Evolving Definitions and Pharmacologic Management of Complex Regional Pain Syndrome

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In this issue of *Anesthesia & Analgesia*, Xu et al.[1] reviewed the IV neuromodulatory treatment options for complex regional pain syndrome (CRPS). This article summarizes many of the advances clinicians and researchers have made diagnosing and managing this multifaceted disease. Such advances include the adoption of more strict criteria for the diagnosis of CRPS and evidence-based systematic reviews on the interventional, pharmacologic, psychologic, behavioral, physical, and functional restoration management of the syndrome.

CRPS was initially described in 1986 by Weir Mitchell in patients who experienced persistent pain after their gunshot wounds healed; he coined the term "causalgia." The syndrome was later called Sudeck's atrophy because of the presence of patchy osteoporosis or reflex sympathetic dystrophy based on the assumption that the sympathetic nervous system was involved. The current name, CRPS, reflects the regional distribution of the pain (although it may spread to other parts of the body) and the complex signs and symptoms associated with this condition.[2,3] Several diagnostic criteria followed, none of which was rigorously validated.[4–8] To have better clinical applicability, 2 sets of criteria have been proposed, one by the International Association for the Study of Pain (IASP)[3] and another by a group of experts.[9] The IASP criteria[3] for CRPS has been characterized as having good sensitivity (1.00) but with low specificity (0.4).[10] This led a group of expert investigators to propose a modified diagnostic criteria ("Budapest criteria").[9,10] Two types of criteria were developed: a "clinical criteria for CRPS" with sensitivity of 0.99 and specificity 0.68 and a "research diagnostic criteria" with sensitivity 0.78 and specificity 0.79. The objective was to maximize the diagnostic sensitivity but have adequate specificity in clinical situations. For the research criteria, the purpose was to equally balance the sensitivity and specificity.[10]

A validation study compared the IASP criteria and the Budapest criteria in 113 patients with CRPS-1 and 47 patients with non-CRPS neuropathic pain.[11] The investigators noted the IASP criteria to have high diagnostic sensitivity (1.00) but low specificity (0.41). Therefore, the IASP criteria may result in a relatively high rate of false-positive diagnoses, potentially leading to unnecessary or inappropriate treatments. In contrast, the Budapest criteria showed the same high sensitivity (0.99) but with improved specificity (0.68).[11] CRPS diagnoses using the Budapest clinical criteria were likely to be accurate 88% of the time with patients with non-CRPS correctly diagnosed 97% of the time. Therefore, the Budapest criteria should be used in the clinical setting and in research studies. This Budapest criteria have also been validated from data accumulated from international centers; a validated severity score has been developed that can be useful for comparative treatment goals in future clinical studies.[12]

Recently, a subset of patients described as having "chronic refractory CRPS" has been identified.[13] This subgroup of patients has the rarest and most severe form of CRPS. Chronic refractory CRPS appears to affect women exclusively; develops after trivial injuries; is characterized by severe pain, hyperpathia, allodynia, and severe functional impairment; and is responsive to opioids. Because the patients have significant therapeutic challenges, the criteria for diagnosis and therapeutic options for chronic refractory CRPS need to be better established.

The various changes in the terminology and the lack of previous validated criteria explain the lack of published level I evidence for the treatment of CRPS. Now that there are standard research criteria, future researchers have adequate tools to conduct randomized controlled trials comparing treatment options. Meta-analyses can then produce evidence-based practice recommendations for this challenging disease.

One of the major advances in the treatment of CRPS is in pharmacologic management. Pharmacologic management runs the gamut of IV, oral, and topical therapies. Xu et al.[1] extensively reviewed IV management. They recommended IV biphosphonates or IV ketamine infusions for refractory cases of CRPS. IV regional blocks with ketorolac and lidocaine or lidocaine alone were noted to provide short-term relief. Although these IV pharmacologic options provide only short-term benefit, the duration of relief can be expected to be better if these therapies are included in a multidisciplinary program. IV ketamine, a drug well known to anesthesiologists, has found a new role in the

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Accepted for publication November 24, 2015.

