DOI: 10.1111/papr.13310

RESEARCH ARTICLE

# The efficacy of oral corticoids in treating complex regional pain syndrome: A retrospective cohort study

**Corinne van den Berg MD** | **Frank J. P. M. Huygen MD, PhD** | **Jitske Tiemensma PhD**

Department of Anesthesiology, Centre for Pain Medicine, Erasmus University Medical Centre, Rotterdam, The Netherlands

**Correspondence**
Corinne van den Berg, Department of Anesthesiology, Centre for Pain Medicine, Erasmus University Medical Centre, Postbus 2040, 3000CA Rotterdam, The Netherlands.
Email: c.vandenberg.6@erasmusmc.nl

**Abstract**

**Objectives:** There is growing evidence supporting the role of inflammatory mechanisms in complex regional pain syndrome (CRPS). Corticoids, as most effective anti-inflammatory drugs, are widely used in treating inflammation. The aim of this study was to retrospectively assess the efficacy of oral corticoid treatment in CRPS patients.

**Methods:** Patients treated at the center of pain medicine in the Erasmus University Medical Centre between January 2015 and January 2020 were approached to partake in this study. Medical records were screened for age, gender, medical history, duration of CRPS, and CRPS severity score. Also, treatment effect, dose and duration, pain scores (NRS), and side effects were extracted from medical records. In addition, global perceived effect was completed in patients treated with corticoids.

**Results:** Between January 2015 and January 2020, twenty-nine CRPS patients received corticoids and met the inclusion criteria. One extreme outlier was excluded and treatment effect was unknown for one patient. Average daily dose was 28.9 mg (range 10–30 mg) and the mean treatment duration was 10.5 days (7–21 days). Fourteen patients (51.9%) responded positively to treatment and thirteen (48.1%) did not respond. Side effects were reported in five patients (17.9%).

**Conclusions:** Corticoid treatment was effective in more than half of the patients. With only mild side effects reported the treatment also appears to be relatively safe. Further research is needed to investigate the efficacy of corticoids in treating (early) CRPS, preferably in an intervention study.

**KEYWORDS**
complex regional pain syndrome, corticoids, treatment

## INTRODUCTION

Complex regional pain syndrome (CRPS) is generally characterized by continuing pain combined with sensory, vasomotor, sudomotor, motor, and trophic symptoms.[1] The pain is disproportional in relation to the initial trauma and the incidence varies between 5.5 and 26.2 per 100.000 person years.[2,3] CRPS is diagnosed based on the International Association for the Study of Pain (IASP) clinical diagnostic criteria, assessing patient's symptoms and signs.[4]

Over the years, it has become clear that several mechanisms play a role in the development and maintenance of CRPS. Increasing evidence supports an exaggerated inflammatory response as one of the major mechanisms. Studies documented increased concentrations of pro-inflammatory cytokines and neuropeptides in systemic circulation, cerebrospinal fluid, and in artificial skin blister fluid on the affected limb of CRPS patients.[5–7] Likewise, median soluble IL-2 receptor (sIL-2R) was increased in CRPS patients' serum compared to healthy blood donors, indicating increased T-cell activity in CRPS.[8]

Historically, CRPS was treated in an all fits one manner. Today, treatment is mostly tailored to the most prominent mechanism(s) present in a specific CRPS case, so-called mechanism-based treatment.[9] No causal therapy for CRPS is available. The mechanism(s) present may be relevant to predict responses to individual treatment options. Corticoids, as most effective anti-inflammatory drugs, are a natural treatment option in cases with prominent inflammation.[10] Corticoids are widely used in treating inflammatory diseases and act anti-inflammatory by interfering with various processes, causing upregulation of the anti-inflammatory genes and downregulation of the pro-inflammatory genes.[11] Additionally, corticoids inhibit transcription factors that control synthesis of pro-inflammatory mediators. Corticoids also inhibit phospholipase A2, causing production of inflammatory mediators.[12,13]

A recent review showed corticoid treatment to be successful in treating CRPS, especially regarding pain relief and improvement in range of motion.[14] However, the optimal route of administration and optimal dose are still unknown. Today, in our clinic, a standardized moderate dose regimen is conducted in patients with clinical signs of inflammation and an elevated sIL-2R level. We conducted this retrospective study to evaluate the effectiveness of our oral corticoid treatment protocol for CRPS in our expert center.

# METHODS

We conducted a retrospective study of all patients with CRPS who visited the center for pain medicine between January 2015 and January 2020. Our clinic is a tertiary referral center with CRPS being one of the fields of expertise. Ethical approval was obtained from the Medical Ethics Committee of Erasmus University Medical Centre Rotterdam (MEC-2020-0408).

## Treatment with oral corticoids

Currently, short-term corticoid treatment is prescribed to CRPS patients with clinical signs of inflammation and elevated sIL-2R levels in our clinic. Treatment contains 30 mg oral prednisolone per day for a duration of at least 7 days.

