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Preventing the Development of Complex Regional Pain Syndrome after Surgery

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COMPLEX regional pain syndrome (CRPS), previously known as *reflex sympathetic dystrophy* (RSD), is used to describe a syndrome of pain and sudomotor or vasomotor instability.[1] This pain syndrome usually has an initiating noxious event in the periphery, is not limited to the distribution of a single nerve, and is disproportionate to the inciting event.[1–3] The Consensus Conference of the International Association for the Study of Pain has subclassified CRPS into two forms: CRPS I (formerly RSD) and CRPS II (formerly causalgia).[4] According to the International Association for the Study of Pain, the diagnosis of CRPS I requires (1) continuing pain, allodynia, or hyperalgesia disproportionate to the injury; (2) evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain; and (3) no other conditions that would otherwise account for the degree of pain and dysfunction.[2] Motor disturbances and trophic changes, such as altered nail and hair growth, may be observed in some cases. CRPS II is a pain syndrome that starts after a nerve injury and is not necessarily limited to the distribution of the injured nerve.[5] The diagnostic criteria are the same as those of CRPS I. Patients with CRPS I or CRPS II can have sympathetically maintained pain or sympathetically independent pain. *Sympathetically maintained pain*, a term introduced in 1986 by Roberts,[6] is pathologic pain that is supported by sympathetic efferent activity, circulating catecholamines, and/or increased sensitivity of α-adrenergic receptors. Sympathetically maintained pain is identified by the ability to lessen the pain by sympatholytic blocks or interventions. Sympathetically independent pain has components of pain from sources other than sympathetic innervation and is believed to be most commonly observed in advanced cases of CRPS that do not respond to sympathetic blocks.[6] Patients with CRPS may present with components of only sympathetically maintained pain or sympathetically independent pain or, more commonly, a combination of pain from each.[7]

Despite increasing research interest, little is known regarding which patients are at increased risk for development of postoperative CRPS and what the optimal perioperative treatment strategy is for those patients undergoing surgery who have a previous history of CRPS. This review outlines the surgical procedures that are believed to increase risk for development of CRPS and describes pharmacologic and regional analgesic techniques that may be of benefit for preventing the development of CRPS after surgery.

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Epidemiology

The development of CRPS is not an uncommon complication after surgery, the incidence varying according to intervention, site of surgery, and setting. A review of 140 cases of CRPS at the Mayo Clinic during a span of 2 yr noted that 16.4% were the result of surgery.[8] The majority of CRPS cases occur after orthopedic surgical procedures. Estimates are 2.3–4% after arthroscopic knee surgery,[9,10] 2.1–5% after carpal tunnel surgery,[11–13] 13.6% after ankle surgery,[10] 0.8–13% after total knee arthroplasty,[14–17] 7–37% for wrist fractures,[3,10,18,19] and 4.5–40% after fasciectomy for Dupuytren contracture.[20–24]

Multiple reasons probably exist for the wide variability in the reported incidence of CRPS after surgery. Before 1994, there was an absence of an accepted standard for the diagnosis of CRPS and a lack of clarity regarding its pathophysiology.[4] It was previously believed that a diagnosis of RSD required the demonstration of a consistent therapeutic response to a sympathetic block. Patients who did not obtain pain relief with a sympathetic block had a pain condition that could not previously be clas-

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sified. The revised 1994 criteria explicitly state that a favorable response to a sympathectomy is not required for the diagnosis of CRPS.[4] Therefore, later studies performed using the current International Association for the Study of Pain criteria may report a higher incidence of CRPS. In addition, the clinical symptoms of acute CRPS may closely resemble those symptoms seen after surgery. Signs of inflammation, pain, hyperalgesia, autonomic disturbances including temperature changes, and edema may be clinically indistinguishable between patients with CRPS and patients recovering from surgery.[25] The incidence of postsurgical CRPS may vary according to the time period during which the follow-up assessment for CRPS was made. In a prospective study, the incidence of CRPS was noticed to diminish over the first 3 months postoperatively, with some stabilization of the prevalence of CRPS at 6 months.[14] Some investigators have reported spontaneous recurrence of CRPS in 50–74% of cases.[26,27] Therefore, studies examining the incidence of CRPS early after surgery may report a higher prevalence of the disease compared to those investigations examining its incidence at a later time. The wide variability in the reported incidence of CRPS may also reflect the study design. Because only two of the clinical investigations[10,14] reporting the incidence of postoperative CRPS were prospective studies, the current epidemiologic data are probably of lower methodologic quality. We agree with Bennett and Harden[28] that the current International Association for the Study of Pain criteria may be overly strict for population-based studies and may be impossible to apply reliably in a retrospective chart review study.

