Four Treatment Strategies for Complex Regional Pain Syndrome Type 1

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Abstract

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Complex regional pain syndrome (CRPS) poses a dilemma for many clinicians due to its unknown etiology and largely unsuccessful treatment modalities. The purpose of this study was to compare the clinical results of 4 treatment modalities for CRPS type 1. A total of 59 patients were divided into 4 groups based on treatment modality: group A, an oral nonsteroidal anti-inflammatory drug (NSAID) (n=10); group B, oral gabapentin (n=12); group C, intravenous (IV) 10% mannitol and steroid (n=11); group D, a combination of IV 20% mannitol and steroid with oral gabapentin (n=26). The patients remained under medical supervision after discharge and were evaluated either once a month or once every 2 months until final follow-up at a mean of 8 months. Patients in group A showed improvement in pain level, finger range of motion, swelling, and grip strength, without statistical significance (P=.076, P=.062, P=.312, and P=.804, respectively). Patients in group B showed significant improvement in pain level (P<.001), and patients in group C showed improvement in pain, finger range of motion, and swelling (P=.127), which rendered functional impairment unchanged. In comparison, patients in group D showed recovery of grip strength and improvement in pain level, finger range of motion, and (P<.001, P=.016, P=.031, and P=.047, respectively). Based on these results, a protocol including a combination of IV 20% mannitol and steroid with oral gabapentin is an acceptable and effective treatment for CRPS type 1.
Complex regional pain syndrome (CRPS), previously referred to as reflex sympathetic dystrophy, a term abandoned at a 1993 consensus conference and replaced by the strictly descriptive CRPS, comprises pain, swelling, vasomotor instability, contracture, and osteoporosis. Complex regional pain syndrome type 1 is initiated by trauma and is often associated with swelling as a result of dependency, extensive trauma, or an excessively tight cast or bandage; it is not associated with an identifiable peripheral nerve injury. Complex regional pain syndrome type 2 is associated with an identifiable peripheral nerve injury, termed causalgia.

Complex regional pain syndrome can begin up to a month after the precipitating trauma. In the classical presentation, in the early phase, the limb is initially dry, hot, and pink, but soon becomes sweaty, cold, and blue. Passing into the late phase, vasomotor instability recedes, the edema resolves, and the limb atrophies.

Patients with CRPS usually experience permanent impairment and disability, which can lead to loss or suspension of work, changes in occupation, and psychological disorders. Therefore, early recognition of CRPS, along with prompt treatment, is important to minimize permanent loss of function.

The pathophysiology of CRPS is controversial. Evidence exists for an inflammatory or sympathetic pathogenesis. Various treatment methods for early CRPS type 1 include physiotherapy, psychotherapy, sympathetic block, intravenous regional blockade, chemical sympathectomy, surgical sympathectomy, and pharmacologic interventions (eg, antidepressants, anticonvulsants, membrane-stabilizing agents, corticosteroids, and free radical scavengers).

Although many treatments have been proposed, few scientifically constructed studies and uncontrolled investigations have yielded certain results. Moreover, the effectiveness of these treatments has not been definitively proven, and they are used variably in different combinations and in different developmental stages of the syndrome.

The purpose of the current study was to compare the clinical results of 4 treatment modalities for CRPS type 1: (1) an oral nonsteroidal anti-inflammatory drug (NSAID); (2) oral gabapentin; (3) intravenous (IV) 10% mannitol and steroid; and (4) a combination of IV 20% mannitol and steroid with oral gabapentin.

### MATERIALS AND METHODS

The Institutional Review Board granted permission for this study. All patients treated with the current regimen were available for review.