Funding: Departmental.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0000000000001157

neuromodulation of patients with CRPS. Low doses in our clinical practice have demonstrated benefit for refractory CRPS, partly from the unique pharmacology of the drug.

Although Xu et al. focused on the IV treatments of CRPS, other parenteral treatments such as IM and subcutaneous calcitonin were not reviewed. A discussion of calcitonin is called for because a network meta-analysis by Wertli et al.[14] recommended short-term calcitonin in the later stages of CRPS. The authors based their statement on 3 publications.[15–17] Other studies were not reviewed.[18–20] Bickerstaff and Kanis[15] noted that 200 IU nasal calcitonin twice a day was no better than placebo (Table 1). Gobelet et al.,[19] however, showed that doses of 300 IU/day nasal calcitonin were better than placebo. It should be noted that the patients studied by Gobelet et al. had physical therapy, whereas patients studied by Bickerstaff and Kanis received no other treatment. Nasal calcitonin, at doses of 200 IU/day, combined with calcium, physical therapy, and stellate ganglion blocks had the same effect as oral paracetamol.[17] For IM calcitonin, a dose of 100 IU a day for 4 weeks was more effective than saline.[16] Subcutaneous injection of 100 IU of calcitonin for 3 weeks, plus physical therapy, was also better than physical therapy alone.[18] However, the authors noted that the higher baseline pain scores in patients who received calcitonin may have been partially responsible for the difference in results. Finally, Schurmann et al.[20] found better results with subcutaneous calcitonin (0.5 mg daily over 8 weeks) compared with a control injection, but only in the reduction of edema. There were no differences in improvements in pain, grip strength, hand function, and temperature difference.

The effect of nasal calcitonin is not uniform. Its efficacy when added to physical therapy is not better than a mild analgesic.[17] IM or subcutaneous calcitonin, conversely, appears to be better than placebo.[16,19] In addition to the network meta-analysis of Wertli et al.,[14] a research synthesis of 21 trials, 5 of which included calcitonin, stated that calcitonin appeared to be effective in CRPS.[21] The authors based their conclusion largely from the "positive results of 1 article" (the study by Gobelet et al.[19]). It should be noted that all studies reviewed criteria other than the IASP or Budapest criteria in diagnosing CRPS (Table 1),[4–8] so a definite diagnosis of CRPS cannot be assured. Calcitonin is also

Table 1. Results of Studies on Calcitonin in Complex Regional Pain Syndrome

Study	Type of study; medications compared; duration of follow-up	Outcome measures	Results	Comments
Bickerstaff and Kanis[15]; 40 patients with algodystrophy after a Colles' fracture	P, R, DB; 400 IU nasal calcitonin daily × 4 wk vs nasal saline, 20 patients per group; no other treatment given; 12-wk follow-up	Clinical assessment (pain, vasomotor and sudomotor changes, hand swelling, finger stiffness, grip strength) and blood and urine determinations	Improvements in pain, swelling, and stiffness in both groups with no difference between groups; decrease in serum calcium in calcitonin group	Diagnosis based on criteria of Atkins et al.,[4] not on the IASP or Budapest criteria
Sahin et al[17]; 35 patients with stage 1 of CRPS	P, R, SB; 200 IU nasal calcitonin with 500 mg/d calcium for 2 mo (18 patients) vs 1500 mg/day paracetamol (17 patients); patients also had PT, stellate ganglion blocks, and TENS; 2-month follow-up	Pain, clinical assessments (allodynia, hyperalgesia, trophic changes)	Patients recovered in all parameters, no difference between groups	Criteria of Schürmann et al.[5] used in diagnosis; patients with stage 1 studied: pain, swelling and edema, hyperhidrosis, warmth, redness
Gobelet et al.[19]; 66 patients with RSD	P, R, DB; 3 × 100 IU nasal calcitonin (33 patients) vs placebo (33 patients). Patients also had PT and TENS; 8-wk follow-up	Pain, range of motion, return to work	Pain, range of motion, and return to work were better improved by calcitonin	Criteria of Kozin et al.[6] and Steinbrocker et al.[7] used in diagnosis
Hamamci et al.[16]; 41 patients with RSD after hemiplegia	IM calcitonin, 1 × 100 IU/day for 4 wk (25 patients) vs IM saline (1 mL/d); all patients had PT; no comment on randomization or blinding; 4-wk follow-up	Pain score; clinical assessments (edema, tenderness, vasomotor and sudomotor changes, ROM of joints)	Significantly lower pain scores in calcitonin group at 4 wk; significantly better results with calcitonin in tenderness, shoulder abduction and external rotation, wrist flexion, and metacarpophalangeal extension	Criteria of Steinbrocker and Argyros[8] used in diagnosing RSD
Gobelet et al.[18]; 24 patients with RSD of the hands or feet after trauma	R, C; subcutaneous calcitonin, 100 IU a day for 3 wk (12 patients) plus PT vs PT alone (12 patients). Follow-up for 8 (pain edema, range of motion) and 12 wk (fitness for work)	Pain score; edema, range of movement; blood and urine assays (calcium, parathyroid hormone, phosphate); return to work	Significantly better pain relief with calcitonin; no difference between the 2 groups in terms of improvement in edema and range of motion, and return to work	Diagnosis of RSD-based on history of trauma and signs and symptoms (pain, edema, hyperhidrosis) and scintigraphic scan

