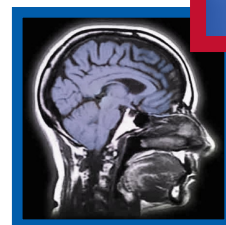
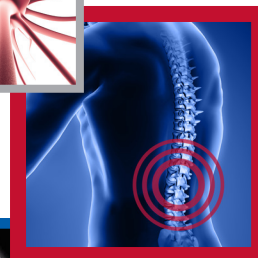
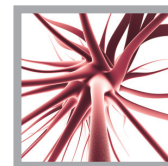


Perioperative management for patients with complex regional pain syndrome



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Practice Points

- The incidence of complex regional pain syndrome (CRPS) varies significantly based on ethnicity, gender and age. This variation may be a result of the different diagnostic criteria used in the different studies.
- CRPS pain is not only modulated by neurons. Glial cells and immune cells play important roles. More research and new medications targeting these structures are needed.
- Preoperative anxiety, preoperative pain intensity, prolonged tourniquet time and motor nerve injury correlate with the development of CRPS.
- Surgical procedures should be delayed until CRPS symptoms are well controlled. In addition, reducing operative and tourniquet time, and choosing a minimally invasive approach, are evidently important factors.
- Preoperative administration of vitamin C as a preventive measure is cost effective and should be strongly considered, not only in CRPS patients, but also in the majority of trauma and orthopedic surgery cases.
- Preoperative ketamine infusion should be part of managing CRPS patients, unless contraindicated.

SUMMARY Our knowledge of complex regional pain syndrome extends from the time of the American Civil War until today. Traumatic or surgical insults can be the precipitating factors in normal patients and can therefore be significant in the exacerbation of the condition. Complex regional pain syndrome patients complain of continuing pain that is disproportionate in severity to the inciting event. The pain is usually accompanied by sensory symptoms, such as allodynia or hyperalgesia, and vasomotor changes, such as changes in color or temperature. There has been increasing research on predicting the development of postoperative complex regional pain syndrome and its prevention. Management includes sympathetic blockades, spinal cord stimulation and medications (such as anticonvulsants, antidepressants, local anesthetics, NMDA antagonists and α -2-adrenergic agonists). In the last few years, several newer medications and supplements to prevent and treat the condition have been studied.

Methodology

We reviewed the PubMed database for peer reviewed articles written in English and published since 1990 using the following mesh terms:

'complex regional pain syndrome' (CRPS), 'causalgia', 'algodystrophy', 'reflex sympathetic dystrophy', 'incidence', 'prevalence', 'pathophysiology', 'preoperative pain', 'postoperative pain',

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‘acute pain’, ‘regional anesthesia’ and ‘blocks’. We also supplemented our search by including other articles brought to our attention during the writing of this article.

Epidemiology

The incidence of CRPS varies significantly based on ethnicity, gender and age. In the USA, Sandroni *et al.* reported in a retrospective chart review of 134 patients that the incidence of CRPS is about 5.5 per 100,000, with a mean age of 41.8 years at initial evaluation. Females (70%) were affected more than males (30%) [1]. In another retrospective European cohort study, it was found that the incidence of CRPS is about 26.2 per 100,000 [2]. The differences in the epidemiology reports may also be an effect of the different diagnostic criteria that were used.

Pathophysiology

The pathophysiology of the sensory and autonomic disturbances in CRPS is not fully understood, but there is growing evidence that an inflammatory process is involved. VEGF, IL-1 receptor antagonist and MCP-1 were found to be significantly elevated in patients with CRPS. Some of these markers are also correlated with the severity of pain [3]. In an article by Walker and Drummond, TNF- α was found to be an important element in promoting inflammation and microvascular disturbances. Targeting these with anti-TNF therapy was suggested [4]. Hyperalgesia was also found to be associated with a subtype of TNF (TNFR1) [5]. Furthermore, blocking TNF- α with thalidomide was found to be effective in about one-third of CRPS patients. This supports a correlation between TNF and CRPS [6]. Though the exact pathophysiologic mechanisms are still not completely clear, there is growing evidence that changes in signal processing and neuroplastic changes are important factors. The ectopic generation of an action potential, facilitation and inhibition of synaptic transmission, formation of new synaptic circuits and neuro-immune interactions are attributing factors [7]. Active and passive processes that are involved in pain production where plastic changes occur are not limited to the peripheral nervous system, but also occur in the CNS; thus many changes are responsible for the windup of neurons [8]. The postsynaptic signaling of neurons, especially with activation of glutamate receptors, has been described [9]. Pain should no longer be viewed as modulated by neurons only; immune cells and glia play pivotal roles in pain