Timing of Surgery

Surgery on an extremity affected with CRPS is generally avoided because of the risk that the symptoms will recur or worsen.[29–31] Unfortunately, as many as 6–10% of patients with CRPS may require surgery on the affected extremity.[32] The optimal time to perform surgery in patients with a history of CRPS remains unknown and may also affect the recurrence rate. Lankford[29] states that sympathetic blocks be performed and the RSD process must be allowed to "cool down" for at least 1 yr, during which time the patient should actively engage in physical therapy before any surgical procedure. For surgical procedures on the knee, Katz and Hungerford[30] suggest that care should be taken to "wait until symptoms of reflex sympathetic dystrophy have subsided." They also recommend physiotherapy and analgesic support with sympatholytic pharmacologic agents and sympathetic blocks before any surgical procedure. The mean time interval reported between resolution of CRPS symptoms and the first procedure to correct mechanical derangement of the knee was 5 months (range, 2–17 months). Under these conditions, 8 of 17 patients (47%) had recurrence of CRPS after surgery. Veldman and Goris[31] "preferred to wait until the signs and symptoms of RSD decreased at rest and perfusion of the affected limb was optimized." These authors emphasized that "surgery in the setting of a cold and/or edematous limb is contraindicated." They recommended treating CRPS patients with peripheral vasodilators or blockade of the sympathetic nervous system to increase blood flow until skin temperature was normal before any surgical intervention. The authors did not specify the time interval before surgery, but the recurrence rate of CRPS was only 13% (6 of 47 patients). In postarthroplasty patients with CRPS, Katz *et al.*[16] state that elective surgery to correct coexistent mechanical dysfunction (aseptic loosening, ligament imbalance, component malalignment) should be delayed until CRPS symptoms are "under good control." The investigators recommended that these CRPS patients undergo a series of sympathetic blocks before the anticipated surgery.

It may be clinically useful to assess distress and pain intensity preoperatively in patients presenting for surgery without a history of CRPS. Preoperative pain has been shown to be a predictor of chronic pain after a variety of surgical procedures.[33] Patients with greater pain before total joint arthroplasty were found to be at greater risk for heightened postoperative pain, irrespective of confounding issues, such as severity of preoperative disease or postoperative complications.[14,34,35] Greater preoperative pain intensity could alter central nociceptive processing pathways, thereby leading to a greater likelihood of development of postsurgical CRPS.[36] This theory was recently confirmed in a prospective study that demonstrated that patients presenting with increased preoperative pain had a higher predilection for the development of postoperative CRPS after total knee arthroplasty.[14] Harden *et al.*[14] suggested that it may be clinically useful to assess the intensity of pain preoperatively and, if it is increased, to implement appropriate interventions before surgery and to monitor such patients more closely for possible postoperative CRPS.

Although the consensus among physicians in the medical community is to wait for the signs and symptoms of CRPS to resolve before performing surgery, there is no evidence-based medical research to support this theory. Increased preoperative pain has been shown to play a significant role in the development of CRPS after total knee arthroplasty. Future prospective studies are needed to determine whether this holds true for other surgical procedures and whether reducing preoperative pain can decrease the incidence of postsurgical CRPS.

Regional Blocks

It has been recommended that CRPS patients undergoing surgery should avoid general anesthesia because the disease process might be "rekindled by surgery under general anesthesia."[37] It has been postulated that

regional anesthesia, by allowing the preoperative onset of sympathetic blockade, may be a more appropriate anesthetic choice for patients with sympathetically maintained pain because it may prevent the recurrence of this syndrome in the postoperative period.[38] Several authors[37,38] have reported cases in which patients with previous CRPS had recurrence during general but not regional anesthesia after surgical procedures. The regional techniques used were epidural anesthesia for lower extremity surgery and brachial plexus blockade for upper extremity surgery. It is important to realize that both of these regional techniques are associated with the preoperative onset of a sympathetic blockade, which could prevent the development of CRPS. The use of stellate ganglion block, intravenous regional block, and epidural block have all been reported as techniques that may be useful in decreasing the incidence of postoperative CRPS.