This retrospective study was performed between January 1999 and July 2010. Inclusion criteria were (1) diagnosis of CRPS type 1 according to the International Association for the Study of Pain (IASP) modified diagnostic criteria (Table 1), (2) no evidence of nerve injury or compression, (3) no sign of sympathetic hyperactivity, (4) presence of symptoms for ≤6 months, (5) symptom occurrence after upper-extremity trauma involving the hand or wrist, (6) >6 months’ follow-up, and (7) normal hand or wrist function before disease occurrence. Exclusion criteria were (1) evidence of nerve injury (peripheral nerve or spinal cord), (2) combined head trauma or brain disease (eg, cerebrovascular attack, aneurysm rupture, or Parkinson’s disease), (3) lower-extremity trauma, (4) peripheral neuropathy (eg, diabetes mellitus), and (5) electrolyte imbalance.

### Table 1

**Modified Diagnostic Criteria for CRPS**

Complex regional pain syndrome (CRPS) describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

To make the clinical diagnosis, the following criteria must be met:

1. **Continuing pain, which is disproportionate to any inciting event**
2. **Must report at least 1 symptom in 3 of the 4 following categories:**
   - **Sensory:** Reports of hyperesthesia or allodynia
   - **Vasomotor:** Reports of temperature asymmetry or skin color changes and/or skin color asymmetry
   - **Sudomotor/Edema:** Reports of edema, sweating changes, or sweating asymmetry
   - **Motor/Trophic:** Reports of decreased range of motion or motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin)
3. **Must display at least one sign at time of evaluation in two or more of the following categories:**
   - **Sensory:** Evidence of hyperalgesia (to pinprick) or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   - **Vasomotor:** Evidence of temperature asymmetry (>1ºC), skin color changes, or asymmetry
   - **Sudomotor/Edema:** Evidence of edema, sweating changes, or sweating asymmetry
   - **Motor/Trophic:** Evidence of decreased range of motion or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. **There is no other diagnosis that better explains the signs and symptoms**

For research purposes, diagnostic decision rule should be at least 1 symptom in all 4 symptom categories and at least 1 sign (observed at evaluation) in ≥2 sign categories.
A total of 59 patients (38 women and 21 men) with a mean age of 48 years (range, 21-78 years) were enrolled in the study. Each patient’s medical history and demographics were reviewed, including type of precipitating factor, symptom onset, interval between precipitating trauma and symptom onset, interval between symptom onset and first visit to the authors’ institution, and history of neuropathic disease. The most common cause of the disease was Colles’ fracture (n=43) (treated with open reduction and internal fixation with volar locking plate [n=6], closed reduction and external fixator application [n=18], and conservative management with sugar-tong splint immobilization [n=19]), followed by radius...
shaft fracture (n=8), both forearm bone fractures (n=5), and proximal humerus fracture (n=3). Twenty-three patients among these cases were transferred to the authors’ institution from other hospitals due to the onset of CRPS during the follow-up period, including 20 cases of Colles’ fracture (treated with open reduction and internal fixation with volar locking plate [n=1], closed reduction and external fixator application [n=6], and conservative management with sugar-tong splint immobilization [n=13]), 2 cases of radius shaft fracture, and 1 case of proximal humerus fracture.

Treatment Regimen

The 59 patients were divided into 4 groups based on treatment modality: (1) group A, oral administration of 50 mg of an NSAID (diclofenac) twice daily for 1 month (n=10; 7 women and 3 men; mean age, 52 years [range, 24-68 years]); (2) group B, oral administration of 300 mg of gabapentin 3 times daily for 1 month (n=12; 8 women and 4 men; mean age, 46 years [range, 27-72 years]); (3) group C, continuous intravenous (IV) administration of 400 mL of 10% mannitol daily (16.7 mL/h) and 7 mg of IV dexamethasone bolus once daily for 7 days (n=11; 6 women and 5 men; mean age, 50 years [range, 21-68 years]); and (4) group D, continuous IV administration of 400 mL of 20% mannitol daily (16.7 mL/h) and 7 mg of IV dexamethasone bolus once daily for 7 days, and oral administration of gabapentin 300 mg once daily on hospitalization day 1, twice daily on hospitalization day 2, and 3 times daily for 1 month beginning on hospitalization day 3 (n=26; 17 women and 9 men; mean age, 48 years [range, 21-78 years]). Patients in groups C and D were admitted to the hospital for 7 days and were discharged on hospitalization day 8.