## Patients

Electronic patient records were searched for patients with CRPS in the period between January 2015 and January 2020. In the Netherlands, hospitals use both International Classification of Diseases (ICD-10) codes and diagnosis-treat combination (in Dutch: Diagnose-behandelcombinatie) codes, also called DBCs. Both codes are used to classify the reason for the visit, given diagnoses, and treatment for a patient. Specific codes are used for CRPS: G90.5, G90.6, and G90.7 as ICD-10 codes and 150 for DBC. Based on these codes, a search was conducted in electronic patient records. Subsequently, all identified patients were approached by letter, email, and/or phone to provide permission to view their medical records, according to the General Data Protection Regulation.[15] Only adult patients (>18 years) were approached. After permission, a single researcher (CvdB) viewed the medical files to assess whether a patient was eligible for inclusion in this retrospective study. The inclusion criteria involved a CRPS diagnosis, based on the IASP clinical diagnostic criteria, and the patient has to be treated at our center for pain medicine. In cases of uncertainty, the other authors were consulted and it was jointly determined whether the patient was eligible. Medical files from eligible patients were viewed entirely from the start of treatment and cases who were treated at our tertiary referral center before the age of 18 remained in the study. Patients referred for a second opinion or preoperative advice were excluded. Due to the lack of medical information, patients who continued treatment started in another hospital were also excluded. Only patients who were treated with corticoids were included in the present study.

## Data collection

After inclusion, a single researcher (CvdB) viewed the medical records. The main study parameter was reported treatment effect. Patients were categorized as either a responder or nonresponder to corticoid treatment based on clinician-reported treatment effects. Medical record was screened for age, gender, medical history, duration of CRPS, serum sIL-2R levels, and CRPS severity score (CSS). The CSS is a tool to quantify clinical features associated with CRPS based on the presence/absence of 16 clinically assessed signs and symptoms (Table 1).[16,17] Furthermore, treatment dose, duration of treatment, pain scores by numeric rating scale (NRS) before and after treatment, and side effects were noted.

In addition, all patients treated with corticoids and from whom clinician-reported treatment effect was present in the medical record were approached by the researcher. Patients' assessment of corticoid treatment was measured using Global Perceived Effect (GPE), taken by telephone. GPE asks the patient to rate how much their condition has improved or deteriorated since corticoid treatment on a 7-point Likert scale, with higher scores indicating more severe conditions (Table 2).

## Statistical analysis

Statistical analysis was performed with IBM SPSS software, version 28 (IBM Corporation, Armonk, NY). Descriptive

**TABLE 1** CRPS severity score by Harden et al.[17]

| Symptoms[a] | Signs[b] |
|---|---|
| Continuing, disproportionate pain | Hyperalgesia to single pinprick |
| Allodynia or hyperalgesia | Allodynia |
| Temperature asymmetry | Temperature asymmetry by palpation |
| Color asymmetry | Color asymmetry |
| Sweating asymmetry | Sweating asymmetry |
| Edema | Asymmetric edema |
| Dystrophic changes | Dystrophic changes |
| Motor abnormalities (weakness, tremor, dystonia, decreased range of motion, and myoclonus) | Motor abnormalities (tremor/myoclonus, dystonia, decreased active range of motion, and weakness) |

[a]Symptoms as reported by the patient and registered as absent or present.
[b]Signs as observed during physical examination by the physician and registered as absent or present.

**TABLE 2** Global perceived effect.

| To what extent have you recovered from your symptoms since starting corticoid treatment? |
|---|
| 1. Very much improved |
| 2. Much improved |
| 3. A little improved |
| 4. No change |
| 5. A little deterioration |
| 6. Much deterioration |
| 7. Very much deterioration |

statistics were used to calculate frequencies of categorical variables and to calculate measures of central tendency and variability of continuous variables. The Shapiro–Wilk test was used to analyze whether continuous variables were normally distributed. Variables with a normal distribution are reported in means and standard deviations, otherwise, medians, and interquartile ranges are used. Depending on the shape of distribution, continuous variables were compared between two groups using either a two-sided independent *t*-test or a two-sided Mann–Whitney *U* test. Categorical variables were compared using the Chi-squared test. A two-tailed *p*-value below 0.05 was considered to indicate statistical significance for all analyses.

# RESULTS

## Patients

One hundred fifty-three patients were treated for CRPS in our expert center between January 2015 and January 2020. All patients were approached to request permission to view their medical records. In total, 123 patients gave consent of which nine patients did not meet eligibility criteria after viewing medical records. A total of 114 patients were eligible for inclusion in the current study. Corticoid treatment was given to 29 (25.4%) of the patients. However, one outlier was excluded and clinician-reported treatment effect was unknown in one, resulting in an analysis of 27 patients (Figure 1). The outlier had an acute flare-up of fulminant CRPS and received a total of 2202.5 mg prednisolone over 238 days. At first, this excessive corticoid treatment seemed effective, but an amputation could not be prevented.

## Responder versus nonresponder

Of the 27 patients, 14 patients (51.9%) were responders, showing positive treatment effects, and 13 (48.1%) were nonresponders, showing no effect to corticoid treatment. Table 3 presents the demographic and clinical characteristics of both responders and nonresponders. There were no differences in baseline characteristics between both groups. Patients received an average daily corticoid dose of 28.9 mg (range 10–30 mg) and mean treatment duration was 10.5 days (range 7–21 days). Table 4 shows treatment specifications compared between responders and nonresponders. There were no significant differences.

In 8 of the 14 responders, effect of corticoid treatment was further specified in medical records; improvement of inflammatory features (swelling, color) was reported in five patients, improvement in function in one, pain relief in five patients, and allodynia improved in one. Duration of the mentioned treatment effect was not clearly described in medical records. In five patients, described effect only persisted during corticoid treatment, and symptoms returned immediately after stopping or a few days later.

