The Treatment of Longstanding Complex Regional Pain Syndrome with Oral Steroids

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Methods. Patients were treated with oral prednisolone in both centers [100 mg daily tapered by 25 mg every 4 days to zero (R1g) at center 1 (C1) and 60 mg daily for 2 weeks lowered 20 mg every 4 days to zero (R1.06g) at center 2 (C2)]. The average pain intensity was recorded by patients using a numeric rating scale before the treatment start, and 6 weeks after treatment onset (treatment duration was respectively 16 days and 22 days at the two centers).

Results. Overall the authors observed no significant reduction in the average pain intensity (P = 0.059), but 2 patients had a consistent reduction in pain intensity with return to baseline pain levels 9 weeks after treatment onset, and 1 patient had ongoing stable pain relief of >50%.

Conclusions. This study provides indications that the efficacy of oral corticosteroids is limited in treating CRPS of more than 3 months duration who did not respond to previous treatment. Randomized controlled studies (with enriched designs), or single subject designs would be required to identify the possible existence of a patient subgroup with a specific disease profile that may benefit from a steroid treatment.

Key Words. Complex Regional Pain Syndrome; Steroids; Chronic Pain

Introduction

Complex Regional Pain Syndrome (CRPS) is a painful, usually posttraumatic condition characterized by sympathetic, sensory, motor and trophic dysfunction in the affected limb [1]. The pathophysiology of CRPS is unknown but an exaggerated inflammatory response to tissue trauma is one of the proposed underlying biological mechanisms. Elevated cytokines levels in skin blister fluid, neurogenic inflammatory reactions, altered activity of mast cells, and markers of oxidative stress have been described [2,3]. The lack of full knowledge of the pathophysiology of the syndrome, and the presence of
variable clinical manifestations has led to difficulty in identifying univocal and accurate diagnostic methods, as well as to effective therapeutic strategies. Anti-inflammatory therapy is one of the proposed treatment approaches. These therapies include corticosteroids, free radical scavengers, and more recently, anti TNF-α and immunoglobulins have been studied in randomized controlled trials (RCTs) [4]. Low costs and ease of administration render steroid treatment of particular interest. In one RCT of high quality [5], treatment with oral prednisolone results indicated significantly better pain reduction than treatment with oral piroxicam in patients with acute CRPS following stroke [6]. Further, in a prospective RCT of moderate quality, [7] prednisolone taken orally yielded notable improvements as compared with placebo in patients with early/acute CRPS. Another RCT of moderate quality describes symptoms improvement with oral methylprednisolone vs placebo in hemiplegic patients who developed a Shoulder Hand Syndrome after stroke treated in an early stage [8]. These data suggest that a treatment with oral steroids may be indicated in early CRPS, yet benefits in longer-lasting disease have not been ascertained. Furthermore, these studies were all performed using diagnostic criteria that are less specific than the most recent Budapest criteria [9]. Therefore, no data are available in the literature about the effectiveness of steroids for CRPS with CRPS defined according to the Budapest criteria.

From a pathophysiological point of view, the use of steroids appears to be a rational treatment approach for early CRPS due to their anti-inflammatory activity. However, the prevalence of ‘inflammatory’ signs, such as swelling, temperature, and color difference is lower at longer disease durations. Moreover, the concentration of pro-inflammatory cytokines in skin-blister fluid is reduced in longer-lasting CRPS when compared to early CRPS [10]. This suggests that anti-inflammatory treatment for these patients might be less effective. On the other hand, a complementary anti-nociceptive effect of steroids at the spinal cord level has been described in experimental studies [11]. Preclinical studies report a reduction of nociceptive behavior after local, epidural, or systemic administration of glucocorticoids in chronic neuropathic pain models in rats [12]. Results from human studies are contradictory. Two RCTs reported significant pain relief in patients with postherpetic neuralgia of more than 1-year duration treated with intrathecal methylprednisolone [13,14]. However, two recent RCTs (one performed in 21 CRPS patients of more than 6 months duration) reported no benefit and a high rate of adverse events after intrathecal methylprednisolone injections [15,16]. These results suggest a rationale for the use of corticosteroids for the treatment of chronic pain states while taking into account the possibility of a measurable risk. However, there is not enough sufficient evidence in the literature focusing on dosage, route, and timing of steroids administration in chronic pain patients. Therefore we decided to investigate the effectiveness of oral steroids in relieving pain in patients with CRPS according to the Budapest criteria of more than 3 months duration. The cut-off of 3 months was used according to the definition of chronic pain given by the International Association for the Study of Pain (IASP) [17]. We conducted a clinical audit in two centers that diagnose and treat CRPS while focusing on steroid-induced analgesia since pain is a prominent symptom for CRPS and an essential feature in the diagnosis of this complaint [9].