Stellate Ganglion Block. Not all regional anesthetic techniques used for upper extremity surgery provide for a perioperative sympathectomy. Many orthopedic surgeons perform carpal tunnel surgery using local anesthetic infiltration.[12] It is unlikely that this anesthetic technique provides a perioperative sympathectomy, and we have observed a high incidence in the recurrence rate of CRPS after surgery.[39] It has been our practice to administer a stellate ganglion block to patients with CRPS undergoing upper extremity surgical procedures in the presence of local or general anesthesia. In a recent retrospective study of 100 CRPS patients undergoing surgery on the affected upper extremity, we observed a reduction in the recurrence of CRPS when performing a perioperative stellate ganglion block.[40] In this study, patients with CRPS were treated aggressively with frequent stellate ganglion blocks and/or intravenous regional blocks in conjunction with hand therapy before surgery. All signs and symptoms of CRPS had resolved before surgery. The median time interval between resolution of CRPS symptoms and surgery was 7–8 months. After completion of the surgical procedure, half of the patients (n = 50) underwent a stellate ganglion block, whereas the other half (n = 50) received no intervention. The recurrence rate of CRPS during the 12-month period after surgery was significantly lower in those patients receiving a perioperative stellate ganglion block (n = 5; 10%) compared with those receiving no intervention (n = 36; 72%). Although probably not feasible, no study has examined the efficacy of administering a stellate ganglion block to patients undergoing surgery without a history of CRPS.

Intravenous Regional Blocks. The regional sympatholysis provided by a stellate ganglion block may benefit CRPS patients who require hand surgery,[29,39–41] but it requires clinical expertise and may result in significant morbidity, including vertebral artery injection, subarachnoid or epidural block, and pneumothorax.[42] Further, stellate ganglion blocks frequently do not produce complete sympathetic interruption of the ipsilateral upper extremity.[43] We believe intravenous regional blocks with clonidine may offer an advantage in the perioperative treatment of patients with CRPS. Prospective, randomized controlled clinical trials have examined the efficacy of intravenous regional blocks with guanethidine,[44–48] reserpine,[45,46] droperidol,[49] atropine,[50] bretyllium,[51] and ketanserin[52] in the management of CRPS. Critical reviews[47,53,54] of these controlled clinical trials have suggested that there was limited support of analgesic effectiveness of intravenous regional blocks with bretylium and ketanserin, consistent data indicating that guanethidine and reserpine intravenous regional blocks were ineffective, and limited data indicating that droperidol and atropine intravenous regional blocks were ineffective. We have previously shown that intravenous regional anesthesia with lidocaine and the α_2-adrenergic agonist clonidine (1 μg/kg) is an effective technique for managing both acute postoperative pain[55] and symptoms of CRPS.[56] Based on these studies,[55,56] we have found that the complications of intravenous regional anesthesia with clonidine are low, and this technique is technically easier to perform than a stellate ganglion block. We recently evaluated the effectiveness of intravenous regional anesthesia with lidocaine and clonidine in preventing the recurrence of CRPS after hand surgery.[57] In this prospective, randomized, double-blind study, 84 patients with a history of CRPS received either intravenous regional anesthesia with lidocaine or intravenous regional anesthesia with lidocaine and clonidine (1 μg/kg) for anesthesia during hand surgery. The recurrence rate of CRPS was significantly lower in those patients receiving intravenous regional anesthesia with lidocaine and clonidine (10%) compared with those patients receiving intravenous regional anesthesia with only lidocaine (74%). Clonidine, has also been administered *via* the epidural[58] or the intrathecal[59] routes in the management of CRPS. Spinally administered clonidine may provide relief of pain in patients with sympathetically maintained pain by reducing sympathetic outflow from preganglionic sympathetic neurons in the spinal cord or by decreasing nociceptive transmission in the dorsal horn.[60] Clonidine also possesses peripheral analgesic properties in patients with sympathetically maintained pain, possibly because it reduces release of norepinephrine from prejunctional α_2 adrenoceptors in the periphery.[61] Data from several clinical investigations support the importance of peripheral adrenergic receptors in the maintenance of sympathetically maintained pain. First, α-adrenergic blockade with intravenously administered phentolamine,[62] phenoxybenzamine,[63] or prazosin[64] reduces pain. Second, intravenous regional anesthesia with guanethidine depletes peripheral catecholamines and can relieve sympathetically maintained pain.[65] Third, intradermal injection of norepinephrine

rekindles sympathetically maintained pain in patients who have previously undergone a sympathectomy.[66] Fourth, topical application of clonidine has been shown to eliminate hyperalgesia only at the site of drug application. This hyperalgesia was later rekindled by the intradermal injection of norepinephrine or phenylephrine.[67]