## Global perceived effect

In total 24 patients completed the GPE. Two patients (1 responder and 1 nonresponder) indicated that they no longer sufficiently remember the treatment. In addition, one patient (responder) could not be reached by telephone. Resulting in a response rate of 88.9%. Based on GPE we distinguished three groups; improvement (GPE 1–3), no change (GPE 4), and deterioration

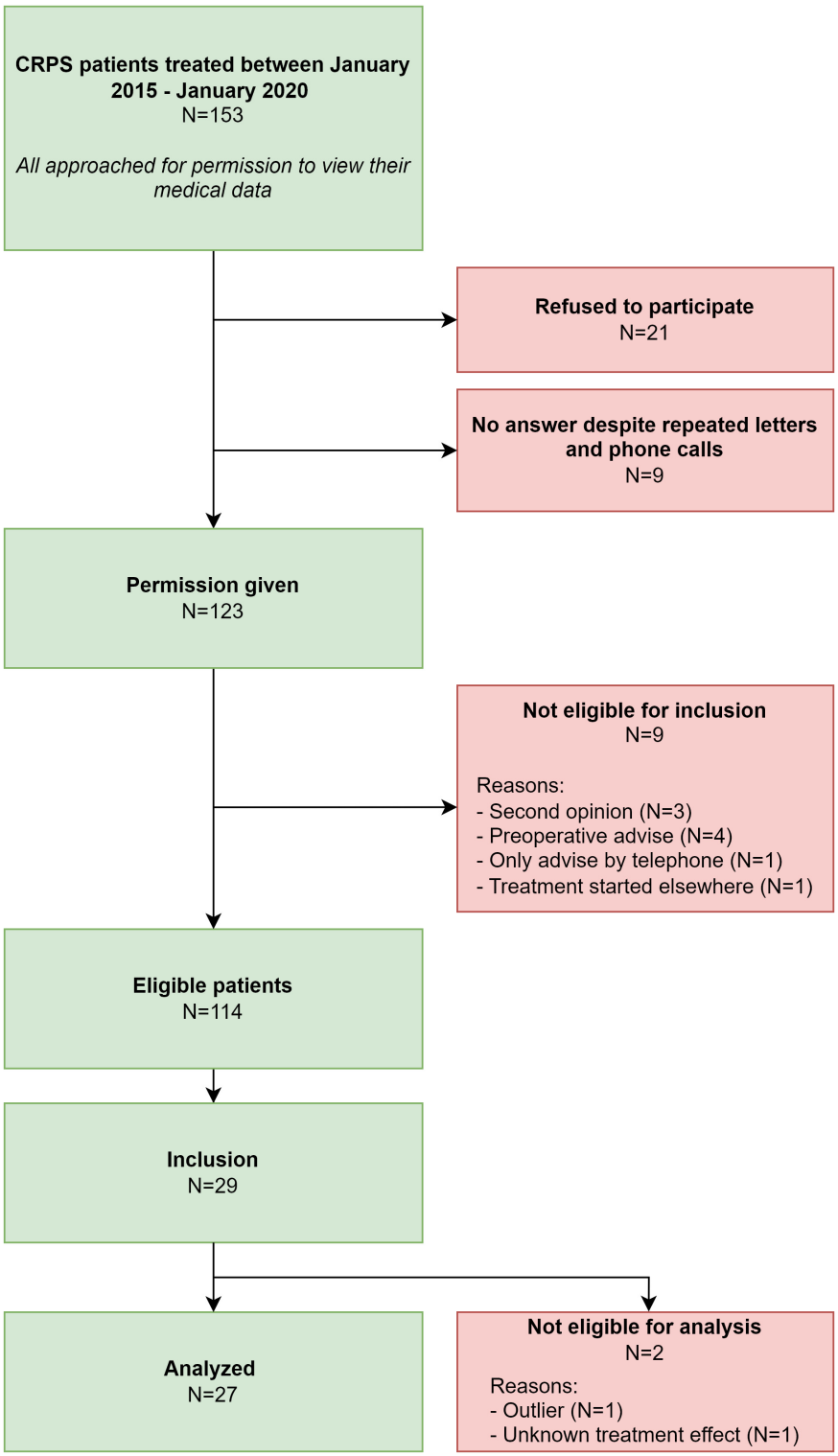


**FIGURE 1** Flowchart of patient selection.

(GPE 5–7). Comparing GPE with clinician-reported treatment effect all responders scored 4 or less and all nonresponders scored 4 or higher (Table 5). The GPE score of the responder group (median 3.0, IQR 3.0–4.0) was significantly lower than in the nonresponder group (median 4.0, IQR 4.0–5.75) ($p<0.001$), with lower scores indicating more improvement.