Patients who presented to the authors’ institution with upper-extremity trauma and associated complications between 1999 and 2004 were randomly allocated to each of the authors. Patients diagnosed with CRPS type 1 were treated with an NSAID, gabapentin, or mannitol and steroid (groups A, B, and C) according to the decisions and preferences of each author. Considering the differences in clinical outcomes based on the various treatment modalities, the results were retrospectively compared and analyzed to elucidate the strengths and weaknesses of each treatment method. As a result, a consistent regimen of 20% mannitol, steroid, and gabapentin (group D) was used in patients with CRPS type 1 by all authors beginning in 2005.

Rehabilitation

Rehabilitation involved daily intensive physical therapy consisting of passive and active finger and wrist range of motion (ROM) exercises. Pain-free self-limited
ROM exercises were encouraged from the start of treatment. Active assisted finger and wrist ROM exercises were initiated on rehabilitation day 2 and continued under the supervision of a physiotherapist. The exercise program initially consisted of isometric strengthening and gentle flexibility. Then, as the patient improved or tolerated more aggressive ROM and stress loading, isotonic strengthening exercises were added to the program. Physiotherapy was usually started at 3 months, although further functional improvement occurred over a much longer period.

**Patient Assessment**

Patients were assessed before treatment and 1 week, 1 month (when medication was completed), and a mean of 8 months (range, 7-13 months) after treatment. The patients remained under medical supervision, being seen once a month or every 2 months by 1 of the authors, until final follow-up.

Clinical assessments included pain level, finger joint ROM, grip strength, pinching, swelling, sweating, and skin color. Patient pain level was evaluated using a visual analog scale (VAS) ranging from 0 (no pain) to 10 (worst pain imaginable). Loss of finger flexion was measured by the distance between the third finger pulp and the distal palmar crease. An effort was made to minimize the interference effects of wrist motion by measuring the dorsal aspect of the wrist during contact with a table with the patient in a sitting position and by measuring the distance from the distal palmar crease of the same axis to that of the third metacarpal bone to the most distal part of the third finger pulp. A Jamar hand dynamometer (Therapeutic Equipment Corporation, Clayton, New Jersey) was used for grip strength. In accordance with the guidelines for the use of the Jamar dynamometer issued by the American Society for Surgery of the Hand, the second grip handle was used for all patients. A mean of 2 successive trials was used for both the injured and the uninjured hand and was recorded as a percentage of the unaffected side, as recommended by the American Society of Hand Therapists. Grip strengths were adjusted by 10% for the nondominant hand. Swelling of the hand and wrist was measured by using the water displacement method. The variation was compared by measuring the water quantity that flowed over from a basin filled with water, into which the hand was submerged to the level of the ulnar styloid process tip. Patient satisfaction with the treatment (no change, better, improved, or resolved) was assessed using a questionnaire completed at final follow-up.

Blood tests were performed before treatment to identify the basal physical status of each patient. In groups C and D, blood tests were performed again at 3 days and 1 week after treatment and at the first follow-up visit to identify the presence of any medication-induced adverse effects or hematological abnormalities during treatment.

Radiographic assessments included 3-phase bone scintigraphy, thermography, and magnetic resonance imaging (MRI) to ensure diagnostic accuracy. Bilateral plain radiographs were obtained before treatment, at 1 month after treatment, and at final follow-up. Bone mineral density (BMD) was determined before treatment and at final follow-up.

**Statistical Analysis**

To reduce measurement errors, measurements were performed in duplicate, and average values were calculated. Intraobserver reliability was recorded using the criteria of Winer et al.\(^1\) Reliability was classified, according to the intraclass correlation coefficient, as absent to poor (0-0.24), low (0.25-0.49), fair to moderate (0.50-0.69), good (0.70-0.89), or excellent (0.90-1.0). An intraobserver reliability of 0.94 was achieved.