modulation and it has been suggested that new therapies should target these non-neuronal structures [10]. Interestingly, glial activation results in glia-to-neuron signaling, this activation results in upregulation of excitatory amino acid receptors and downregulation of GABA receptors [11]. In a prospective study that included 53 patients (including 22 patients that met the diagnostic criteria for CRPS established by the International Association for the Study of Pain), Alexander *et al.* reported that although there are no specific markers found in the cerebrospinal fluid of CRPS, a pattern was found in 50% of patients. This pattern showed elevated IL6, GFAP nitric oxide synthetase, calcium and glutamate. Elevation of Manchester Clinical Placement Index instead of the elevated GFAP was found in some cases. There was also a decrease in IL6 and IL10 levels found [12]. Alexander *et al.* also reported increased CD14+ and CD16+ monocyte subgroups in patients with CRPS [13]. Recently, in a prospective study that included 208 CRPS patients, Alexander *et al.* reported the presence of a significant correlation between proinflammatory cytokines and their soluble receptors in CRPS subjects when compared with healthy control subjects. There is correlation found between TNFR1 and hyperalgesia, though it is not statistically significant ($p = 0.32$). A limitation of the study that is acknowledged by the authors themselves is the absence of grading of symptoms, which, if performed, may have led to correlation of clinical symptoms with plasma analytic levels. These findings will definitely help in the development of new target therapies [14]. There has been growing interest in the molecular signature of the disease. Orlova *et al.* reported that there is expression modulation of 18 noncoding miRNAs in CRPS patients. Also in that study, which included 61 patients, it was reported that VEGF, IL-1 receptor antagonist and MCP-1 were elevated in CRPS patients [3]. The dysfunction of small diameter axons in peripheral nerves is critical in both CRPS types 1 and 2 [15].

Precipitating factors

A multicenter cohort study involving 596 patients correlated intra-articular fractures, fracture dislocations and rheumatoid arthritis with the development of CRPS type 1 [16]. In a prospective, randomized study conducted on 77 patients scheduled for total knee arthroplasty, it was found that preoperative anxiety and preoperative pain intensity correlated with the development of postoperative CRPS [17]. In an observational

study performed on 160 patients, Demir *et al.* reported that motor nerve injury is an important risk factor [18]. Recently, it was found that there is increased risk for developing this syndrome in siblings younger than 50 years [19]. As of now, there is no specific inheritance pattern found; however, familial predisposition to the disease was reported [20]. Genetic factors predisposing to this condition need further study.

Reflex sympathetic dystrophy (RSD), which is currently known as CRPS type 1, is frequently associated with arthroscopic knee surgery [21]. Cooper and Delee recommended epidural catheter placement as an initial approach for managing RSD, as it also provides somatic blockade that will facilitate joint mobilization [22].

Even minor procedures can be precipitating factors for the development of CRPS. There are case reports describing postoperative CRPS after a transradial approach to coronary catheterization [23,24] and after placement of an arterio-venous hemodialysis graft [25].

Evaluation of the relative risk of developing the condition is a very important step for a more accurate risk/benefit ratio analysis prior to surgery. A prospective study that included 34 patients scheduled for a repeat carpal tunnel release found that reflex-evoked vasoconstrictor response recorded with laser Doppler imaging can be used to evaluate the relative risk for developing CRPS type 1 in those patients [26]. A limitation of the study was the fact that although the patients were assigned to the two study groups based on their preoperative laser Doppler imaging, there was no knowledge of the baseline sympathetic function of these patients before the first surgery, which can be a confounder to the results of the study.

Management

There is no standard perioperative approach for preventing the development of, or managing existing cases of, CRPS during surgery and the postoperative period. In this article, we will summarize current approaches, as well as newer approaches, that we consider reasonable to follow in preventing the development, and also preventing the exacerbation of already diagnosed CRPS cases during the preoperative period.

The timing of surgery, the choice of the anesthetic technique, use of prophylactic medications and supplements, as well as postoperative pain managements, are among the main factors that we will discuss.

Preventive measures

Marx *et al.* reported a standardized protocol in a case series to prevent the recurrence of RSD. That protocol included waiting until the signs and symptoms of RSD have vanished, decreasing operative and tourniquet time, and choosing a minimally invasive approach performed by the same surgical team. It also involved administering calcitonin 2–4 days preoperatively and up to 4 weeks postoperatively, adequate pain control and early postoperative functional mobilization [27]. The chosen population sample that previously had RSD with no control group is a significant limitation to the report. Also, they advised waiting until signs and symptoms vanished, which is not always achievable for CRPS patients. A more practical approach is that surgery should be delayed until the symptoms are well controlled.