## sIL-2R levels

There were no significant differences in the distribution of sIL-2R levels before ($p=0.765$) and after ($p=0.753$) corticoid treatment between the responders and nonresponders (Figure 2 and Table 4). In both groups, a difference in sIL-2R level before and after was reported,

**TABLE 3** Demographic and clinical characteristics of participants received corticoid treatment.

| | Responder | Nonresponder | |
|---|---|---|---|
| | *N*=14 | *N*=13 | Significance |
| Gender | | | 1.00 |
| Female | 13 (92.9%) | 12 (92.3%) | |
| Male | 1 (7.1%) | 1 (7.7%) | |
| BMI | 26.99±4.61 | 26.68±4.36 | 0.861 |
| Age at the start corticoid treatment, years | 40.28±15.01 | 43.07±15.53 | 0.639 |
| CRPS duration at start treatment, months (median, IQR) | 53.28 (15.75–110.25) | 42.38 (6.5–49.0) | 0.369 |
| Affected limb | | | 0.154 |
| Upper limb | 2 (14.3%) | 4 (30.8%) | |
| Lower limb | 12 (85.7%) | 9 (69.2%) | |
| Affected side | | | 0.915 |
| Left | 8 (57.1%) | 7 (53.8%) | |
| Right | 6 (42.9%) | 5 (38.5%) | |
| Both | 0 | 1 (7.7%) | |
| Initiating event | | | 0.661 |
| Trauma | 11 (78.6%) | 7 (53.8%) | |
| Surgery | 2 (14.3%) | 5 (38.5%) | |
| Spontaneous | 1 (7.1%) | 1 (7.7%) | |

*Note*: Values are presented as number (%) for categorical variables and mean ±SD or median (IQR) for continuous variables.
Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation.

**TABLE 4** Comparison of treatment specifications and side effects between responders and nonresponders.

| | Responder | Nonresponder | |
|---|---|---|---|
| | *N*=14 | *N*=13 | Significance |
| Duration of treatment, days | 10.86±3.23 | 10.08±1.44 | 0.432 |
| Daily dose, mg | 27.69±5.99 | 30±0 | 0.178 |
| Total dose, mg | 275.96±59.16 | 304.61±38.43 | 0.078 |
| sIL-2R before treatment, pg/mL | 4432.92±1681.84 | 4641.36±1681.84 | 0.765 |
| sIL-2R after treatment, pg/mL | 3887.27±1531.54 | 3625.00±2057.78 | 0.753 |
| Δ sIL-2R | 997.00 (−397.00; 3031.00) | 220.50 (−142.50; 1948.00) | |
| Side effects | | | 0.260 |
| Yes | 4 (28.6%) | 1 (7.7%) | |
| No | 8 (57.1%) | 7 (53.8%) | |
| Unknown | 2 (14.3%) | 5 (38.5%) | |

*Note*: Values are presented as number (%) for categorical variables and mean ± SD or median (IQR) for continuous variables.
Abbreviations: IQR, interquartile range; mg, milligram; pg/mL, picograms per milliliter; SD, standard deviation; sIL-2R, soluble IL-2 receptor; Δ, delta.

but the difference showed to be both positive and negative. Meaning in some patients sIL-2R level after treatment was higher than before treatment, and in others, levels fell.

## CRPS severity score

Table 6 shows the proportion of symptoms and signs in responders and nonresponders according to the CSS at first outpatient visit in our center. Median pain scores at the time of visit and 24 h before the visit were comparable between both groups. Two symptoms (i.e., subjective symptoms reported by patients) were significantly higher in the nonresponder group than in the responder group: affected side colder ($p=0.035$) and nail changes ($p=0.029$). Affected side warmer was significantly higher in the responder group ($p=0.037$). In signs (i.e., objective signs observed by the physician) no significant differences between both groups were found. In addition, the mean CRPS severity score was comparable between both groups.

**TABLE 5** Global perceived effect spread across responders and nonresponders.

| | Global perceived effect[a] | | |
|---|---|---|---|
| | **Improvement (1–3)** | **No change (4)** | **Deterioration (5–7)** |
| Clinician-reported treatment effect | | | |
| Responder ($N=12$) | 7 | 5 | 0 |
| Nonresponder ($N=12$) | 0 | 7 | 5 |

[a]GPE was completed by 24 patients (12 responders and 12 nonresponders).