The differences between variables (pain level, loss of finger flexion, grip strength, and swelling) before treatment, at 1 week and 1 month after treatment, and at final follow-up were analyzed with the Wilcoxon signed rank test. For comparing the 4 treatment modalities, statistical analyses were performed using 1-way analysis of variance (ANOVA), followed by post-hoc Scheffe test, to determine significant differences among the means of the data groups. Statistical analyses were performed using SPSS version 20.0 statistical software (SPSS, Inc, Chicago, Illinois). Data are presented as mean±SD, and a value of \(P<.05\) was considered statistically significant.

**RESULTS**

Mean interval between trauma and symptom onset for all patients was 49 days (range, 23-74 days); for patients with Colles’ fracture, 36 days (range, 24-48 days); for patients with radius shaft fracture, 41 days (range, 29-64 days); for patients with both forearm bone fractures, 34 days (range, 27-45 days); and for patients with proximal humerus fracture, 51 days (range, 37-74 days). Mean interval between symptom onset and presentation to the authors’ institution for all patients was 91 days (range, 1-149 days).

At final follow-up, group A showed improvements in terms of pain and finger ROM, without statistical significance (\(P=.076\) and \(P=.062\), respectively). However, weakness in grip strength and swelling remained a functional impairment. In group B, mean VAS score decreased from 8.8±0.9 before treatment to 1.6±0.9 at final follow-up (\(P<.001\)), indicating a significant improvement in pain level. No improvements were observed in terms of finger ROM, grip strength, or swelling in this group (\(P=.057\), \(P=.727\), and \(P=.238\), respectively). In group C, mean VAS score decreased from 8.4±1.0 before treatment to 2.6±1.7 at 1 month after treatment and to 1.8±0.5 at final follow-up (\(P<.001\)). Loss of finger flexion decreased from 6.2±2.7 cm before treatment to 2.4±1.4 cm at 1 month and to 0.1±0.1 cm at final follow-up (\(P=.014\)). Swelling decreased from 335±11.9 mL...
before treatment to 308±9.2 mL at 1 month and to 307±10.9 mL at final follow-up (P=.038), indicating a significant improvement. However, the improvement in mean grip strength was not enough to be statistically significant (P=.127).

In group D, mean VAS score decreased from 8.6±1.1 before treatment to 4.3±1.6 at 1 week, 1.7±0.8 at 1 month, and 1.3±0.7 at final follow-up (P=.001). All patients in group D achieved nearly full finger flexion at 1 month: 6.3±2.4 cm before treatment, 4.5±2.1 cm at 1 week, 2.3±1.1 cm at 1 month, and 0.1±0.1 cm at final follow-up (P=.016) (Figure 1). Swelling markedly decreased from 337±13 mL before treatment to 320±10.9 mL at 1 week, 307±10.2 mL at 1 month, and 304±8.9 mL at final follow-up (P=.031). Furthermore, mean grip strength improved from 65%±12% of the unaffected side before treatment to 76%±11.6% at 1 week, 85%±9.4% at 1 month, and 91%±6.3% at final follow-up (P=.047) (grip strength was adjusted by 10% for the nondominant hand for analysis) (Figure 2). The results are summarized in Table 2 and Figure 3.

According to a comparison of the groups in regard to symptoms, pain level improved significantly in every group except for group A (P=.033). In addition, in terms of finger ROM recovery and swelling reduction, groups C and D showed better results than groups A and B (P=.047 and P=.038, respectively), whereas grip strength remarkably improved only in group D (P=.019). The distribution of patient satisfaction differed according to the treatment modality: group A, no change in 6 patients, better in 3, improved in 1, and resolved in 0; group B, no change in 4 patients, better in 6, improved in 2, and resolved in 0; group C, no change in 0 patients, better in 4, improved in 5, and resolved in 2; and group D, no change in 0 patients, better in 5, improved in 10, and resolved in 11 (Figure 4).