Methods

The participating centers were the outpatient pain clinic, Department of Pain Medicine, The Walton Centre in the United Kingdom (C1), and the VU University Medical Center in The Netherlands (C2), which are specialized in CRPS diagnosis and treatment. At C1, steroid therapy for CRPS had been part of routine care based on the evidence from positive RCTs (see above), and the patients were treated as a convenience sample of those who attended the outpatient clinic either as new or follow-up patients, after start of a registered clinical audit designed to confirm the usefulness of this therapy. Verbal consent was taken at C1 after discussion of the therapy method, in line with routine practice. At C2 an informed consent was obtained after verbal explanation whereby the medical ethics review board waived the requirement for ethical approval as this was a non-experimental study and the evaluation took place within the boundaries of regular care.

Patients

CRPS patients were diagnosed by pain specialists, using the Budapest criteria [9] (“New IASP criteria”). In C1, Budapest clinical criteria were used, while in C2 the research version was used, which has a higher specificity. Patients were included if they were 18 years or older, had a disease duration of more than 3 months, and had only experienced unsatisfactory pain relief with standard drug treatment in accordance with respective national guidelines [18,19].

Patients who were unable to consent, patients with diagnosed psychiatric disorders, with diabetes, malignancy, pregnancy, active infections, a history of kidney failure, severe liver disease or established gastric ulcer, myasthenia gravis, hypersensitivity, or allergy to prednisolone, who used anti-coagulants, and those with additional significant pains were excluded as per the centers’ routine practice for the treatment of this group.

Treatment Protocol

At both centers, patients continued to take their routine pain medications. However, where drug treatments had been adapted during the past 4 weeks, consent and

1 In the United Kingdom, clinical audit is a quality improvement process that seeks to enhance patient care and outcomes through systematic review of care against explicit criteria, and consequent implementation of change [35].
Steroids for CRPS

steroid treatment start was deferred until four weeks had passed. Concomitant physical/occupational therapies were allowed during the study period. The treatment protocol applied at C1 was recommended by a clinician-investigator (FB) with experience in using steroids for the treatment of early CRPS [20]. The treatment consisted of 100 mg of oral prednisolone daily, tapered by 25mg every 4 days to zero (± 1 g prednisolone/16 days). Stomach protection with 20 mg Omeprazole OD was prescribed in all cases. The treatment at C2 consisted of 60 mg of oral prednisolone daily for 2 weeks, followed by a tapering period of 8 days (lowered 20 mg every 4 days) (± 1.08 g prednisolone/22 days). Stomach protection medication was provided if required.

Assessments

In C1 patients completed a Brief Pain Inventory (BPI) [21] and were asked to commence taking the medication either that day, or the next day. The BPI consists of several 11-point (0–10) numeric pain rating scales of which the average pain intensity ('please rate your pain on average') was considered the main outcome for this audit. Each patient was also provided with a follow-up BPI for completion at four weeks after the end of the treatment course (i.e., about 6 weeks after treatment start).

In C2 patients were asked to score their actual pain ('please rate your actual pain') three times a day—morning, afternoon, and evening—according to a Numeric Rating scale (NRS) [22] (1–10 scale). The mean of all NRS scores registered during the week preceding the assumption of steroids was considered as the “average pain” at baseline. The average of NRS scores registered by patients during the sixth week was used for follow up.

In both centers patients were asked to record any important events or adverse events during the treatment period. Patients reporting substantial changes to their pain after treatment were followed up until their pain had normalized.

Statistics

Analyses were performed according to the intention to treat principle. Standard comparative statistics were used to compare frequencies (Chi square test) or means (Paired samples t-test and Mann–Whitney U test). Nonparametric correlation test (Spearman’s rho) was used to study associations between variables. Significance was established at \( P < 0.05 \) (two-tailed). Data were analyzed with IBM SPSS statistics version 20.

Results

Between May 2009 and December 2010 (C1) and between April 2011 and October 2012 (C2), 31 patients with CRPS were included. During that time, approximately 85 patients were seen at C1 and 105 patients in C2 fitting the diagnostic criteria. Demographics and disease characteristics are given in Table 1. The mean age at time of research was 47 years. The whole group consisted predominantly of females, while in C1 male were predominant. The median disease duration was 15 months, (11.5 months C1 vs 17 months C2, Mann–Whitney-U; \( P = 0.21 \)). Upper extremities were more frequently affected than the lower extremities (18 vs 13, Pearson chi-square with one degree of freedom = 3.533, \( P = 0.07 \)). In both centers the most predominant trigger event was a fracture.