Recently, the effect of vitamin C on prevention of CRPS following surgery was studied. Vitamin C was found in many studies to decrease the incidence of postoperative CRPS [28–30]. In a multicenter, randomized, double-blind study that included 416 patients comparing three different daily doses of vitamin C, a 500-mg daily dose of vitamin C decreased the prevalence of CRPS after wrist fractures. The study is limited, however, by the wide confidence intervals, confounding factors and lack of precision [28–30]. The same dose of vitamin C for the same duration proved beneficial in a pilot prospective cohort study of 27 patients. The patients in this study had 32 arthroplasties of the first carpometacarpal joint [31] and 40 implantations for trapezio-metacarpal arthritis [32] without developing CRPS. In a chart review study that also included radio-clinical follow-up that was performed on 392 patients, Besse *et al.* reported that a prophylactic, 1-g daily dose of vitamin C resulted in a fivefold decrease in the relative risk of developing CRPS after ankle surgery [33].

Anesthetic & intraoperative management

The anesthetic plan of CRPS is not limited to the choice between regional anesthesia and general anesthesia, but also involves selecting medications used during anesthesia.

In a prospective, controlled study that included 301 patients undergoing carpal tunnel release, the incidence of CRPS was approximately 8.3%. There was no difference found in the development of CRPS in patients who received general anesthesia, intravenous regional anesthesia with lidocaine or intravenous anesthesia with

lidocaine and clonidine, in comparison with patients who received a brachial plexus block. This study also showed a positive correlation between tourniquet time and the development of CRPS. This implicates tissue ischemia as a possible iatrogenic factor [34].

Despite the one study quoted above, the authors believe that regional anesthesia is a better choice than general anesthesia, especially in patients with established cases of CRPS. Toshniwal *et al.* reported managing patients with RSD with brachial plexus blockade. One limitation of the study was the small sample size [35]. Most importantly, these patients need an aggressive pain management protocol postoperatively, and placement of a peripheral or neuroaxial catheter will help during both intraoperative and postoperative periods. It is not unreasonable, in some instances, to place a catheter for regional anesthesia the day before surgery, especially in trauma patients who may already be admitted, and start the local anesthetic infusion for these patients preoperatively.

Jadon and Agarwal reported managing a 47-year-old patient with a history of CRPS undergoing radical mastectomy, axillary clearance and skin grafting by placing a cervical epidural catheter to provide a surgical block after injecting 7 ml of 2% lidocaine. The catheter was then used for postoperative pain management by administering 0.125% bupivacaine and 2.5 µg/ml of clonidine [36]. Although this particular case went well, many anesthesiologists would be very reluctant to administer that volume of local anesthetic in the cervical epidural space. More studies must be done to confirm the safety of this technique and establish a reasonable volume to be given before recommending its frequent use on humans.

Ketamine, an *N*-methyl-*D*-aspartate antagonist, proved beneficial in many studies for the management of CRPS, most notably in resistant cases. In a retrospective chart review study that included 369 ketamine infusions in 49 patients, an infusion duration of as short as 30 min significantly reduced the Visual Analog Scale score for up to 3 weeks postinfusion with only minimal side effects [37]. Another retrospective review of 33 cases found that repeated subanesthetic ketamine infusions had a cumulative effect on CRPS symptoms. Side effects reported included the feeling of inebriation [38]. In a double-blind, placebo-controlled study that included 40 patients, Schwartzman *et al.* reported significant improvement in many pain parameters

for up to 9–12 months postoutpatient ketamine infusion. In this study, ketamine was administered for 10 successive days (4 h/day) on an outpatient basis [39]. Sigtermans *et al.* reported in a prospective, randomized, controlled trial that infusion of low-dose ketamine with individualized dose titration led to a reduction of pain in CRPS patients that lasted up to 11 weeks [40]. In a case report, ketamine in combination with midazolam resulted in complete and long-term relief of CRPS symptoms in a 17-year-old female who suffered CRPS after strain injury of her right wrist and hand [41]. The addition of midazolam to ketamine also reduces its agitation side effects [42]. Although it is useful in many patients with resistant CRPS, ketamine does have side effects that need to be studied. In addition to its psychotropic effects, the drug was also found to cause reversible liver and renal effects [43].

α -2-adrenergic agonists decrease sympathetic tone and are used, not only in the management of CRPS, but frequently in acute pain management. Unfortunately, there are limited data on the beneficial effects of systemic α -2-adrenergic agonists as sole agents for the prevention or management of CRPS. However, it is known that administration in conjugation with *N*-methyl-*D*-aspartate antagonists decreases their neurotoxic effects [44]. Epidural clonidine infusion at 50–100 µg/h was reported in a prospective, double-blind, randomized trial comparing clonidine administration with placebo in 26 patients with a history of refractory CRPS. Epidural clonidine was administered for a mean of 43 days in 19 of those patients, with a mean of 32 µg/h. The study group did benefit from a decrease in the Visual Analog Scale and there was an associated decrease in blood pressure and heart rate [45].