Few medication-induced adverse effects were observed during the study. Five cases of dizziness (3 in group B and 2 in group D) and 4 cases of somnolence (2 in group B and 2 in group D) were reported, but these symptoms resolved spontaneously within 1 week with no other treatment. No adverse effects of mannitol or steroid were observed in groups C and D. Furthermore, no patient who had a coexisting disease experienced an exacerbation of the other conditions, and none required a change in the treatment of the disease.

**Discussion**

A comparison of the clinical results of 4 treatment modalities for CRPS type 1 revealed that a combination therapy of IV 20% mannitol and steroid with oral administration of gabapentin led to improve-
ments in pain level, finger ROM, swelling, and grip strength.

In many ways, CRPS is a challenge because of its unknown etiology and largely unsuccessful treatment modalities. Numerous therapeutic methods have been introduced, but none have shown definitive results. A previous study on the natural course of CRPS type 1 reported that most patients do not progress to the late phase of the disorder and that some symptoms might improve spontaneously over time (the authors used NSAIDs for the treatment of CRPS and achieved results similar to those of group A in the current study). Functional impairment, such as grip strength and fibrosis, which is an important factor in a patient’s quality of life, did not improve. In other words, an improvement in the signs and symptoms of CRPS does not always indicate functional improvement. Moreover, when the morbid period is extended into the late phase, symptoms and signs deteriorate accordingly, but permanent impairments may remain. However, the methods presented in many studies, when implemented during the early stage of the disease, demonstrate better therapeutic effectiveness. This means that although the natural course of the signs and symptoms of CRPS is optimistic, the risk of functional impairment or extending to the late phase with poor prognosis is high, and, accordingly, active treatment of CRPS type 1 during the early stage is necessary.

Tan et al treated CRPS using only gabapentin. In their study, patients remained as inpatients for 6 weeks, during which gabapentin was administered in incrementally increasing doses from the initial dosage of 600 mg/day until satisfactory pain level was achieved. This treatment showed significant effectiveness for pain control but was not effective for edema, vasomotor or sudomotor changes, or limb dysfunction. Tan et al and Perez et al reported their results of CRPS treatment using mannitol as a free radical scavenger. In these 2 studies, 1 L of 10% mannitol was administered by subclavian vein infusion every 24 hours for 7 to 10 days, followed by 4-hour periods of IV infusion for 5 days. Symptomatic improvement was observed in the CRPS patients who began the treatment comparatively early, but no significant differences were evident compared with the placebo group.

Zyluk and Puchalski reported on the therapeutic effectiveness of the combination of mannitol and dexamethasone, noting a statistically significant improvement in pain and finger ROM but no improvement in grip strength. In the current study, the patients in groups A, B, and C showed improvements similar to those seen in the aforementioned studies, but the patients in group D showed recovery of grip strength as well.

Improvements in clinical results according to evaluation contents showed significant differences among groups: Pain level improved significantly in all groups except group A; finger ROM and swelling significantly improved in groups C and D compared with groups A and B; and grip strength significantly improved in group D compared with groups A, B, and C. In terms of patterns of improvement, differences were observed among treatment modalities: Groups A and B showed gradual improvements during the 8-month follow-up period, whereas groups C and D showed >80% of improvement in overall clinical outcomes within 1 month after treatment initiation.

Mannitol has a hyperosmolar effect, but in the current study, it also acted as a free radical scavenger in CRPS type 1. Free radical scavenger therapy is based
on the assumption that CRPS type 1 is caused by an exaggerated inflammatory response to trauma, mediated by an overproduction of toxic oxygen and hydroxyl free radicals. Steroids have a strong anti-inflammatory potential and profoundly alter both the cellular and humoral immune responses. They inhibit the production of various inflammatory factors critical in generating and propagating the inflammatory response, such as interleukins, cytokines, and chemotactic agents. Nonetheless, the mechanism of action of anticonvulsants is unknown, and gabapentin, which is effective in other clinical conditions characterized by neuropathic pain, has begun to take its place among the wide variety of therapeutic alternatives. It stabilizes excitable nerve membranes, reduces neuronal hyperexcitability, and depresses segmental and descending excitatory mechanisms. These findings support the use of gabapentin to treat neuropathic pain, despite the lack of complete knowledge of its analgesic mechanism.