The average pain at baseline was available for all patients. Two patients in C2 were lost to follow up, so that the average pain at follow up was available for 29/31 patients. Overall the average pain intensity had decreased by 1 point (6.3 at baseline vs 5.8 after treatment, 95% CI: \(-0.03 \) to 1.87, \( P = 0.059 \) (Table 1). Nonparametric correlation test showed no relationship of age (correlation coefficient = \(-0.079 \), \( P = 0.68 \)) or disease duration (correlation coefficient = \(-0.022 \), \( P = 0.9 \)) with change in average pain.

Sixteen patients showed a reduction in average pain, with a minimum of 0.1 and a maximum of 8 points (Table 1). Ten patients had an increase in the average pain intensity with a minimum of 0.2 to a maximum of 3.5 points. The C1 patient with the best response (#11) had recurring CRPS, with relapses of the complaint followed by remissions in the course of time [23]. He experienced an episode of spontaneous recovery from CRPS with re-appearance before this audit. His pain returned about 6 months after the audit and then seemed to be responsive to repeat treatment with steroids (data not shown). When excluding this patient, overall 4/30 patients (13%) had ≥2 points pain relief (1C1 - 6%, 3C2 - 27%), and three patients (10%) had >50% pain relief (OC1, 3C2). Follow-up data from two patients in the latter group (#27 and #31) revealed that average pain intensity had returned to baseline levels at 9 weeks after the start of the intervention, and the remaining patient continued to have substantially reduced pain until today (#30).

Side Effects

In C1, one patient (#13) reported in retrospect that she had felt ‘fantastic’, from the third treatment day until 3 days after treatment. Although she reported that she had a very good pain relief during that time, from NRS 7 to NRS 2 (Table 1), she found it difficult to distinguish between her perceived psychological ‘high’, and actual pain relief. None of the patients in C2 reported comparable psychological side effects.

During the treatment, a total of 6 patients classified the following side effects as ‘severe’ (4 C1, 2 C2): malaise, depression, “violently sick”, stomachache in two cases, and fatigue. In two of these cases, both at C1, therapy was discontinued: pt. 12 stopped after 280 mg prednisolone, and pt. 17 stopped at day 11 after a total of 850 mg prednisolone.
Table 1  Demographics and disease characteristics in both centers

<table>
<thead>
<tr>
<th>Pt</th>
<th>Center</th>
<th>Age</th>
<th>Gender</th>
<th>Disease duration*</th>
<th>Affected limb</th>
<th>Trigger event</th>
<th>Sensory symptoms</th>
<th>Vasomotor symptoms</th>
<th>Sudomotor symptoms</th>
<th>Motor/trophic symptoms</th>
<th>Sensory signs</th>
<th>Vasomotor signs</th>
<th>Sudomotor signs</th>
<th>Motor/trophic signs</th>
<th>Pain intensity at baseline</th>
<th>Pain intensity 6 weeks after treatment</th>
<th>Difference in pain intensity (baseline-week 6)</th>
<th>P value</th>
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<td>52</td>
<td>M</td>
<td>9</td>
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<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
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<td>17</td>
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<td>Y</td>
<td>Y</td>
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<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
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<td>Sprain</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>9</td>
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<td>Y</td>
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<td>Y</td>
<td>N</td>
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<td>Sprain</td>
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<td>46</td>
<td>M</td>
<td>6</td>
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<td>Using vibration tools</td>
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<td>Lower</td>
<td>Metatarsal fracture</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
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<td>43</td>
<td>M</td>
<td>120</td>
<td>Lower</td>
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<td>Y</td>
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<tr>
<td>Mean C1</td>
<td>50.2 (SD ± 8.7)</td>
<td>11.5 (IQR: 5.724)</td>
<td>7.1 (SD: 1.6)</td>
<td>6.7 (SD: 2.1)</td>
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<td>28</td>
<td>F</td>
<td>39</td>
<td>Upper</td>
<td>Wrist fracture</td>
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<td>Y</td>
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<td>Y</td>
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<td>Y</td>
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<td>M</td>
<td>317</td>
<td>Lower</td>
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<td>Y</td>
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<td>C2</td>
<td>43</td>
<td>F</td>
<td>12</td>
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<td>Spontaneous</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>Wrist fracture</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>6.1</td>
<td>5.9</td>
<td>0.2</td>
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</tr>
<tr>
<td>27</td>
<td>C2</td>
<td>51</td>
<td>F</td>
<td>25</td>
<td>Lower</td>
<td>Tibia and fibula fracture</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>6.7</td>
<td>0.3</td>
<td>6.4</td>
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</tr>
<tr>
<td>28</td>
<td>C2</td>
<td>68</td>
<td>F</td>
<td>5</td>
<td>Upper</td>
<td>Wrist fracture</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>4.5</td>
<td>3.0</td>
<td>1.5</td>
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</tr>
<tr>
<td>29</td>
<td>C2</td>
<td>32</td>
<td>F</td>
<td>21</td>
<td>Lower</td>
<td>Ankle fracture</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>8.2</td>
<td>na</td>
<td>0.2</td>
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</tr>
<tr>
<td>30</td>
<td>C2</td>
<td>70</td>
<td>F</td>
<td>4</td>
<td>Lower</td>
<td>Fibula fracture</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>5.1</td>
<td>1.0</td>
<td>4.1</td>
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</tr>
<tr>
<td>31</td>
<td>C2</td>
<td>19</td>
<td>F</td>
<td>17</td>
<td>Upper</td>
<td>Not known</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>9.0</td>
<td>1.0</td>
<td>8.0</td>
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<tr>
<td>Mean C2</td>
<td>42.8 (SD ± 16.2)</td>
<td>17 (IQR: 11-37)</td>
<td>6.1 (SD: 1.7)</td>
<td>4.4 (SD: 2.8)</td>
<td>0.09</td>
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<tr>
<td>Mean C1 + C2</td>
<td>47.1 (SD ± 12.7)</td>
<td>15 (IQR: 6-28)</td>
<td>6.8 (SD: 1.7)</td>
<td>5.8 (SD: 2.6)</td>
<td>0.059</td>
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</table>