Intravenous regional blocks with guanethidine have been studied as a method of decreasing the postoperative incidence of CRPS in a surgical population presenting without a history of this disease.[68] Intravenous regional blocks with guanethidine, which deplete norepinephrine in postganglionic adrenergic nerves, were first described in 1974 by Hannington-Kiff[69] as a potential treatment modality for patients with CRPS. Sennwald[23] later advocated the perioperative prophylactic use of intravenous regional blocks with guanethidine in all female patients undergoing fasciectomy for Dupuytren disease because he observed a 40% incidence of CRPS in this surgical population. However, this practice could not be validated in a recent prospective randomized, double-blinded study of 71 patients undergoing fasciectomy.[68] Patients were randomly assigned to receive either intravenous regional blocks containing 20 mg guanethidine or placebo. This study revealed that CRPS developed in seven patients: five in the guanethidine group and two in the placebo group. The authors concluded that intravenous regional blocks with guanethidine were an ineffective modality in the prevention of CRPS. These findings are consistent with the other data showing a lack of efficacy for intravenous regional blocks with guanethidine in the management of CRPS.[47,53,54] However, because of the low incidence of postoperative CRPS (10%) observed in this intravenous regional block guanethidine study,[68] it may have been insufficiently powered to demonstrate significant differences between the two treatment groups. Many more patients need to be enrolled in this clinical trial before statements pertaining to analgesic efficacy can be made. The low incidence of CRPS may have resulted from the use of axillary nerve block as the primary anesthetic technique (90%) in this study. The perioperative use of axillary blocks have been suggested to aid in the prevention of CRPS.[38]

Epidural Block. For surgical procedures involving the lower extremities, the use of epidural anesthesia may be an appropriate choice in reducing the incidence of postoperative CRPS. Epidural analgesia may reduce the incidence of CRPS by providing for a perioperative sympathetic block and possibly reducing the neuroendocrine "stress response" to surgery. An epidural anesthetic has been recommended as the regional anesthetic technique of choice for patients with lower extremity CRPS who are undergoing surgery.[37,38,70] The optimal timing and duration of treatment for performing a perioperative epidural or sympathetic block is not known. Cramer *et al.*[70] recommend a protocol including a hospital stay with epidural catheter placement and infusion of local anesthetic, with or without opiate medication, at least 12 h before the planned procedure. This protocol requires that the epidural infusion be maintained for 3–6 days to prevent sympathetic response or flare of CRPS. These authors[70] emphasize the importance of using a preemptive analgesic technique as the accepted standard for patients with CRPS I or II who are undergoing surgery. Interestingly, these authors did not include the use of clonidine in their epidural infusions, which has been reported to be beneficial in patients with CRPS.[58] Epidural clonidine has been demonstrated to be efficacious in the treatment of refractory CRPS, although there were significant episodes of sedation and hypotension and a high incidence of infection (6 of 19 patients) reported when epidural clonidine was infused for a mean of 43 days.[58] Unfortunately, the only literature examining the efficacy of epidural analgesia for reducing the incidence of postoperative CRPS has been published in the form of case reports.[37,38,70] Future prospective studies are needed to address the safety, efficacy, proper timing, duration, and appropriate analgesic (local anesthetic, opioid, clonidine) for patients at increased risk for development of CRPS.

