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REVIEW ARTICLE

Glucocorticoid treatment in patients with complex regional pain syndrome: A systematic review

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Abstract

Background and objective: The pathophysiology of complex regional pain syndrome (CRPS) is multifactorial, with an exaggerated inflammatory response being the most prominent. Treatment for CRPS is carried out according to the presenting pathophysiological mechanism. Anti-inflammatory treatment with glucocorticoids is therefore an option. The aim of this study was to systematically review the efficacy of glucocorticoids in CRPS.

Databases and data treatment: Embase, Medline, Web of Science and Google Scholar were systematically searched for articles focusing on glucocorticoid treatment and CRPS. Screening based on title and abstract was followed by full-text reading (including reference lists) to determine the final set of relevant articles. Bias was assessed using the revised Cochrane risk-of-bias-tool for randomized trials (Rob2).

Results: Forty-one studies were included, which reported on 1208 CRPS patients. A wide variety of glucocorticoid administration strategies were applied, with oral being the most frequently chosen. Additionally, researchers found great heterogeneity in outcome parameters, including clinical symptoms, pain relief and range of motion. The use of glucocorticoids caused an improvement of parameters in all but two studies. In particular, improvement in pain relief and range of motion were reported. Using glucocorticoids in CRPS of longer duration (i.e. more than 3 months) appears to be less effective.

Conclusion: Based on the present review, there is evidence to support glucocorticoid treatment in CRPS. However, the ideal administration route and dose remain unclear. We therefore recommend future research via an intervention study, as well as studies on the aetiological mechanisms and corresponding optimal treatment because CRPS pathogenesis is only partially understood.

Significance: Several studies point towards CRPS being an inflammatory response after tissue or nerve damage, with higher levels of pro-inflammatory cytokines in serum, plasma, cerebrospinal fluid and artificial skin blisters. Inflammation provides a possible role for glucocorticoids in treating CRPS. This

systematic review provides a structured overview of glucocorticoid treatment in patients with CRPS. Improvement in pain and range of motion is shown. Systematic review registration number: PROSPERO-CRD42020144671.

1 | INTRODUCTION

Complex regional pain syndrome (CRPS) is a clinical disorder characterized by continuous, disproportionate pain and sensory, vasomotor, sudomotor and motor trophic changes (Bruehl, 2015). Diagnosis is based on signs and symptoms. Currently, the new International Association for the Study of Pain (IASP) clinical diagnostic criteria (i.e. the Budapest or Harden Bruehl criteria) are most frequently used (Harden et al., 2010). The pathophysiology of CRPS is multifactorial, including inflammation, peripheral and central sensitization, altered autonomic function, brain changes and immunological mechanisms, with an exaggerated inflammatory response as a major mechanism. Although the inflammatory response occurs especially in the acute phase, it is not limited to this phase. The existence of an inflammatory response is supported by increased concentrations of pro-inflammatory cytokines (IL1, IL6, IL8 and TNF-α) in serum; cerebrospinal fluid; artificial skin blister fluid (Alexander et al., 2005, 2012; Huygen et al., 2002; Schinkel et al., 2006); and reduced serum levels of anti-inflammatory cytokines (IL4, IL10 and transforming growth factor beta-1) (Bruehl, 2010; Parkitny et al., 2013). Additionally, 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 patients (Bharwani, Dirckx, Stronks, et al., 2017).

Multiple underlying pathophysiologic mechanisms, both peripheral and central, cause a heterogeneous clinical picture of CRPS patients. These mechanisms may differ across patients and within individual patients over time and are essential in treating CRPS. In general, each individual requires a combination of physical rehabilitation, physiotherapy and additional medication. Today, treatment is conducted according to the presenting pathophysiologic mechanism believed to be the most prominent in a specific CRPS case (Bharwani, Dirckx, & Huygen, 2017). Therefore, in cases of inflammation, treatment with glucocorticoids is a regularly chosen option.

In 2012, our research group conducted a review of immunomodulating medication in CRPS. We assessed the effects of glucocorticoids, tumour necrosis factor-α antagonists, thalidomide, bisphosphonates and immunoglobulins (Dirckx et al., 2012). Glucocorticoids (i.e. the most effective anti-inflammatory drug) may play a key role in CRPS treatment (Barnes, 2010; Rhen & Cidlowski, 2005). No known reviews focus specifically on glucocorticoids in CRPS treatment, which was the rationale for performing this systematic review of the efficacy of glucocorticoid treatment in CRPS patients.

2 | METHODS

The protocol for this systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO; identifier number: CRD42020144671). The study was conducted according to the PRISMA statement (Moher et al., 2009).

2.1 | Search strategy

To find relevant articles, a systematic search was conducted in Embase, Medline, Web of Science and Google Scholar from inception to 15 October 2019. On 19 September 2021, an additional search identified articles published between 15 October 2019 and 19 September 2021. Appendix S1 contains details on the search strategies for the databases and results.

