Retrospective Evaluation

Prednisolone in Complex Regional Pain Syndrome

Nilgun Simsir Atalay, MD[1], Ozlem Ercidogan, MD[2], Nuray Akkaya, MD,[1] and Fusun Sahin, MD[1]

From: [1]Pamukkale University Medical School, Department of Physical Medicine and Rehabilitation, Denizli, Turkey; [2]Okmeydanı Education and Research Hospital, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey

Address Correspondence:
Nilgun Simsir Atalay, MD
Pamukkale University Medical School
Department of Physical Medicine and Rehabilitation
Denizli, Turkey
E-mail:
drnilgunatalay@gmail.com

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Background: Although there are several studies of systemic corticosteroid therapies in various doses and various durations in complex regional pain syndrome (CRPS), the outcome measurement parameters are limited to the range of motion measurements, edema, and symptoms of CRPS.

Objective: To investigate the effects of prednisolone on clinical symptoms, pain, hand grip strength, range of motion, as well as on functional ability and quality of life in patients who developed CRPS after traumatic upper extremity injury.

Study Design: Retrospective evaluation.

Methods: Forty-five patients who used prednisolone for CRPS of the upper extremity were retrospectively studied. Prednisolone was started with a dose of 30 mg and tapered by 5 mg every 3 days until discontinuation after 3 weeks. Clinical symptoms (morning stiffness, cold intolerance, shoulder pain, numbness of fingers, hyperesthesia, abnormal sweating, and cyanosis that is exacerbated by exposure to cold temperature), pain (Visual Analogue Scale-Rest [VAS-R] and VAS-Activity [VAS-A]) were reviewed. The muscle strength with grip strength (GS) (kg), lateral pinch (LP) (pound), tip-to-tip pinch (TP) (pound), and chuck pinch (CP) (pound) measurements; the joint range of motion with using third finger tip-distal crease distance (FT-DC) (cm); functional ability with Quick-Disabilities of the Arm, Shoulder and Hand (Q-DASH) score; and quality of life with Short Form-36 (SF-36) score were evaluated.

Results: Mean age was 43.53 ± 11.43 years. After 3 weeks of therapy, patients showed significant improvements in clinical symptoms compared to the basal assessments ($P < 0.05$). The comparison of pre- and post-treatment results revealed that VAS-R, VAS-A, GS, LP, TP, CP, FT-DC, Q-DASH scores, and all SF-36 subscores were significantly improved ($P < 0.05$).

Limitations: The retrospective design and data collection procedure was limited to the medical records of patients.

Conclusion: A short-term oral prednisolone therapy significantly reduced the symptoms and signs of CRPS, and improved the functional abilities and quality of life.

Key words: Complex regional pain syndrome, prednisolone, function, quality of life

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Complex regional pain syndrome (CRPS) that results from a painful condition or immobilization is a clinical entity characterized by sustained pain, allodynia, hyperalgesia, edema, skin blood supply disturbances, abnormal sudomotor activity, motor symptoms, and trophic disturbances (1). The pain, weakness, and sensory disturbances in the affected limb result in functional disability. Moreover, activities of daily living and quality of life are negatively affected and workforce loss occurs in patients with CRPS (2,3).

The etiologic factors for CRPS include mild inju-

ries, fractures, sprains, immobilization, and surgical interventions. CRPS is classified into 2 types: CRPS-1 (without any nerve injury) or CRPS-2 (with apparent nerve injury) (1,4). The etiologic factor is not associated with the severity of subsequent pain and functional loss (5). Because there are no specific diagnostic tests, diagnosis is usually based on history, clinical examination, and related laboratory tests (6).

The treatment options for CRPS include exercise therapy, spinal cord stimulation, sympathetic nerve blocks, transcutaneous electrical stimulation, and medical treatment (e.g., non-steroidal anti-inflammatory drugs, tricyclic antidepressants, antiepileptics, corticosteroids, opioid analgesics, intrathecal baclofen, or calcitonin), with variable success rates (6-8).

Although there are several studies of systemic corticosteroid therapies in various doses and various durations in CRPS, the outcome measurement parameters are limited to the range of motion measurements, edema, and symptoms of CRPS (9-12). In the present study, we aimed to investigate the effects of prednisolone on clinical symptoms, pain, hand grip strength, range of motion, as well as on functional ability and quality of life in patients who developed CRPS after a traumatic upper extremity injury.