Preemptive Multimodal Analgesia

It has been hypothesized that one of the pathophysiologic mechanisms of CRPS is an ongoing barrage of nociceptor input from the peripheral to the central nervous system leading to a state of central hyperexcitability.[70–72] Current analgesic techniques are aimed at reducing central sensitization that arises from noxious inputs across the entire postoperative period (preventative analgesia) and not just those brought about by incision (preemptive analgesia).[73,74] There is evidence that "preventative analgesic" techniques demonstrate analgesic benefit and are likely to prevent the development of central hyperexcitability.[75] Further, total or optimal pain relief allowing normal function is difficult to achieve with a single drug or method.[76] It is currently recommended that combined analgesic regimens (multimodal analgesia) that operate through different mechanisms or sites be used.[76] Preemptive multimodal analgesic techniques have demonstrated efficacy in reducing the incidence of postoperative CRPS after anterior cruciate ligament (ACL) surgery. A recent retrospective study of 1,200 patients undergoing ACL surgery examined the efficacy of administering a preemptive multimodal analgesic technique (n = 500) *versus* a standard postoperative pain protocol (n = 700).[77] Patients in the preemptive multimodal group received 1,000 mg acetaminophen every 6 h and 50 mg rofecoxib daily starting 48 h before surgery. In addition, 30 min before surgery, a femoral nerve block and an intraarticular injection of bupivacaine–clonidine–morphine were performed. Postoperative analgesia included acetaminophen, rofecoxib, controlled-release oxyc-

odone, and a cryotherapy cuff. In contrast, patients in the standard postoperative analgesic group received no preemptive analgesics before surgery and were given ibuprofen and acetaminophen with oxycodone on an as-needed basis postoperatively. All patients were subsequently enrolled in a 6-month accelerated rehabilitation protocol.[78] This protocol emphasizes full knee extension on the first postoperative day and immediate weight-bearing according to the patient's tolerance. By the second postoperative week, the patients with 100° range of motion participate in a guided exercise and strengthening program. By the fourth week, patients are permitted unlimited activities of daily living and may return to light sports activities as early as the eighth week. After 6 months, patients are allowed to return to full sports participation if they have met criteria of full range of motion, have no effusion, have good knee stability, and have completed a running program. Our current study revealed significantly lower pain scores and a greater number of patients able to complete this prescribed 6-month rehabilitation protocol among those receiving multimodal treatment. In addition, a significantly ($P < 0.001$) higher incidence of complications was observed at 1-yr follow-up in the standard treatment group compared with the preemptive multimodal group. Long-term complications included a higher incidence of anterior knee pain (14% *vs.* 4%), a greater number of patients requiring repeated arthroscopy for lysis of scar tissue (8% *vs.* 2%), and a higher incidence of CRPS (4% *vs.* 1%) in the standard analgesic group compared with the preemptive analgesic group, respectively. There are several possible reasons for the reduction in the incidence of CRPS observed in the preemptive multimodal group. Preemptive analgesic techniques have been shown to be efficacious in reducing both postoperative pain after ACL surgery[79–81] and the incidence of certain types of neuropathic pain syndromes.[82–84] It is currently believed that there is a continuum of pain after surgery ranging from acute to chronic, and effective treatment of acute pain, especially when accompanied by a neuropathic component, may prevent the development of chronic pain syndromes.[33,85] It is possible that the improved pain control observed in our patients undergoing ACL surgery with a preemptive multimodal analgesic technique contributed to a reduction in the incidence of CRPS. Furthermore, the improved analgesia and enhanced postarthroscopic convalescence allowed a greater number of patients to participate in a physical therapy program.

Prospective, randomized, controlled clinical trials have demonstrated the efficacy of physical therapy in reducing pain and improving active mobility in patients with CRPS.[86,87] Patients who are unable to participate in a rehabilitation program after arthroscopic knee surgery may be at increased risk for development of postoperative knee complications such as delay in strength recovery, prolonged stiffness, anterior knee pain, and CRPS.[88–90] The use of postoperative physical therapy is a common practice after orthopedic surgical procedures, but there are no controlled clinical trials examining its efficacy on reducing the incidence of CRPS. Finally, the use of intraarticular clonidine may have played a role in reducing the incidence of CRPS after ACL surgery. In addition to providing significant postoperative analgesia after arthroscopic knee surgery,[91,92] intravenous regional block with clonidine has also been shown to be effective in the management of CRPS of the knee.[93] We have observed similar efficacy when clonidine (1 μg/kg) is administered *via* the intraarticular route.[94] In addition to its ability to potentiate the analgesic effect of local anesthetics, clonidine might also be useful during peripheral nerve blocks to prevent neuropathic pain after surgery by modulating local cytokine expression.[95] The role of preemptive multimodal analgesic techniques in conjunction with physical therapy and rehabilitation after surgery seems promising, but further research is needed before any definitive conclusion can be made.