Pt: patient; N: no; Y: yes
SD: standard deviation.
*Months. Median (Interquartile range)
Discussion

This study found low efficacy of oral steroids in the treatment of CRPS with >3 months pain duration. Pain intensity did not significantly decrease after administration of relatively high doses of oral prednisolone, with comparable results in both analyzed centers. Positive results with oral corticosteroids are described in the literature for the treatment of early/acute pre-Budapest criteria CRPS, while to our knowledge, our data provide the first published evidence describing the efficacy of oral steroids in longer-lasting CRPS fulfilling the Budapest criteria.

The rationale for using anti-inflammatory treatment of CRPS is based on evidence that aberrant inflammatory mechanisms are one of the major pathophysiological pathways underlying the onset and the maintenance of the syndrome [24]. Findings from human in vivo experiments show that concentrations of TNF-α and interleukin (IL)-6 in blister fluids are greater in the CRPS affected limb than in the unaffected limb [25]. TNF-α and IL-6 concentrations are also higher in skin biopsies from patients with CRPS than in patients with fractures who do not have CRPS [26]. In serum, concentrations of soluble TNF-α receptors and the pro-inflammatory cytokines TNF-α, IL-1 and IL-8 are increased in early CRPS (<3 months) [27,28]. Elevated activity of mast cells and increased markers of oxidative stress have also been reported [2,3]. Corticosteroids have been proposed for the treatment of CRPS because they can reduce inflammations by suppression of the production of mediators such as cytokines, chemokines, and neuropeptides. They also play a role in the modulation of the cellular immune response, reducing phagocytosis, antigen response, and cytokine production mediated by immune cells. Two RCTs of high/moderate quality showed benefit from oral steroid treatment of early CRPS. In one RCT, oral prednisolone (40 mg daily for 14 days) resulted in significantly better pain reduction than treatment with 20 mg oral piroxicam [6]. In another RCT, 10 mg oral prednisolone, administered three times a day for a maximum of 12 weeks, resulted in significant pain reduction [7]. Furthermore, two case series reported significant pain reduction after treatment with steroids (40–60 mg prednisolone for 2–4 days) followed by a tapering period of 4–7 days in patients with median disease duration of 2 or 3 months, and 60–80 mg of prednisone for 2–4 days, in 11 patients with a median disease duration of 8 weeks, respectively [29,30]. However, the method of administration was unclear in both of these studies.