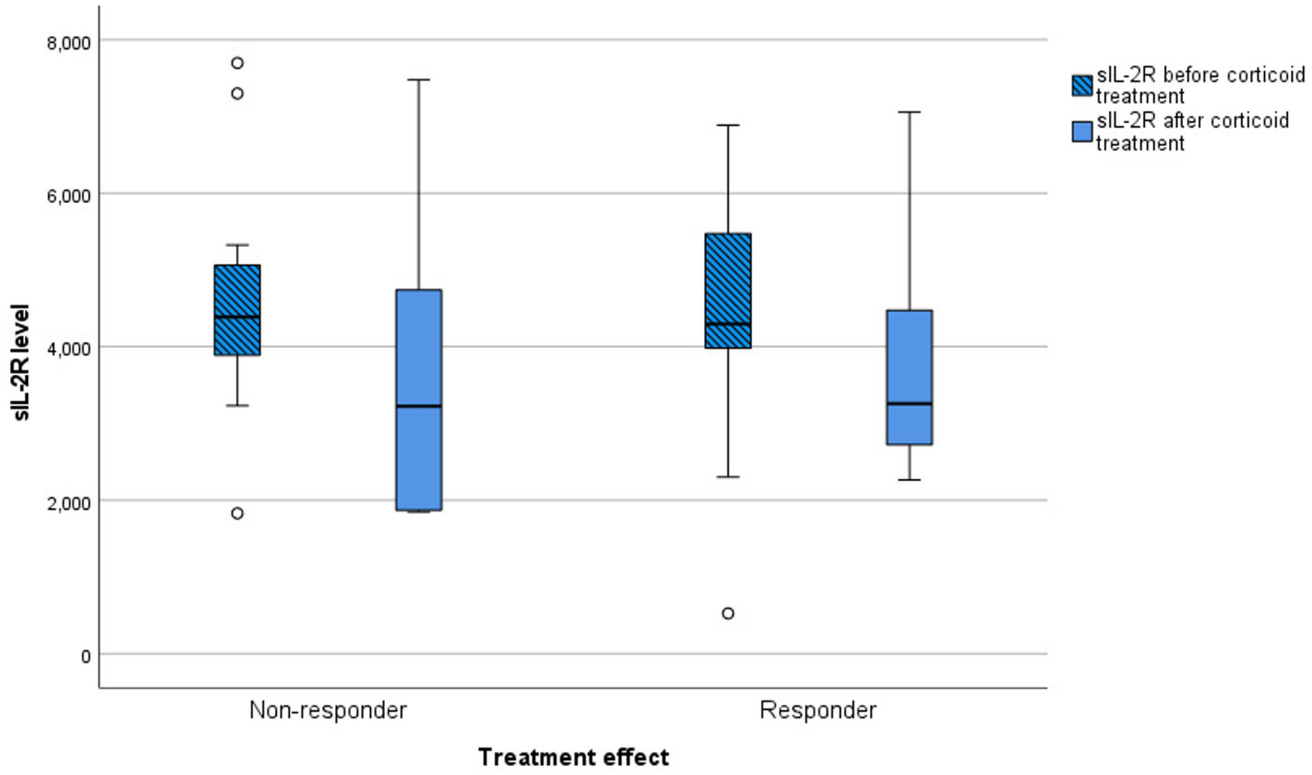


**FIGURE 2** Boxplot of the mean sIL-2R levels before and after corticoid treatment between the responders and nonresponders.

## Side effects

Side effects were reported in five patients, four responders and one non-responder. The nature of the side effects was not well documented in all patients, but vomiting, dizziness, and occurrence of a wound were reported in four out of five. In sixteen patients no side effects were described in medical records.

# DISCUSSION AND CONCLUSIONS

As described in this retrospective study, corticoid treatment was prescribed to 29 CRPS patients treated in our expert center between January 2015 and 2020. Patients received a moderate daily dose, average 28.9 mg/day, and were treated for 21 days or less. Corticoid treatment seemed to be effective in more than half of the CRPS patients when looking at clinician-reported treatment effect and GPE.

Inflammation plays a major role in the pathophysiology of CRPS.[6,18] Therefore, corticoid treatment appears to be a key drug in treating CRPS because of the anti-inflammatory and immunosuppressive effects. However, the corticoid treatment policy is variable according to the current CRPS guidelines. The Dutch guidelines, last updated in 2014, advise restraint due to possible side effects.[19] The German guidelines reported the ideal experience with a relatively high dose of glucocorticoids, starting with 100 mg daily and tapering off by 25 mg each for 4 days.[20] In the second edition of the guidelines in the United Kingdom, corticoid treatment is not mentioned.[21] On the contrary, the fifth edition of practical diagnostic and treatment guidelines for CRPS in the United States notes that a short course of steroids may be indicated in early CRPS with prominent inflammation. Longer courses are unproven, and there are numerous serious contraindications to chronic steroid use.[22]