Methods

We retrospectively reviewed medical records of the patients who were in follow-up at our physical therapy and rehabilitation department, hand rehabilitation clinic for traumatic upper extremity injury and in whom CRPS developed and prednisolone was used.

The diagnosis was made on the basis of clinical findings and according to International Association for the Study of Pain (IASP) criteria (7,13). Definite CRPS was defined as the presence of severe pain and tenderness in an extremity with at least one of the evidences of sympathetic failure including hyperesthesia, cyanosis or other skin discolorations, edema or swelling, and dystrophy (7).

Clinical findings and demographic data including age, gender, hand dominance, mechanism of injury, and injured tissues were collected from the medical records of the patients.

Prednisolone was started with a dose of 30 mg and tapered by 5 mg every 3 days until discontinuation after 3 weeks. The range of motion exercises and contrast bath therapy were also recommended to the patients. The contrast bath therapy was done by the patient at home after careful instruction. Briefly, the patient had to submerge his/her hand and wrist into hot water heated to 43˚C for 10 minutes, then into cold water at 15˚C for one minute, followed by hot water again for at least 4 minutes (14). The total duration for this therapy was 30 minutes. The results of basal measurements and those after 3 weeks of therapy were collected from the medical records for all patients. The common symptoms of CRPS including morning stiffness, cold intolerance, shoulder pain, numbness of fingers, hyperesthesia, abnormal sweating, and cyanosis that is exacerbated by exposure to cold temperature were reviewed from the medical records and recorded as "present" or "absent" (15). The pain was assessed using Visual Analogue Scale-Rest (VAS-R) and VAS-Activity (VAS-A); the muscle strength with grip strength (GS) (kg), lateral pinch (LP) (pound), tip-to-tip pinch (TP) (pound), and chuck pinch (CP) (pound) measurements; the joint range of motion using third finger tip-distal crease distance (FTDC) (cm), functional ability with Quick-Disabilities of the Arm, Shoulder and Hand score; and quality of life with Short Form-36 score.

Pain Severity

Visual Analogue Scale (VAS) is a 10-cm scale that measures the severity of pain. The scale has different descriptors at each end on a horizontal line (0 = no pain and 10 = worst pain). The patient marks the point that represents the severity of his/her pain on the line. The VAS score is the distance in centimeters from the zero end of the line to the point that the patient marked.

Grip Strength

The hand grip strength was evaluated with a Jamar dynamometer. Measurements were taken with the patient in the sitting position with the elbow at 90° of flexion, and with the forearm and wrist in the neutral position (16). The average of 3 measurements was calculated and used in the analysis.

Pinch Grip

Pinch grip strength was measured from the injured extremity by a pinch meter in 3 different positions for lateral, tip-to-tip, and chuck pinches. The average of 3 measurements was calculated and used in the analysis (16).

Grip strength and pinch grip strength were considered as "0" in patients who could not grip the Jamar dynamometer and the pinch meter in all 3 positions in pre- and post-treatment assessments.

Joint Range of Motion

The distance from third finger tip to the palmar distal crease in centimeters was recorded in the patient with fisted hand (17).

Functional Assessment

Quick-Disabilities of the Arm, Shoulder and Hand (Q-DASH) is a self-administered questionnaire that assesses the physical function and symptoms of patients with upper extremity impairment (18). At least 10 out of 11 items should be answered in order to calculate a Q-DASH score. The questionnaire uses a 5-choice response scale for each subscale and the total score is calculated from the sum of the subscores (0 = no disability, 100 = most severe disability).

Quality of Life

Quality of life was assessed by Short Form-36 (SF-36), which was translated into Turkish, and the reliability and validity studies were completed by Kocyigit et al (19). The major distinctive feature of SF-36 is that it includes the self-assessment of health status. The scale consists of 36 items that measure 8 dimensions of health: physical function, social function, pain, vitality, emotional role disability, physical role disability, mental health, and general health. The SF-36 assesses the perceived physical and mental health over the last 4 weeks. Subgroup scores range from 0 to 100, with the higher scores indicating a better health status.

Statistical Analysis

All statistical analysis was performed by using SPSS 17.0 program. Descriptive statistics were given as mean ± standard deviation. Clinical data were evaluated by descriptive statistics and frequency analysis. Comparison of improvements for clinical symptoms between pretreatment and post treatment were evaluated by ki-square test. Comparison of VAS-R, VAS-A, grip strength, Q-DASH, and SF-36 values between pretreatment and post treatment were evaluated by paired samples t-test. $P < 0.05$ was accepted to be statistically significant for the P value.