The article by Schurman et al.,[20] written in German, was not included because details of the study could not be ascertained.

CRPS = complex regional pain syndrome; DB = double blind; IASP = International Association for the Study of Pain; P = prospective; PT = physical therapy; R = randomized; ROM = range of motion; RSD = reflex sympathetic dystrophy; SB = single blind; TENS = transcutaneous electrical nerve stimulation.

associated with numerous side effects including pruritus, headache, vertigo, epigastric pain, and hypocalcemia.[17,19] Based on the levels of evidence used by Xu et al., nasal, IM, and subcutaneous calcitonin would all have ratings of 2B-. The causes for the low rating include lack of information on randomization and blinding.

The roles of interventional, physical, and functional restoration as well as psychologic and behavioral treatments in patients with CRPS have been extensively reviewed.[22–26] These treatment modalities are important, especially because the optimal treatment of CRPS requires a multidisciplinary approach. Pain medicine practitioners are encouraged to be aware of these developments. In particular, there is a significant role for interventional pain therapy combined with multidisciplinary treatment options. These options include the early use of spinal cord stimulation for CRPS.[27]

We have come a long way in managing CRPS. One of the authors remembers the early years when there was nothing to offer pharmacologically to patients with CRPS. Despite these advances, much work remains to be done. In view of the older nonvalidated criteria used in the diagnosis of CRPS, the calcitonin studies need to be repeated. Validated criteria for the diagnosis should be adhered to in the inclusion of patients in future studies. Randomized controlled studies are needed to critically evaluate the role of sympathetic nerve blocks and other types of regional anesthesia in patients with CRPS. Spinal cord stimulation with various new waveforms needs to be clinically evaluated in patients with CRPS. Variations in waveform may explain why some patients respond to spinal cord stimulation, whereas others do not. Intrathecal therapies for dystonia, an important symptom of CRPS, require further exploration based on promising initial data.[28] The safety of repeated ketamine infusions needs to be reviewed in light of recent evidence of toxicity.[29–31] Because oral therapy is the mainstay of outpatient treatment, a comprehensive review and appropriate recommendations of oral therapy for CRPS would be a welcome addition to the literature. This contribution by Xu et al.[1] is a welcome start in this direction. ■

DISCLOSURES

Name: Honorio T. Benzon, MD.
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Attestation: Honorio T. Benzon approved the final manuscript.
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RECUSE NOTE

Dr. Spencer Liu is the Section Editor for Pain Medicine for *Anesthesia & Analgesia*. This manuscript was handled by Dr. Steven L. Shafer, Editor-in-Chief, and Dr. Liu was not involved in any way with the editorial process or decision.

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