic nerve block and concomitant ketamine infusion, which suggests the importance of blocking the maintaining afferent nociceptive barrage, as well as central sensitization [138]. Recently, 42 patients with refractory CRPS type I underwent 5-day inpatient, continuous intravenous (iv.) ketamine (0.6–0.8 mg/kg/h, maximum of 60 mg/h) infusion combined with continuous epidural anesthesia (bupivacaine, dilaudid and clonidine). Lorazepam 1 mg per ore was administered every 6 h [153]. After inpatient treatment these patients were given outpatient ketamine iv. boosters of 100–250 mg over 4 h. This protocol was administered for 2 consecutive days at 2–4-week intervals for 2 months. Patients were evaluated at 12 and 24 weeks. Pain score was the primary outcome measure. Side effects were recorded.

The majority of patients were severely affected: 92.9% (40 out of 42) had CRPS affecting their entire body and 100% had a NRS of 10 (0 being no pain and 10 the worst pain imaginable). During the infusion 64.3% (27 out of 42) patients reported nausea; 38.1% (16 out of 42) vomited; 4% (2 out of 42) had mild liver function elevation; and one patient, 2.4% (1 out of 42), had delirium. At 12 weeks, 61.9% (26 out of 42) reported pain improvement (>3 NRS decrease). At 24 weeks, 30.9% (13 out of 42) had significant pain reduction. There were no significant psychomimetic or other complications [153].

As noted above, the overwhelming majority of reports demonstrate the effectiveness of racemic or (*S*)-ketamine for the treatment of CRPS in all stages of severity. There is one report of four refractory patients that failed subanesthetic (*S*)-ketamine [140]. The index autopsied case of severe CRPS has demonstrated significant posterior horn cell loss, possibly of inhibitory neurons in the DH [44]. Higher analgesic doses or combined therapy with immune-modulating agents may be required in these patients.

Complications of ketamine therapy

Although ketamine has been safely used for over 35 years in clinical anesthesia and intensive care, concerns have been raised regarding NMDA antagonist-induced neurotoxicity. This has been demonstrated in the adult and developing rat brain [154]. These effects are prevented by the administration of clonidine and GABA-agonists [155], and have not to our knowledge been reported in humans [121]. A study evaluating ketamine sedation in brain-injured patients, with duration and dosage similar to the

5-day anesthetic dosage utilized above, had no significant morbidity or mortality [156,157]. A detailed neuropsychological evaluation of patients pre- and post-ketamine 6-week coma for CRPS that included intellectual and academic abilities, executive functioning/processing speed, attention, learning and memory demonstrated significant improvement in brief attention and processing speed and no cognitive deficits [140]. The major complication of the coma study was infection. Seven patients had respiratory infections and six had lower urinary tract infections. All were successfully treated with antibiotics. Transient rises in liver enzymes, creatine kinase (CK) and CK-myocardial band (CKMB), occurred during treatment. Five of these patients were taking high doses of analgesic, antidepressants and seizure medications. Under anesthesia, 16 of 20 patients developed elevation of liver enzymes and creatine phosphokinase (CPK), which returned to reference range at 10–14 days after the infusion. All patients had normal ratios for CPK:CKMB, which were below 10%.

Subanesthetic infusion protocols that did not utilize clonidine or midazolam had a 93% incidence of psychomimetic effects. Nausea was noted in 63% of patients, vomiting in 47% and headache in 37%. Liver function and blood pressure remained normal [55].

The major side effects in the outpatient protocol (utilizing midazolam and clonidine) in four of nine patients receiving ketamine were nausea, headache, tiredness or dysphoria. No patient reported hallucinations, delusion, blurred vision or out-of-body experiences. There were no liver or cardiac abnormalities [54]. Two studies have demonstrated possible ketamine impairment of short-term memory. The subjects in the first study were abusing other drugs, including alcohol, which makes the role of ketamine difficult to determine [158]. The second study demonstrated upregulation of dopamine D1 receptors in chronic ketamine abusers. It also demonstrated no deficits in working memory, executive attention, reaction time, verbal learning and memory, fluency and motor function [159]. A detailed description of the outpatient intravenous ketamine treatment procedure used at our clinic is included in the APPENDIX.

Conclusion

As a greater understanding of the basic mechanisms that underlie CRPS is achieved, a targeted molecular approach, such as down-regulating the NMDA receptor by uncoupling Src or blocking the upregulation of the NMDA-2B subunit, will be possible in the future [160,161].

Ketamine protocols have been demonstrated to be effective and safe therapy in severe refractory CRPS patients when multidisciplinary drug regimes have failed.