Pharmacologic Therapies

A variety of drugs, including calcitonin,[10,96] carnitine,[32] corticosteroids,[41] ketanserin,[32] vitamin C[97,98] and mannitol,[26,99] have been administered perioperatively in an attempt to decrease the incidence of CRPS after surgical procedures. Unfortunately, only two of these clinical trials[10,97] evaluated these interventions in a prospective randomized double-blind manner.

Free Radical Scavengers. Free radical scavengers have been used based on the assumption that CRPS is induced by an exaggerated inflammatory response to tissue injury, mediated by an excessive production of toxic oxygen radicals.[97,98] The efficacy of a wide variety of free radical scavengers, including dimethylsulfoxide,[100–104] *N*-acetylcysteine,[104] mannitol,[26,99] carnitine,[32] and vitamin C,[97,98] has been investigated in the treatment of CRPS. Promising results have been described with dimethylsulfoxide and *N*-acetylcysteine, but no study to date has examined the efficacy of administering either one of these two drugs in the prevention of perioperative CRPS.

Vitamin C. The only prospective, randomized, double-blind, placebo-controlled study to examine the efficacy of administering free radical scavengers for the prevention of CRPS was reported using vitamin C.[97] Vitamin C is a natural antioxidant that is reported to scavenge both hydroxyl radicals[105] and superoxide radicals that produce hydroxyl and other free radicals.[106] Zollinger *et al.*[97] evaluated the efficacy of administering either 500 mg vitamin C or placebo daily for 50 days to 123 adults with 127 wrist fractures. These patients were treated conservatively without undergoing surgical intervention. The investigators reported a significant reduction in the incidence of CRPS in the vitamin C group (7%) compared with the placebo group (22%) at 1-yr follow-up (95% confidence interval for differences

2–26%). Cazeneuve *et al.*[98] confirmed the benefits of vitamin C in a prospective nonrandomized study in patients with wrist fractures presenting for surgery. The authors evaluated 195 patients with isolated closed displaced fractures of the distal radius, which were reduced and stabilized by intrafocal pinning. One group included 100 patients who did not receive vitamin C supplementation. The second group included 95 patients who received vitamin C (1 g daily) for 45 days, starting on the day of fracture. The incidence of CRPS was five times lower in the vitamin C group (2.1% *vs.* 10%). This simple, safe, and inexpensive technique may have significant implications in the development of protocols for the prevention and management of CRPS. Future studies are necessary to determine the efficacy, dosage, and timing of administration of vitamin C in patients with CRPS and those surgical procedures that may be associated with a high incidence of development of this syndrome postoperatively.

Mannitol. Mannitol is also a scavenger of reactive oxygen species[100] and may be therapeutically useful in the prevention of postsurgical CRPS. Veldman and Goris[31] performed a prospective, nonrandomized study of 47 patients with a confirmed diagnosis of CRPS who were presenting for surgery on the affected extremity. At the time of the operation, CRPS had been present for 3 months to 13 yr (median, 1.5 yr). The investigators waited until the signs and symptoms of CRPS decreased at rest, and these patients were treated with peripheral vasodilators and sympathetic blocks before surgery. Patients were given 1,000 ml intravenous mannitol, 10%, over a 24-h period starting at induction of general anesthesia. In addition, the authors avoided the use of tourniquet hemostasis on the theoretical grounds that it could adversely alter oxygen consumption as well as lead to increased formation of toxic oxygen radicals after tourniquet deflation and reperfusion. Recurrence of CRPS was observed in 6 of the 47 patients (13%). This study demonstrated a low recurrence rate using these preventive measures, but the failure to include a control group makes interpretation of this data difficult. The prophylactic use of perioperative mannitol has not been studied in those orthopedic surgical procedures that may be associated with increased risk of CRPS.