Results

A total of 45 patients with a mean age of 43.53 ± 11.43 (range, 22 – 67) were included to the study; of them 25 (55.6%) were women and 20 (44.4%) were men. With respect to employment status of the patients, 16 (35.6%) were housewives, 14 (31.1%) were employed, 7 (15.6%) were retired, 5 (11.1%) were government employees, 2 (4.4%) were farmers, and one (2.2%) was a student. The injury was in the non-dominant hand and in the dominant hand in 28 (62.2%) and 17 (37.8%) patients, respectively. The mechanism of the injury was falls in 25 (55.6%), industrial injuries in 9 (20%), home accidents in 6 (13.3%), and motor vehicle injuries in 5 (11.1%) patients. Thirty-three (73.3%) patients had bone fracture, 9 (20%) had tendon injury, and 3 (6.7%) had nerve injury. The demographical and clinical characteristics of the patients are shown in Table 1.

Most common symptom at the beginning of treatment was morning stiffness which was present in 73.3% (n = 33) of the patients. Least common symptom was shoulder pain which was present in 24.4% (n = 11) of the patients. Cold intolerance was present in 64.4% (n = 29), hyperesthesia was present in 64.4% (n = 29), numbness of fingers was present in 51.1% (n = 23), abnormal sweating was present in 48.9% (n = 22), and cyanosis on exposure to cold was present in 37.8% (n = 17) of the patients. After 3 weeks of therapy, morning stiffness significantly improved to 51.1% (n = 23) ($P = 0.001$), shoulder pain 8.9% (n = 4) ($P = 0.002$), cold intolerance 44.4% (n = 20) ($P = 0.001$), hyperesthesia 31.1% (n = 14) ($P = 0.001$), numbness of fingers 33.3% (n = 15) ($P = 0.001$), abnormal sweating 17.8% (n = 8) ($P = 0.001$), and cyanosis on exposure to cold 22.2% (n = 10) ($P = 0.001$) . The positivity rates of pre- and post-treatment symptoms are shown in Table 2.

Table 1. *Demographic and clinical features of patients.*

	N = 45 (%)
Age (years)	43.53 ± 11.43
Sex	
Female	25 (55.6)
Male	20 (44.4)
Dominant hand	
Right	43 (95.6)
Left	2 (4.4)
Injured hand	
Dominant	17 (37.8)
Non-dominant	28 (62.2)
Cause of injury	
Falls	25 (55.6)
Industrial injuries	9 (20)
Home accidents	6 (13.3)
Motor vehicle injuries	5 (11.1)
Type of injury	
Fracture	33 (73.3)
Tendon injury	9 (20)
Nerve injury	3 (6.7)

Table 2. *Comparison of symptoms between pretreatment and posttreatment.*

	Pretreatment (+) (%)	Posttreatment (+) (%)	*P*
Morning stiffness	33 (73.3)	23 (51.1)	0.001
Cold intolerance	29 (64.4)	20 (44.4)	0.001
Shoulder pain	11 (24.4)	4 (8.9)	0.002
Numbness of fingers	23 (51.1)	15 (33.3)	0.001
Hyperesthesia	29 (64.4)	14 (31.1)	0.001
Abnormal sweeting	22 (48.9)	8 (17.8)	0.001
Cyanosis on exposure to cold	17 (37.8)	10 (22.2)	0.001

Table 3. *Comparison of evaluation parameters between pretreatment and posttreatment.*

	Pretreatment (n = 45)	Posttreatment (n = 45)	*P*
Visual Analogue Scale-Rest	3.48 ± 2.58	1.24 ± 1.82	0.001
Visual Analogue Scale-Activity	6.21 ± 2.94	2.87 ± 2.43	0.001
Grip strength (kg)	2.32 ± 4.76	8.8 ± 7.74	0.001
Lateral pinch (pound)	3.3 ± 5.8	9.75 ± 6.86	0.001
Tip-to-tip pinch (pound)	2.0 ± 3.67	5.55 ± 4.46	0.001
Chuck pinch (pound)	2.31 ± 4.1	6.84 ± 5.02	0.001
Finger tip-distal crease distance (cm)	4.3 ± 2.42	1.97 ± 2.13	0.001
Quick-Disabilities of Arm, Shoulder, Hand	64.07 ± 20.85	33.83 ± 21.33	0.001
SF-36 Physical function	65.88 ± 21.95	76.55 ± 22.48	0.001
SF-36 Physical role disability	7.22 ± 22.37	29.44 ± 40.34	0.001
SF-36 Pain	40.4 ± 23.92	66.28 ± 25.92	0.001
SF-36 General health	63.48 ± 21.14	67.95 ± 20.58	0.02
SF-36 Vitality	58.22 ± 23.48	65.66 ± 21.6	0.001
SF-36 Social function	55.44 ± 32.44	74.16 ± 25.61	0.001
SF-36 Emotional role disability	39.57 ± 44.69	69.12 ± 43.87	0.001
SF-36 Mental health	57.35 ± 26.64	65.07 ± 23.17	0.001