Inflammation is only one of the established biological mechanisms underlying CRPS, which may exert differential effects in individual patients perhaps reflecting the different clinical manifestations of the syndrome. Furthermore, when following individual patients over time, inflammatory markers are reported to be more present in the early phase of the disease [31]. However, a study of Wesselsdijk et al. [10] showed markers of inflammation are not related to the course of the disease in chronic CRPS patients. Even as levels of TNF-α and IL-6 diminish during the course of the disease no clear improvement of inflammatory signs were found, and most of the analyzed patients still reported more pain. A more recent study of Lenz et al. (2013) [31] found that all measured cytokine levels in blister fluid of CRPS patients were comparable to those of non-CRPS patients from about 6 months of analgesic treatment after disease onset, and that the titers of these markers were not related to treatment outcome. These results indicate that inflammatory mechanisms may only be partially responsible for the signs and symptoms of CRPS1.

On the other hand, corticosteroids do not only have anti-inflammatory proprieties. A complementary analgesic effect of steroids, which may be mediated by modulation of GABAergic and/or opioidergic mechanisms as well as voltage gated calcium channels, in vitro, and at the spinal cord level in rodent models, has been described [11]. Furthermore, there is evidence found in preclinical and clinical studies in the efficacy of glucocorticoids for the treatment of chronic pain conditions [12–14]. Based on these observations, the use of steroids for the treatment of chronic CRPS may be justified. However, one RCT in 21 CRPS patients with more than 6 months disease duration did not show clinical benefit from a single intrathecal methylprednisolone bolus and this study was terminated prematurely because of a high rate of adverse events [15]. In our study with oral prednisolone only two patients had significant side effects. On the other hand, when excluding one patient with recurring disease, or borderline disease duration (>30), only two patients experienced clear (>50%) if temporary pain reduction. These two patients might represent a steroid-responsive subgroup.

Limitations in our study should be acknowledged.

The most important shortcoming of our study is the absence of a placebo group. Furthermore, a disease duration cut-off of 3 months was used, which is in agreement with the definition of chronic pain according to the IASP [17]. In the available literature, data about CRPS patients treated with steroids of about 3 months duration or less have been presented [6,7,8,29,30]. However, the use of this cut-off point meant that patients with a large range of disease durations were evaluated. Indeed, the median disease duration in our sample was 15 months, with 80% of the patients having disease duration of ≥6 months and 61% of the patients with disease duration of ≥1 year. Restricting the included patients to those with an intermediate disease duration (i.e., 3–12 months) could have led to different results. Nevertheless, no overall correlation between disease duration and pain relief could be established in our study. There is indication for the existence of distinct subtypes based on clinical phenotypes of the illness rather than disease duration and the presence of sequential stages of the syndrome is still a matter of debate [32]. The existence of subtypes of CRPS based on differences disease mechanism may provide an explanation for our finding of a trend toward an improvement observed in some of our patients.
Pain intensity was assessed in two different ways in the two centers, which may have introduced evaluation bias between the two centers. However, a study of Forouzanfar et al. [33] where a single pain rating was compared with the average pain intensity measured 3 times a day in a group of 50 CRPS1 patients has shown a high degree of agreement between both measurements. Patient selection at both centers may have led to selection bias. Reasons for not offering treatment to other patients seen during the treatment period were not recorded and their responses may have differed from that of the treated group.

Therapeutic regimens were also different. However, high doses of steroids were used in both institutions with a final end-treatment dose that was comparable between the two centers (1g/16 days at C1 and 1.08g/22 days at C2). Although the combined effect of interventions provided to the patients in this study was limited in these refractory patients, the influence of other interventions (pain medication and exercise/vocational rehabilitation) may have influenced results.

Moreover, although pain is the cardinal symptom of CRPS, it is not the only one. In our study we evaluate the effect of steroids only on pain relief, but we cannot say whether this therapeutic approach had any effect on the other signs and symptoms of CRPS. A high quality RCT showed only limited effects for improvement in range of motion of oral prednisolone when compared to piroxicam in patients with early CRPS after stroke [6]. In addition, another high quality trial on bier blocks with lidocaine and prednisolone and a RCT of poor quality on oral corticosteroids found no improvement on range of motion when compared to placebo [4]. Nevertheless, understanding the effect of steroids on other disease and health related outcomes are of interest. Similarly, patients’ CRPS was only broadly phenotyped, using Budapest categories (Table 1). When exploring steroid-responsive subtypes it would be interesting to separately record swelling, or high limb temperature, or assess patients with quantitative sensory testing (QST) [34].

We conclude that our study provides indications that oral corticosteroids are generally not very effective in treating pain in patients with CRPS of more than 3 months duration and not responding to previous treatment while they may cause important side effects. An important analgesic effect was observed in maximally 13% of our patients. Randomized controlled studies, designed to assess such low frequency responses, such as with enriched-, or single subject designs, might help to clarify whether there is a small subgroup of patients responding to oral steroid treatment, and characterize such a group.

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