**TABLE 6** CRPS severity score: presence of symptoms and signs of CRPS in each group.

| | Responder | Nonresponder | |
|---|---|---|---|
| | *N*=14 | *N*=13 | Significance |
| NRS at the time of visit | 7.0 (6.0–7.5) | 7.3 (7.0–8.0) | 0.156 |
| NRS 24 h before visit | 7.5 (5.8–9.5) | 8.0 (6.7–8.2) | 0.825 |
| Symptoms | | | |
| Continuing pain | 14 (100) | 13 (100) | NA[a] |
| Allodynia and/or hyperalgesia | 14 (100) | 13 (100) | NA[a] |
| Allodynia | 11 (78.6) | 13 (100) | 0.077 |
| Hyperalgesia | 12 (85.7) | 12 (92.3) | 0.586 |
| Temperature asymmetry | 14 (100) | 13 (100) | NA[a] |
| Affected side warmer | 6 (42.9) | 1 (7.7) | 0.037 |
| Affected side colder | 4 (28.6) | 9 (69.2) | 0.035 |
| Variable; warm/cold | 4 (28.6) | 3 (23.1) | 0.745 |
| Color asymmetry | 13 (92.9) | 13 (100) | 0.326 |
| Red | 5 (35.7) | 7 (53.8) | 0.343 |
| Blue | 7 (50.0) | 5 (38.5) | 0.547 |
| Other color | 1 (7.1) | 1 (7.7) | 0.326 |
| Sweating asymmetry | 9 (64.3) | 7 (53.8) | 0.581 |
| Edema | 13 (92.9) | 10 (76.9) | 0.244 |
| Dystrophic changes | 10 (71.4) | 11 (84.6) | 0.410 |
| Nails | 5 (35.7) | 10 (76.9) | 0.029 |
| Hair | 8 (57.1) | 6 (46.2) | 0.535 |
| Skin | 2 (14.3) | 3 (23.1) | 0.451 |
| Motor abnormalities | 14 (100) | 12 (92.3) | 0.290 |
| Weakness | 14 (100) | 12 (92.3) | 0.290 |
| Tremor | 7 (50.0) | 2 (15.4) | 0.057 |
| Dystonia | 3 (21.4) | 7 (53.8) | 0.081 |
| Decreased ROM | 13 (92.9) | 10 (76.9) | 0.244 |
| Myoclonus | 5 (35.7) | 1 (7.7) | 0.080 |
| Signs | | | |
| Hyperalgesia to pinprick | 4 (28.6) | 3 (23.1) | 0.745 |
| Allodynia[b] | 11 (78.6) | 12 (92.3) | 0.315 |
| Temperature asymmetry on palpation | 9 (64.3) | 7 (53.8) | 0.581 |
| Affected side cooler | 6 (42.9) | 7 (53.8) | 0.568 |
| Affected side warmer | 3 (21.4) | 0 | 0.077 |
| Color asymmetry | 8 (57.1) | 10 (76.9) | 0.276 |
| Red | 3 (21.4) | 4 (30.8) | 0.580 |
| Blue or pale | 4 (28.6) | 6 (46.2) | 0.345 |
| Mottled | 1 (7.1) | 0 | 0.326 |
| Scar | 0 | 0 | NA[a] |
| Sweating asymmetry | 2 (14.3) | 1 (7.7) | 0.511 |
| Increased on affected side | 2 (14.3) | 1 (7.7) | 0.586 |
| Decreased on affected size | 0 | 0 | NA[a] |
| Asymmetric edema | 8 (57.1) | 3 (23.1) | 0.072 |
| Dystrophic changes | 3 (21.4) | 5 (38.5) | 0.333 |
| Nails | 1 (7.1) | 2 (15.4) | 0.747 |
| Hair | 1 (7.1) | 2 (15.4) | 0.747 |

(Continues)

**TABLE 6** (Continued)

| | Responder | Nonresponder | |
|---|---|---|---|
| | *N*=14 | *N*=13 | Significance |
| Skin | 2 (14.3) | 3 (23.1) | 0.780 |
| Motor abnormalities affected side | 13 (92.9) | 12 (92.3) | 0.957 |
| Tremor or myoclonus | 1 (7.1) | 0 | 0.326 |
| Dystonia | 7 (50.0) | 3 (23.1) | 0.148 |
| Decreased ROM | 12 (85.7) | 10 (76.9) | 0.557 |
| Weakness[c] | 13 (92.9) | 12 (92.3) | 0.957 |
| CRPS severity score | 11.3±1.69 | 11.1±1.34 | 0.734 |

*Note*: Values are presented as number (%) for categorical variables and mean ±SD or median (IQR) for continuous variables.

Abbreviations: IQR, interquartile range; NA, not applicable; ROM, range of motion; SD, standard deviation.

[a]No *p*-value is available because the variable is 100% present or absent in both groups.

[b]Allodynia is normally calssified into light touch, deep joint pressure, vibration, cold, and warm). Due to missing of this specification in medical records, the specification of allodynia is not described in this table.

[c]Weakness is normally rated in the severity score as 1/5: flicker of movement, 2/5: movement with gravity, 3/5: movement against gravity, 4/5: weak. However, this ratio was not mentioned specifically in medical records and is therefore not described here.

All patients treated with corticoids in this study received a moderate dose (between 7.5 and 40 mg/day) of oral prednisolone. Treatment was shown to be effective in 51.9% of the patients. Patients in this study already suffer from CRPS for 1–58 months at the first visit to our expert center, and the CRPS duration at the start of corticoid treatment is between 6.5 and 110 months. Therefore, it is likely that the longer duration of CRPS in our patients plays an important role in the shown treatment effectiveness. Especially in the acute stage of CRPS, the classical signs of peripheral inflammation are described: pain, increased temperature, swelling, redness, and loss of function.[23,24] In this phase, corticoid treatment is likely to be effective. However, at least in the majority of patients with longer-existing CRPS the acute inflammation extinguished and there is residual damage. In this stage with residual damage, which may be both peripheral and central, the anti-inflammatory effect of given corticoid treatment will be minimal or even absent. Barbalinardo et al. indeed showed limited efficacy in CRPS patients with a duration of more than 3 months.[25]

In addition to CRPS duration, warm and cold CRPS subtypes may also play a role.[26] Looking at CSS we found significant differences in some symptoms related to inflammation. The affected side was significantly warmer in responders, while the affected side was significantly colder in nonresponders. This may indicate warm CRPS in the responder group and cold CRPS in the nonresponder group. However, in other symptoms related to inflammation: color asymmetry, sweating asymmetry, and edema no differences were found. Furthermore, the signs related to inflammation were comparable between both groups. In addition, it is known that inflammation still plays a role in cold CRPS, with present levels of pro-inflammatory cytokines.[27]

The increased inflammatory activity in CRPS could also be related to dysfunction of the hypothalamic–pituitary–adrenal axis (HPA axis). HPA-axis impairments are present in inflammatory and autoimmune diseases such as rheumatoid arthritis, Crohn's disease, multiple sclerosis, and asthma.[28,29] All diseases associated with increased inflammatory activity—just like CRPS. In addition to stress, both physical and psychological, the HPA axis can also be activated by inflammatory mediators.[30] Activation of the HPA axis causes endogenous cortisol production, which has an inhibitory effect on the HPA axis, also known as negative feedback. Subsequently, activated negative feedback can ensure suppressed inflammation. Only one study regarding the functioning of the HPA axis in CRPS exists. Park and Ahn showed that a relatively high frequency of spontaneous pain attacks was associated with a reduced cortisol awakening response and flattened slope of the diurnal cortisol decline.[31] Reduced cortisol levels indicate dysfunction of the HPA axis, which also can influence the effect of corticoid treatment.