Expert commentary

The components of CRPS have been identified and validated. A great deal of progress has been made in understanding synaptic plasticity of PTNs that lead to both LTP and long-term depression of their excitability. The state of central sensitization is critical to the maintenance and spread of the pain suffered. The immune system and its interaction with the pain matrix can both induce

and maintain the process. Fundamental to the syndrome is the NMDA receptor, particularly those with upregulated NR2B subunits. In addition to the afferent barrage from mechano-insensitive C-fibers and A- δ fibers, BDNF is released by nociceptive afferents and can modify the receptor. There is dynamic interplay between the peripherally sensitized nociceptive fibers in the area of injury, retrogradely transported neurotrophic factors and monocytes at the site of injury that modulate the NMDA receptor, at the DH. It is clear from the treatment of patients with CRPS in different stages of illness that ketamine blockade of the receptor is effective. It is also clear that the psychomimetic manifestations of the drug can be safely managed with benzodiazepines, both during treatment and afterwards. In our infusion unit, all patients must undergo a detailed psychiatric examination to rule out schizophrenia, manic depressive illness and prior drug abuse or post-traumatic stress syndrome before receiving ketamine. Approximately 10% of patients will fail this screen. Hundreds of ketamine infusions have been given safely as outpatient therapy. Two nurses with full life support training administer the drug. All patients are monitored for cardiac rhythm, oxygen saturation and blood pressure. A physician evaluates treatment progress during each infusion.

The Institutional Review Boards at Drexel University, Saarbrücken and Tübingen all required monitoring of the parameters noted. It is well documented that ketamine may cause an increase in intraocular pressure, malignant hyperthermia, increased blood pressure and hypersalivation, as well as its well-known psychomimetic properties. These are the major reasons for the close monitoring required.

The drug works, to some degree, in all patients. Unfortunately, the outpatients on subanesthetic protocols are not cured, but 70–80% of patients return to a better life. The coma protocol has been spectacular in 50% of patients, who prior to treatment were on huge doses of narcotics and were bedridden. They have been returned to life. Unfortunately, the 50% of patients treated with anesthetic doses fail over time and the illness returns, but in general, not to the same degree.

Five-year view

The progress made over the last 5 years in elucidating basic mechanisms of PTN function has been spectacular. Electrophysiology at the dendritic spine level accompanied by immunochemistry and receptor physiology is elucidating the enzymatic cascades that determine cell hyperexcitability. It is clear that genomics and proteomics will determine the genetic switches that modulate the system. There are clinically distinct CRPS subtypes: a relatively limited syndrome with vasomotor signs predominating; a relatively limited syndrome with neuropathic pain and sensory abnormalities predominating; and a florid CRPS syndrome similar to classical description of reflex sympathetic dystrophy. We feel that cluster analysis based solely on signs and symptoms, although a large step forward, is less powerful than clusters based on both clinical and biomarker profiles as a way to identify distinct CRPS subtypes. We hypothesize that there are markers in blood and cerebrospinal fluid that, when used in conjunction

with the signs and symptom categories, can define subtypes of CRPS patients, and these biomarkers can also be used to predict disease severity and progression. Lumping CRPS patients into one group makes both the targeting of effective therapies and the selection of a homogeneous patient population for clinical trials extremely difficult. Current clinical trials may fail to demonstrate efficacy, even though the drug under study may be efficacious in a subset of patients. The determination of biomarkers that define subtypes of CRPS will be invaluable in the future design of clinical trials and will allow for a higher level of clinical efficacy to be attained by a greater number of patients. In addition, the identification of CRPS subtypes may aid in elucidating the different mechanisms involved in its pathophysiology. Drugs are already available that have not been tested in a randomized double-blind placebo-controlled fashion that are safe and have the scientific experimental rationale to be successful in CRPS. Ifenprodil specifically blocks the NR2B receptor, which is attracting attention as a specific subunit of the NMDA receptor that may be critical for the maintenance of pain in CRPS. Thalidomide and lenalidomide have both been found to be effective in a subset of CRPS patients. One mechanism of their actions is to suppress inflammatory cytokines that actively stimulate PTNs, as well as block glutamate release. Pentoxifylline and ibudilast, phosphodiesterase inhibitors, are excellent candidates to block the activation

of microglia that is important in the induction of persistent pain states. Antibody therapies to block NGF or possibly BDNF may be utilized, as they are important components of pain mechanisms. Specific modulation of the NMDA receptor, as recently demonstrated by interruption of its association with Src, may be forthcoming. Combined immune and neurogenic approaches to treatment may be necessary in refractory patients. Until more specific molecular approaches can be utilized, ketamine will help severely affected patients.