SF-36: Short Form-36

Grip strength and pinch grip strength could be tested in 16 (35.5%) patients; but 29 (64.5%) patients could not grip the dynamometer and pinch meter in the pre-treatment assessment. On the other hand, the grip strength and pinch grip strength could be tested in 42 (93.3%) patients; but 3 (6.7%) patients could not grip the dynamometer and pinch meter in the post-treatment assessment.

The comparison of pre- and post-treatment results revealed that VAS-R, VAS-A, GS, LP, TP, CP, FT-DC, Q-DASH scores, and all SF-36 subscores were significantly improved after 3 weeks of therapy ($P < 0.05$). VAS-R improved from 3.48 ± 2.58 to 1.24 ± 1.82, VAS-A from 6.21 ± 2.94 to 2.87 ± 2.43, GS from 2.32 ± 4.76 to 8.8 ± 7.74, LP from 3.3 ± 5.8 to 9.75 ± 6.86, TP from 2.0 ± 3.67 to 5.55 ± 4.46, CP from 2.31 ± 4.1 to 6.84 ± 5.02, FT-DC from 4.3 ± 2.42 to 1.97 ± 2.13, Q-DASH score from 64.07 ± 20.85 to 33.83 ± 21.33, SF-36 Physical Function from 65.88 ± 21.95 to 76.55 ± 22.48, SF-36 Physical Role Disability from 7.22 ± 22.37 to 29.44 ± 40.34, SF-36 Pain from 40.4 ± 23.92 to 66.28 ± 25.92, SF-36 General Health from 63.48 ± 21.14 to 67.95 ± 20.58, SF-36 Vitality from 58.22 ± 23.48 to 65.66 ± 21.6, SF-36 Social Function from 55.44 ± 32.44 to 74.16 ± 25.61, SF-36 Emotional Role Disability from 39.57 ± 44.69 to 69.12 ± 43.87, and SF-36 Mental Health from 57.35 ± 26.64 to 65.07 ± 23.17 (Table 3).

Discussion

In the present retrospective study investigating the effects of prednisolone on clinical symptoms, grip strength, joint range of motion, functional ability, and quality of life in patients who developed CRPS after traumatic upper extremity injury, the prednisolone treatment resulted in favorable effects on these parameters.

The incidence of CRPS is estimated to vary from 5.46 to 26.2 per 100,000 person-years (used to indicate the incidence of new cases over a period of time). In adult patients, CRPS more commonly involves the upper extremity, and fracture is the most common initial event. The CRPS is 3.4 to 4 times more likely to occur in women than men. The mean age at the time of CRPS diagnosis varies from 47 to 52 years, with no gender difference between men and women (20,21). The patients in the present study all had upper extremity injuries and were under follow-up in our hand rehabilitation clinic. The most common etiologic factor was the fracture, the number of women was relatively higher, and the mean age was 44 years.

In the case of peripheral nerve and tissue damage, various chemical mediators are released to cause sustained A-delta and polymodal C fibers stimulation, subsequent to which an initially localized pain is followed by continuous pain (22). The nociceptor barrage caused by the injury may alter the processes in the dorsal horn cell to facilitate A beta mechanoallodynia and to cause abnormal noradrenergic sprouting in the dorsal root ganglia (23). In addition to reducing the leukotriene synthesis by inhibiting the metabolism of arachidonic acid, corticosteroids also inhibit substance P and CGRP, as well as modulate synthesis of neuropeptides in dorsal root ganglia sensory neurons (9,24).

In a randomized placebo-controlled study, a total of 23 CRPS patients were treated either with 10 mg twice daily prednisone for 3 weeks and a tapered dose for up to 12 weeks (n = 13) or with placebo (n = 10). Treatment with prednisone led to 75% improvement in all 13 patients as compared to only 2 out of 10 patients in the placebo group (9). In another randomized controlled trial comparing the 40 mg/day prednisolone with piroxicam treatment in patients with CRPS following stroke, significant improvement was reported with prednisolone treatment for one month (10). Likewise, Braus et al (11) used 32 mg/day methylprednisolone in 4 divided doses for 2 weeks and tapered the dose over 2 weeks in patients with CRPS after stroke, and found significant improvements in 91% of patients.