Dexmedetomidine is another α -2-agonist that is eight-times as potent as clonidine. It was proven to reduce the number of morphine requests in a randomized, prospective, double-blind study performed on 50 total abdominal hysterectomy patients, thus resulting in fewer morphine side effects [46]. A dexmedetomidine infusion, in conjugation with a subanesthetic ketamine infusion, was reported to manage the acute symptoms of CRPS in a 47-year-old female [47]. More prospective randomized clinical trials should be done to confirm such effects.

Few studies reported the beneficial effect of steroids [48–50]. Although this is theoretically sound, taking into consideration the proposed inflammatory condition of the disease,

there are no consistent data demonstrating that anti-inflammatory treatments confirm such benefit.

In a pilot study that included ten patients, intravenous magnesium sulfate was also stated to decrease patient reports of pain [51].

It is not uncommon to manage cases of CRPS with peripheral nerve stimulators and spinal cord stimulation [52,53]. Special consideration for those patients is warranted. Bipolar cauterization should be used during surgery for those patients, as a unipolar cautery may affect the device even if it is turned off. Intraoperative cauterization may risk causing burns at the site of leads in contact with the spinal cord. It is advisable to always call the different stimulator companies for consultation. Another aspect of managing spinal cord stimulator patients is that they are not candidates for epidural catheter placement, since threading an epidural catheter may potentially displace the fluoroscopically-implanted lead(s).

Another consideration is patients who have had previous chemical or radiofrequency sympathetic ablation [54,55]. Sympathetic ablation is still a controversial treatment for CRPS, but a number of CRPS patients may have considered it [56]. These patients may experience hemodynamic changes, especially in trauma cases or long cases where there are major fluid changes.

Postoperative management

CRPS patients may experience a flare in their symptoms during the postoperative period. A multimodal approach, including regional anesthesia and intravenous medications, is recommended. Most CRPS patients are on anticonvulsants, antidepressants and many other adjuvant medications. Patients should be allowed to resume their oral pain medications as early as oral intake is tolerated. As suggested above, early mobilization and rehabilitation should be done as soon as possible postoperatively [27]. Sometimes, in spite of providing continuous regional anesthesia, postoperative pain is hard to manage in CRPS patients. Adjuvant medications may be added to the local anesthetic infusion through the indwelling catheters. Clonidine is one medication that can be added, especially in the epidural space. Ketamine intravenous infusion should also be considered in the postoperative period, an infusion of ketamine in a subanesthetic dose (10–20 mg/h) can be helpful in the immediate postoperative period, particularly in hospitalized patients, as it may provide extended

analgesia even after discharge. This is a very cost-effective way of administering the drug that many patients may need for the management of their symptoms regardless of surgery.

Other adjuvant pain medications, such as gabapentin, should be considered as part of the multimodal pain management plan. Perioperative gabapentin proved to have synergistic effect with morphine [57].

On discharge, methadone is a reasonable opioid medication to be prescribed [58]. The *N*-methyl-D-aspartate antagonist actions of methadone are beneficial, not only for the management of CRPS pain, but for neuropathic pain in general. A plan for physical and psychological rehabilitation should continue as soon as possible postoperatively. Cognitive behavior therapy helps reconceptualize the cognitive perception of pain and decrease catastrophizing. This will result in decreased stress and subsequently, the release of catechol amines – a significant mediator in the pathogenesis of CRPS [59,60]. The effectiveness of different rehabilitation techniques varies significantly but overall, rehabilitation techniques are important, if not the most important, cornerstones in managing CRPS. Desensitization techniques have been shown to be beneficial in managing CRPS patients [61]. van de Meent *et al.* reported that pain exposure physical therapy can result in complete remission without the need for medications or interventional procedures [62]. We strongly advise the use of multimodal approach in managing CRPS patients. Medications and interventional procedures do help increase compliance with rehabilitation techniques.

Future perspective

Recently, there has been increasing interest in preventative measures. Studies using vitamin C as a supplement are likely to expand its use, especially in trauma cases. We also think there will be an era of expanded research investigating the benefits of α -2-agonists, specifically dexmedetomidine infusion. Dexmedetomidine counteracts many of the adverse effects accompanying ketamine infusion, thus we feel that its potentially synergistic effect with ketamine infusion merits further study. There will also be more frequent use of peripheral nerve stimulators and spinal cord stimulators in the management of early CRPS cases, as well as in the immediate postoperative period, to help facilitate rehabilitation. We hope that in the near future a meta-analysis

study will help establish standard guidelines regarding the timing of surgery, intraoperative and postoperative management of CRPS cases.

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Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a

No writing assistance was utilized in the production of this manuscript.

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