Carnitine. Carnitine and the acylcarnitine esters have been shown to play an important role in intracellular metabolism, including the ability to decrease the production of toxic free radicals. Mechanisms of action are diverse and include (1) stimulation of mitochondrial oxidation of long-chain fatty acids; (2) conversion of long-chain acyl-coenzyme A, a potent inhibitor of several enzyme systems, into long-chain acylcarnitine; (3) membrane repair by reacylation of peroxidized fatty acyl groups in phospholipids; (4) stimulation of the microcirculation in ischemia by repletion of interstitial carnitine, which in turn exchanges with long-chain acylcarnitine; (5) membrane stabilization by a small portion of long-chain acylcarnitine; and (6) stimulation of the mitochondrial synthesis of docosahexaenoic acid, a physiologic important fatty acid in phospholipids of brain, skeletal muscle, and heart.[32] Carnitine and riboflavin have been shown to be efficacious in the management of CRPS in pediatric patients.[32] For the prevention of perioperative CRPS, Moesker[32] recommends a combination of oral carnitine (3 g/day) and intravenous ketanserin (4 mg/h) starting 24 h before surgery and continuing these medications for 48 h postoperatively. A recent prospective study examined the efficacy of using this protocol in the treatment of patients with CRPS who were presenting for surgery (unpublished data, Albert Moesker, M.D., Ph.D., Refaja Hospital, The Netherlands, September 21, 2002). At 9 months postoperatively, the investigators reported that 19% of postsurgical patients were pain free, 52% still required intermittent oral medications, and 29% still required treatment in the pain management center on a bimonthly basis for symptoms of CRPS. However, failure to include a control group in this study makes interpretation of the data difficult. Future prospective, randomized, placebo-controlled studies using carnitine and ketanserin are necessary before this protocol can be advocated for the perioperative treatment of patients with CRPS.

Other Pharmacologic Therapies

Calcitonin. Calcitonin is a polypeptide hormone produced in the thyroid gland that regulates blood concentrations of calcium and bone calcium metabolism. The unexpected finding of binding sites for calcitonin in the central nervous system has oriented attention to the antinociceptive activities of calcitonin.[107] The analgesic mechanism of calcitonin remains unclear. Several mechanisms of action have been proposed to explain the antinociceptive properties of calcitonin, including serotoninergic and catecholaminergic mechanisms, Ca^{2+} fluxes, protein phosphorylation, endorphin production, cyclooxygenase inhibition, and histamine inference.[107,108] The role of calcitonin in neurogenic inflammation has also been explored.

It was hypothesized more than 100 yr ago that an exaggerated inflammatory response is one of the possible pathophysiologic mechanisms that contribute to the signs and symptoms of CRPS.[109] Many studies have confirmed the obvious similarities between classic signs of inflammation and clinical features of acute CRPS since this observation.[110] A recent study by Weber *et al.*[111] provided the first evidence that neurogenic inflammation might be enhanced in CRPS, either because the release of neuropeptides from primary afferents is facilitated or because their inactivation is hampered. A recent study quantified and confirmed the important role of neuropeptides, including calcitonin and calcitonin gene–related peptide, in patients with CRPS.[112] Several clinical trials have evaluated the efficacy of administering

calcitonin in an attempt to decrease the symptoms of CRPS. Calcitonin administered subcutaneously or by intranasal spray over 3–4 weeks demonstrated mixed results in the treatment of CRPS. Two studies[113,114] observed no significant difference between calcitonin and control, whereas two other studies[115,116] demonstrated a beneficial effect. Even the reviews of these calcitonin clinical trials were contradictory. Perez *et al.*,[54] in a meta-analysis on randomized clinical trials, concluded that quality-weighted and unweighted effect sizes were small but significant to conclude that treatment with calcitonin seems to be effective in the treatment of pain in patients with CRPS. In contrast, Kingery,[53] in a critical review of controlled clinical trials, concluded that the evidence for the efficacy of calcitonin was inconclusive.