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Key issues

- The nociceptive barrage from the area of injury (C-mechano-insensitive fibers) appears to be critical for the central sensitization of pain transmission neurons.
- The corelease of glutamate, substance P and calcitonin gene-related peptides lift the Mg²⁺ block of the NMDA receptor.
- The NMDA receptor is critical for Ca²⁺ induced intracellular cascades.
- Long-term potentiation is induced by increased intracellular calcium concentration.
- Central sensitization of the pain transmission neuron is essential in chronic pain states.
- The induction of chronic pain states are thought to require microglial activation whereas astrocytic activation is important in pain maintenance.
- In chronic pain states, the NR2B subunit of the NMDA receptor is upregulated.
- The efficacy of ketamine is thought to result from its ability to block the NMDA receptor.
- Different ketamine protocols may be required for patients at different stages of complex regional pain syndrome.
- The safe use of intravenous ketamine requires careful patient selection and the concomitant administration of midazolam and clonidine.

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- **First randomized controlled trial of inpatient continuous ketamine protocol.**

Appendix

Prior to treatment with ketamine in our center, all patients are diagnosed with complex regional pain syndrome (CRPS) based on the International Association for the Study of Pain criteria (IASP) and Budapest Criteria [6]. The majority of patients suffered spontaneous and evoked pain at a level of 8–10 on a Likert numerical rating scale (NRS; end points 0 no pain; 10 worse pain imaginable for at least 6 months). Most patients had pain of 1–5 years duration. All patients had failed standard therapy that included pharmacological, interventional, physical and psychological modalities. Failure is defined as no benefit of treatment or pain relief of less than 2 weeks. A refractory designation includes failure of: physical therapy; psychological therapy; combined therapy with NSAIDs, tricyclic or serotonin-specific reuptake inhibitors, anticonvulsants or low or high potency opioids; and at least two interventional procedures that included selective nerve blocks, epidural anesthesia, brachial plexus or radicular blocks, sympathetic ganglion blocks, spinal cord stimulation, surgical sympathectomy or intradural delivery systems.

All patients are diagnosed by the same neurologist (Robert J Schwartzman) and the same psychologist. The psychological profile and testing is extensive (approximately 3 h) and includes general parameters of intellectual function, as well as the Adult Suicide Ideation Questionnaire (ASIQ) and the Beck Depression Inventory-II. Specific effort is expended to uncover manic depression, schizophrenia, prior drug abuse and post-traumatic stress disorder. Depressed patients are treated, but the aforementioned psychiatric diagnoses are exclusion criteria. All patients undergo an extensive cardiac evaluation that includes a clinical evaluation by the same cardiologist, a 12-lead ECG, echocardiogram (ECHO) and tilt table evaluation. All patients have a complete blood count, liver profile, blood urea nitrogen, electrolyte panel and thyroid-stimulating hormone. Further exclusion criteria are severe hypertension, hyperthyroidism and ischemic heart disease or failure, as well as allergies to ketamine or midazolam. The inclusion and exclusion criteria are evaluated by an anesthesiologist, psychiatrist, cardiologist and neurologist (Robert J Schwartzman). Approximately 10% of patients screened are excluded primarily for psychiatric reasons.

The infusion suite is attended by two nurses who are advanced cardiac life support (ACLS) certified. The patients' cardiac rhythm (ECG), oxygen saturation and blood pressure are continuously monitored. Complete blood count and electrolyte profiles are obtained at the end of the infusion. Clonidine (0.1 mg per orem) and midazolam 2 mg prior to and following the 4-h infusion is administered intravenously. Clonidine potentiates NMDA receptor blockade, has pain-relieving effects and prevents the neurotoxic side effects noted in rodents [154]. Zofran 4 mg is utilized for nausea if necessary. They are accompanied to the suite and escorted home by a relative or friend. Midazolam 2 mg is utilized prior to the ketamine infusion for sedation and to block agitation and vivid dreams. All patients are infused intravenously with ketamine (200 mg) in 100 ml of normal saline over 4 h (50 mg/h). The infusion protocol for outpatient treatment is 80 mg the first day (20 mg/h), 100 mg the second (25 mg/h) and 150 mg on day 3 (37.5 mg/h). On the fourth through to the tenth day, ketamine is infused at 50 mg/h for 4 h and maintained at this dose. The initial protocol is ten infusions of 4 h over 10 days (5 days on, 2 days off, 5 days on). Boosters of 200 mg of ketamine in 100 ml of saline over 4 h are given at 2 weeks, 1 month, 2 months and 3 months.

Side effects of this protocol are headache, nausea, tiredness, difficulty sleeping and dysphoria, which occur in approximately 25% of patients and are either self limited or controlled with 2–4 mg of ativan. There were no serious side effects. We ascribe this to careful psychiatric screening, midazolam and clonidine during the procedure, a quiet controlled atmosphere in the infusion suite and 2–4 mg of midazolam after the procedure if necessary. Ativan® (2 mg) is advised prior to sleep.