In addition to the possible dysfunction of the HPA axis, forms of glucocorticoid resistance could also be related. The response to corticoids is not only determined by the concentration of corticoids but also by differences in individual glucocorticoid sensitivity. In the general population, it is estimated that around 30% of people are nonresponders or "glucocorticoid resistant."[32] This glucocorticoid sensitivity causes a variety of clinical responses and therefore may also influence the shown efficacy of corticoid treatment in this study.

We found variable sIL-2R values with both positive and negative differences in sIL-2R levels before and after corticoid treatment. Meaning in some patients sIL-2R level after treatment was higher than before treatment, and in others, levels fell. In addition to a possible role for glucocorticoid resistance, this variation is probably because the sIL-2R was not determined immediately before and after treatment. For example, sIL-2R before was

measured 117–0 days before start of treatment. In four patients sIL-2R level was measured during treatment and not afterward. Where the sIL-2R level of another patient was determined 99 days after ending treatment. It is also suggested that the effect of corticoid administration on circulating sIL-2R levels depends on the state of immune activation and the duration of the corticoid exposure.[33] Therefore, we postulate dosage of corticoid treatment probably also plays a role.

Corticoid treatment can cause side effects, which are often dose and time dependent.[12,34] In this study, side effects were described in only five patients (17.9%). Despite the not well-documented nature of these side effects the reported effects showed to be mild: vomiting, dizziness, and occurrence of a wound. The results of this study thus showed treatment with oral corticoids appears to be relatively safe.

This study has several limitations. First, the retrospective design and the associated reliance on what was reported in the medical records. Therefore, we encountered missing data. Due to a lack of clear specification of clinician-reported treatment effects in medical records, we were unable to indicate which effect (pain relief, improvement of inflammatory features, and improved function) was shown in the responder group. For example, NRS before and after corticoid treatment was only reported in two responders. Before treatment, both patients reported pain NRS 8 and both showed a decrease in NRS: 1 and 3 points decrease. Also, the results of GPE could be biased by patients' memory. The more so, given the relatively the long period between treatment and completion of the questionnaire. In addition, GPE ratings also depend on current status.[35] However, when comparing clinician-reported treatment effect with GPE we found all responders scored 4 or less and all nonresponders scored 4 or higher. Meaning all responders showed no change or improvement, while all nonresponders showed no change or deterioration. So patients did remember whether there was an effect or not despite long period between treatment and completion of GPE. Furthermore, the small sample size is a limitation. Only 29 patients received corticoid treatment and were included, of whom we could only analyze 27 patients. This small number makes it difficult to draw firm conclusions about the efficacy of corticoids in treatment of CRPS. Additionally, patients included in this study were treated in a tertiary referral hospital. Most patients in our clinic already suffered from CRPS for several years, and they are often treatment-resistant to other treatments. As mentioned above, the CRPS duration at the first visit to our expert center and also at the start of corticoid treatment was longer existing. In addition to the already described possible influence on the treatment effect, this also ensures that our findings might not be generalizable to newly diagnosed CRPS patients.

In conclusion, treatment with oral corticoids appears to be effective and relatively safe in more than half of the patients. Future research should examine the efficacy of oral corticoids in a controlled study. To establish potential predictors of treatment response, it would be helpful to focus on mechanism-based treatment and thus focus on CRPS patients with clinically prominent inflammation.

## AUTHOR CONTRIBUTIONS

Corinne van den Berg drafted the manuscript. Jitske Tiemensma and Frank J. P. M. Huygen co-authored this manuscript. All authors critically edited, read, and approved the final manuscript.

## FUNDING INFORMATION

No funding was received to assist with the preparation of this manuscript.

## CONFLICT OF INTEREST STATEMENT

Frank J. P. M. Huygen reports personal fees from Abbott; grants and personal fees from Saluda; and personal fees from Boston Scientific, Grunenthal, and Pfizer outside the submitted work. Corinne van den Berg and Jitske Tiemensma report no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

## ORCID

*Corinne van den Berg* https://orcid.org/0000-0003-0017-7204

## REFERENCES

1. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med. 2007;8:326–31.
2. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. Pain. 2003;103:199–207.
3. de Mos M, de Bruijn AGJ, Huygen FJPM, Dieleman JP, Stricker CBH, Sturkenboom MCJM. The incidence of complex regional pain syndrome: a population-based study. Pain. 2007;129:12–20.
4. Harden NR, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for complex regional pain syndrome. Pain. 2010;150:268–74.
5. Huygen FJ, De Bruijn AG, De Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ. Evidence for local inflammation in complex regional pain syndrome type 1. Mediators Inflamm. 2002;11:47–51.
6. Bruehl S, Warner DS. An update on the pathophysiology of complex regional pain syndrome. Anesthesiology. 2010;113:713–25.
7. Alexander GM, Peterlin BL, Perreault MJ, Grothusen JR, Schwartzman RJ. Changes in plasma cytokines and their soluble receptors in complex regional pain syndrome. J Pain. 2012;13:10–20.
8. Bharwani KD, Dirckx M, Stronks DL, Dik WA, Schreurs MWJ, Huygen F. Elevated plasma levels of sIL-2R in complex regional pain syndrome: a pathogenic role for T-lymphocytes? Mediators Inflamm. 2017;2017:2764261.
9. Mangnus TJP, Bharwani KD, Dirckx M, Huygen F. From a symptom-based to a mechanism-based pharmacotherapeutic