Kissling *et al.*[96] were the first to report the efficacy of perioperative calcitonin in the prevention of recurrence of CRPS after surgery. In this prospective, nonrandomized study, 18 patients with clinical symptoms of CRPS were given daily prophylactic treatment with calcitonin (100 U subcutaneously or *via* nasal spray). The mean duration of prophylactic treatment was 4 days before and 23 days after surgery. This study revealed only one recurrence of CRPS (5.6%) in those patients receiving perioperative calcitonin therapy. For comparison, these authors performed a retrospective analysis of 74 patients with CRPS who underwent similar surgery without prophylactic calcitonin. Analysis of the data revealed a recurrence of CRPS in 28% of these cases. The authors concluded that patients with a history of CRPS undergoing orthopedic surgery should receive prophylactic calcitonin. Administration of calcitonin has also been investigated as a potential method of decreasing the incidence of CRPS in patients undergoing surgery without a previous history of this disease.[10] Unlike the positive results observed in the study by Kissling *et al.*,[96] Riou *et al.*[10] were unable to report a beneficial effect with the perioperative administration of calcitonin to orthopedic surgical patients. In this prospective, randomized, double-blind study, 91 patients undergoing orthopedic procedures of the wrist, knee, and ankle received either calcitonin (n = 51) or placebo (n = 40). Calcitonin (100 U) was administered subcutaneously for 4 consecutive weeks starting the week before surgery. This study revealed a similar postoperative incidence of CRPS in those patients receiving either calcitonin (n = 4; 7.8%) or placebo (n = 5; 12.5%). These studies by Riou *et al.*[10] and Kissling *et al.*[96] examined calcitonin prophylaxis under different surgical conditions. Kissling *et al.*[96] administered calcitonin to patients undergoing surgery with a history of CRPS, whereas Riou *et al.*[10] examined efficacy of this drug in patients without such a history. Further, similar criticism can be made about this study[10] as the intravenous regional block guanethidine study.[68] The low incidence of postoperative CRPS (10%) observed in both of these studies[10,68] makes the sample size too small to determine whether a clinically significant difference exists between the treatment and placebo groups. Further large-scale randomized prospective studies are needed to establish the efficacy of calcitonin both as a method of decreasing the recurrence of CRPS and its incidence in high-risk orthopedic surgical procedures.

Ketanserin. Ketanserin, a serotonin type 2 receptor antagonist, may have potential analgesic properties that could benefit patients with CRPS.[117] Serotonin plays a significant role in the modulation and transmission of autonomic pain pathways.[118] In the animal model, serotonin amplifies the vasoconstrictor response to sympathetic stimulation or the application of noradrenaline[119] and acts synergistically with histamine, prostaglandin F2α, and angiotensin II.[120] These effects, which are antagonized by ketanserin, seem to be mediated by serotonin type 2 receptors. In humans,[121,122] serotonin has demonstrated vasoconstrictor activity comparable to that of sympathomimetic agents, which is antagonized by ketanserin and not phentolamine. These results suggest that the vasoconstrictor effect is mediated by serotonergic and not α-adrenergic receptors. In addition to an antiserotonergic effect, ketanserin has been shown to reduce concentrations of norepinephrine significantly in humans.[123] These pharmacologic properties may make ketanserin a useful analgesic in the perioperative treatment of patients with CRPS. Although intravenous regional blocks with ketanserin have demonstrated efficacy in the treatment of CRPS,[52] its benefit was not confirmed in a controlled clinical trial when administered *via* the intravenous route.[124] There is only one clinical investigation to examine the efficacy of perioperative ketanserin in the prevention of CRPS.[32] In this prospective trial, intravenous ketanserin (4 mg/h) starting 24 h before surgery and continued for 48 h postoperatively was found to be effective in decreasing the recurrence of CRPS in patients undergoing orthopedic surgical procedures of the affected extremity. However, the analgesic effect may not have been totally attributable to ketanserin because the investigation also included the use of carnitine.

Conclusion

The development of CRPS after orthopedic surgery is not uncommon. The paucity of randomized controlled clinical trials for the prevention of postoperative CRPS underlies the difficulty encountered by clinicians in choosing an optimal perioperative treatment strategy. Most clinicians emphasize that surgery on the extremity affected with CRPS is to be avoided because of concern that the symptoms will recur or worsen. The consensus in the existing literature is to wait until the signs and symptoms of CRPS have resolved before performing any surgical procedures, although there is currently no evidence-based data to support this belief. The use of re-

gional nerve blocks that provide for a perioperative sympathectomy may be advantageous with or without general anesthesia for CRPS patients who requiring surgery. Upper extremity surgical procedures may benefit from a perioperative stellate ganglion block or intravenous regional anesthesia with clonidine rather than guanethidine. Although a wide variety of pharmacologic agents have been advocated for the prophylactic treatment of CRPS, only vitamin C has been shown to be beneficial in prospective, placebo-controlled studies. Larger randomized, controlled investigations are necessary before any definitive conclusion can be made regarding the efficacy of calcitonin, mannitol, corticosteroids, carnitine, and ketanserin. The role of preemptive multimodal analgesic techniques in conjunction with physical therapy and rehabilitation after surgery seems promising, but further research is needed before any definitive conclusion can be made. Finally, the optimal timing and duration of treatment for using perioperative regional nerve blocks or pharmacotherapy in patients with CRPS has yet to be established.

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