Guo et al (25) fractured the tibia of rats to evoke hindpaw warmth, spontaneous extravasation, edema, allodynia, and periarticular bone loss, an experimental model that resembles CRPS-1. Methylprednisolone infusion was effective on hindpaw warmth, spontaneous extravasation, and edema via inhibition of post-junctional substance *P* signaling, while the treatment with methylprednisolone had no effect on the allodynia or periarticular bone loss. In the present study, prednisolone treatment was effective on CRPS symptoms including pain, morning stiffness, cold intolerance, shoulder pain, numbness of fingers, hyperesthesia, abnormal sweating, and cyanosis that is exacerbated by exposure to cold temperature. However, because we did not performed graphical assessment or follow-up the patients, we could not draw a conclusion on the effects of prednisolone on bone loss.

Bianchi et al (12) investigated 31 patients with a CRPS diagnosis predominantly on the hand (n = 25) and found significant improvement on parameters of functional abilities and clinical severity (pain, swelling, and range of motion) in 31 patients with upper or lower extremity CRPS after prednisolone treatment (started with a dose of 40 – 60 mg in proportion to the clinical severity and used for about 2 weeks). In this study, change in quality of life was not documented; however, they calculated the clinical severity by combining VAS, strength, swelling, thumb finger opposition, fist closure, functional ability, wrist flexion and extension, and found statistically significant improvement.

Early active mobilization physical therapy combined with analgesic drugs is the primary therapy for CRPS. In the randomized controlled study including 135 CRPS patients, physical therapy led to better results compared to occupational therapy and to a control group (26). In the present study, all patients who developed CRPS were treated with prednisolone in addition to active range of motion exercises and contrast bath therapy as part of the follow-up protocol of our hand rehabilitation clinic.

Functional impairments and decreased quality of life have been shown in CRPS patients. Kıralp et al (2) reported that 13 out of 106 CRPS patients, who participated to a rehabilitation program, could not turn to their work-life and experienced disability. Accordingly, Savas et al (15) investigated the effects of symptoms on activities of daily living in 30 CRPS patients. After at an average follow-up time of 18 months following the treatment, pain particularly persisted and the im-

pairments in the activities of daily living on the basis of DASH and SF-36 scores were maintained. In another study, the authors studied the CRPS patients who were followed-up for at least 6 months with the Nottingham Health Questionnaire, EuroQoL 5D, and Sickness Impact Profile. The patients had complaints of pain during activity, sleep disorders, and energy problems, and there were negative impacts on their home life, work life, and personal care (27). Similarly, Galer et al (28) evaluated 31 CRPS patients retrospectively, and reported sleep disorders in 80% of the patients and decreased quality of life in more than 45%. Tan et al (29) published the results of a retrospective study on 42 adolescent CRPS patients who had been diagnosed approximately 12 years ago and reported that all SF-36 scores except for the mental and emotional function subscores were negatively affected in these adolescents compared to controls. Significant improvements were observed in all quality of life scores with corticosteroid treatment in the present study. Thus, early diagnosis and treatment would be beneficial in patients with CRPS, a disease affecting the quality of life so much. In that respect, the key feature of the present study is the concomitant investigation of functional ability and quality of life in CRPS patients treated with a corticosteroid.

All patients included to the present study complied with the treatment, possibly due to the low dose, and relatively short duration of treatment. Of note, none of the patients developed uncontrolled hypertension or gastrointestinal problems, or had to discontinue therapy due to side effects.

The major limitations of the present study are the retrospective design and data collection procedure limited to the medical records of patients. Because of the lack of a control group, it is possible that some patients were missed, especially those with spontaneous regression. Furthermore, because we did not start treating the patients who had a contraindication for corticosteroid use, such as those with hypertension and/or diabetes mellitus, the side-effect profile found in the present study may not reflect the general population. Also, we could not give clear information about the additional effects of physical techniques and exercise therapy, which were used in combination with the drug therapy.

Conclusion

In conclusion, our findings are consistent with the literature stating that in CRPS patients disability is an important problem which seriously affects activities of daily living and a short-term oral prednisolone therapy significantly reduces the symptoms and signs of CRPS following traumatic injuries of the upper extremity and improves the functional abilities and quality of life.

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