treatment in complex regional pain syndrome. Drugs. 2022;82:511–31.
10. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids–new mechanisms for old drugs. N Engl J Med. 2005;353:1711–23.
11. Becker DE. Basic and clinical pharmacology of glucocorticosteroids. Anesth Prog. 2013;60:25–31; quiz 32.
12. Ericson-Neilsen W, Kaye AD. Steroids: pharmacology, complications, and practice delivery issues. Ochsner J. 2014;14:203–7.
13. Williams DM. Clinical pharmacology of corticosteroids. Respir Care. 2018;63:655–70.
14. van den Berg C, de Bree PN, Huygen F, Tiemensma J. Glucocorticoid treatment in patients with complex regional pain syndrome: a systematic review. Eur J Pain. 2022;26:2009–35.
15. EU General Data Protection Regulation (GDPR). Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), OJ 2016 L 119/1.
16. Harden NR, Bruehl S, Perez R, Birklein F, Marinus J, Maihofner C, et al. Development of a severity score for CRPS. Pain. 2010;151:870–6.
17. Harden RN, Maihofner C, Abousaad E, Vatine JJ, Kirsling A, Perez R, et al. A prospective, multisite, international validation of the complex regional pain syndrome severity score. Pain. 2017;158:1430–6.
18. Parkitny L, McAuley JH, Di Pietro F, Stanton TR, O'Connell NE, Marinus J, et al. Inflammation in complex regional pain syndrome. A systematic review and meta-analysis. Neurology. 2013;80:106–17.
19. Perez RS, Zollinger PE, Dijkstra PU, Thomassen-Hilgersom IL, Zuurmond WW, Rosenbrand KC, et al. Evidence based guidelines for complex regional pain syndrome type 1. BMC Neurol. 2010;10:20.
20. Birklein F, Schlereth T. Aktuelles zur Therapie des komplex-regionalen Schmerzsyndroms. Nervenarzt. 2013;84:1436–44.
21. Turner-Stokes L, Goebel A, Guideline Development Group. Complex regional pain syndrome in adults: concise guidance. Clin Med (Lond). 2011;11:596–600.
22. Harden RN, McCabe CS, Goebel A, Massey M, Suvar T, Grieve S, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 5th edition. Pain Med. 2022;23:S1–S53.
23. Birklein F, Schlereth T. Complex regional pain syndrome-significant progress in understanding. Pain. 2015;156(Suppl 1):S94–S103.
24. Bharwani KD, Dirckx M, Huygen FJPM. Complex regional pain syndrome: diagnosis and treatment. BJA Educ. 2017;17:262–8.
25. Barbalinardo S, Loer SA, Goebel A, Perez RS. The treatment of longstanding complex regional pain syndrome with oral steroids. Pain Med. 2016;17:337–43.
26. Bruehl S, Maihöfner C, Stanton-Hicks M, Perez RS, Vatine JJ, Brunner F, et al. Complex regional pain syndrome: evidence for warm and cold subtypes in a large prospective clinical sample. Pain. 2016;157:1674–81.
27. Dirckx M, Stronks DL, van Bodegraven-Hof EA, Wesseldijk F, Groeneweg JG, Huygen FJ. Inflammation in cold complex regional pain syndrome. Acta Anaesthesiol Scand. 2015;59:733–9.
28. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. Ann N Y Acad Sci. 2012;1261:55–63.
29. Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. J Steroid Biochem Mol Biol. 2010;120:76–85.
30. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017;17:233–47.
31. Park JY, Ahn RS. Hypothalamic-pituitary-adrenal axis function in patients with complex regional pain syndrome type 1. Psychoneuroendocrinology. 2012;37:1557–68.
32. Quax RA, Manenschijn L, Koper JW, Hazes JM, Lamberts SW, van Rossum EF, et al. Glucocorticoid sensitivity in health and disease. Nat Rev Endocrinol. 2013;9:670–86.
33. Sauer J, Rupprecht M, Arzt E, Stalla GK, Rupprecht R. Glucocorticoids modulate soluble interleukin-2 receptor levels in vivo depending on the state of immune activation and the duration of glucocorticoid exposure. Immunopharmacology. 1993;25:269–76.
34. Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis. 2009;68:1119–24.
35. Kamper SJ, Ostelo RWJG, Knol DL, Maher CG, de Vet HCW, Hancock MJ. Global perceived effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. J Clin Epidemiol. 2010;63:760–766.e761.

**How to cite this article:** van den Berg C, Huygen FJPM, Tiemensma J. The efficacy of oral corticoids in treating complex regional pain syndrome: A retrospective cohort study. Pain Pract. 2023;00:1–10. https://doi.org/10.1111/papr.13310