Pain is likely the primary problem that prevents a patient from participating in therapy because of decreased tolerance and motivation. Patients in groups A, B, and C in the current study reported discomfort caused by pain during the treatment period, and no improvement in pain level was attained in the early stage of treatment. Consequently, these patients could not undergo scheduled physiotherapy, but tolerable physiotherapy only. In contrast, patients in group D achieved satisfactory pain control at the initial stage of treatment. The treatment regimen used in group D might enhance pain relief so that effective early ROM exercises can be performed. Furthermore, owing to the anti-inflammatory potential of steroids, as well as the free radical reduction effects of mannitol, this treatment protocol might delay the progression to the late phase of the disease. Moreover, the proactive and effective implementation of early ROM exercises, before any occurrence of limb atrophy, contractures, or fibroses, could enable patients to experience improvement not only in finger ROM and swelling, but in grip strength as well.

Some adverse effects were evident during the treatment period, but the severity of symptoms was mild, and they resolved with no particular treatment. In previous studies, dizziness and somnolence were reported as the most frequent adverse effects of anticonvulsants, but the symptoms tended to disappear within 22 to 61 days. In the current study, adverse effects of gabapentin occurred but resolved spontaneously within 1 week with no other treatment. This result likely reflected heightening drug compliance of the patients through the use of incremental doses of gabapentin during 3 days, rather than using the maintenance dose (300 mg 3 times a day) initially. The diuretic effect of mannitol is observed mostly in cases of oliguria but much less in patients with normal renal function. All patients had normal renal function. Blood tests performed during the treatment period showed normal white blood cell counts and differential counts, whereas elevated liver enzyme and gastrointestinal symptoms were not noted. No steroid-induced adverse effects were observed in this study. For steroid administration, a moderate dose (IV prednisolone 0.5-1 mg/kg/day) was used for the short term (1 week) and excluded patients who showed absolute contraindication for steroids.

Patients who received IV mannitol and steroid therapy were hospitalized for 1 week, a shorter period than that for other treatment methods, which required 4 to 6 weeks of hospitalization. The short period of hospitalization enabled the patients to return to daily life much quicker after functional recovery, owing to the symptomatic improvement. In addition, using a certain safety dose for drug administration reduced the uncertainty and allowed the application of a consistent treatment method, which led to the patients’ sense of stability.

This study had some limitations. First, it was a retrospective analysis. The patients in groups A, B, and C were treated in the authors’ institution between 1999 and 2004. Since they were not randomly selected, the clinical results were not based on a planned study, but rather on a review of medical records. Treatment methods were selected according to the preferences of the authors, and through discussions among authors on establishing treatment methods, including a consistent therapy for group D, were consecutively conducted since 2005. Second, any patients who had CRPS type 1 symptoms for >6 months were excluded. Patients who had CRPS type 1 symptoms for <6 months achieved good results after treatment. However, for many patients, a great deal of time may pass from symptom onset to diagnosis and treatment, limiting the number of patients who can receive the proper treatment for CRPS. When >6 months pass from symptom onset, the patient might enter the late phase of the disease, with a progression in limb atrophy, contractures, and fibroses. In such cases, treatments usually are ineffective, making permanent functional impairment likely.

CONCLUSION

When various treatment modalities for CRPS type 1 were compared, the combination therapy of IV 20% mannitol and steroid with oral administration of gabapentin contributed to comparatively short hospitalization, which resulted from improvements in pain, finger ROM, swelling, and grip strength. Furthermore, few complications were due to the medications. These results suggest that this protocol could be an effective alternative method for treating CRPS type 1.

REFERENCES