2.2 | Study selection

We imported all search results into EndNote to ensure no articles were duplicated (Bramer et al., 2017). Studies had to comply with predefined inclusion and exclusion criteria. We sought original articles which met the following criteria: adult humans (≥18 years of age) with CRPS, treatment with glucocorticoids and available description of treatment effects. The types of studies included randomized controlled studies (RCTs), observational studies, case series and reports; we excluded literature reviews and animal studies and articles published in languages other than English. No geographical restrictions were applied. Two reviewers (i.e. PB and CB) independently screened the retrieved abstracts for eligibility. For each eligible abstract, they reviewed the full publication. Discrepancies between the reviewers were resolved by discussion until a consensus was reached. Additionally, we reviewed the identified articles' reference lists for additional studies that the search strategy potentially missed.

2.3 | Data extraction and quality assessment

The following items were recorded per study: study design, sample size, mean age of participants, CRPS criteria utilized, location and duration of CRPS symptoms, intervention details and outcome measurements. The reviewers (i.e. P.B. and C.B.) independently evaluated the potential risk of bias according to various bias assessment tools tailored to each study type. Three tools were chosen in advance: the Newcastle–Ottawa quality assessment Scale (NOS) for case–control and cohort studies (Wells et al., 2013), the Risk Of Bias In Non-randomized Studies (ROBINS-I) for non-randomized trials and the revised Cochrane risk-of-bias tool (RoB 2) for RCTs (Sterne et al., 2016; Sterne et al., 2019). We ultimately used ROB2 for the RCTs, as the other articles did not fit within the study designs assessed by NOS and ROBINS-1.

3 | RESULTS

3.1 | Included studies

The searches across the databases yielded 2.163 articles (see Figure 1). After screening titles and abstracts and assessing their eligibility based on their full text, 41 articles were included (11 case reports and case series, six retrospective studies, 15 prospective studies, one clinical audit and eight RCT's). The 41 included articles investigated a total of 1208 patients diagnosed with CRPS and treated with glucocorticoids. Regarding geographic location: 15 studies were conducted in nine European countries, seven in the United States, five in Canada, four in Korea, three in India, two in Turkey, and one each in Australia, Japan, and Argentina. Furthermore, two studies were multicentre studies with two countries involved. Outcomes were extracted for all included studies. Table 1 presents detailed study characteristics grouped by the various routes of glucocorticoid treatment.

3.2 | Diagnostic criteria

The included studies used various diagnostic CRPS criteria (see Table 2). Only nine of 41 included articles (Barbalinardo et al., 2016; Eun Young et al., 2016; Jamroz et al., 2020; Kim et al., 2016; Kumowski et al., 2019; Lee et al., 2012; Park et al., 2020; Vas & Pai, 2012; Winston, 2016) utilized the new IASP clinical diagnostic criteria which are also called the Budapest or Harden Bruehl criteria. More than half of the articles ($n = 21$) did not describe the criteria set. It was not possible to confirm whether the patients in these articles met one or more of the CRPS criteria sets. However, these patients were diagnosed by the authors as having reflex sympathetic dystrophy, algodystrophy or CRPS (Christensen et al., 1982; Dirksen et al., 1987; Duncan et al., 1988; Dwyer, 1952; Glick, 1973; Glick & Helal, 1976; Grundberg, 1996; Kalita et al., 2006, 2016; Kinov, 2001; Klein & Klein, 1991; Poplawski et al., 1983; Russek et al., 1953; Steinbrocker et al., 1953; Sussman, 1952; Tountas & Noguchi, 1991; Varitimidis et al., 2011; Zanotti et al., 2017; Zych-Litwin & Litwin, 2019; Zyluk, 1998; Zyluk & Puchalski, 2008).

3.3 | CRPS manifestations

Table 3 summarizes the study characteristics of all included studies. More than half of the articles (i.e. 28 of 41) included only CRPS patients with affected upper extremities (Ali Taskaynatan et al., 2004; Atalay et al., 2014; Braus et al., 1994; Christensen et al., 1982; Dirksen et al., 1987; Duncan et al., 1988; Dwyer, 1952; Eun Young et al., 2016; Grundberg, 1996; Kalita et al., 2006, 2016; Kim et al., 2016; Kinov, 2001; Kumowski et al., 2019; Lee et al., 2012; Lukovic et al., 2006; Mowat, 1974; Park et al., 2020; Rosen & Graham, 1957; Russek et al., 1953; Sigler & Ensign, 1951; Steinbrocker et al., 1953; Sussman, 1952; Varitimidis et al., 2011; Vas & Pai, 2012; Winston, 2016; Zyluk, 1998; Zyluk & Puchalski, 2008). Eleven included patients with both upper and lower extremities affected (Barbalinardo et al., 2016; Bianchi et al., 2006; Glick, 1973; Glick & Helal, 1976; Jamroz et al., 2020; Kozin et al., 1976, 1981; Munts et al., 2010; Okada et al., 2002; Poplawski et al., 1983; Tountas & Noguchi, 1991) and only two articles were limited to the lower extremities (Zanotti et al., 2017; Zych-Litwin & Litwin, 2019).

Regarding the initiating event, the majority of included studies reported CRPS after trauma or surgery. Additionally, eight articles included patients diagnosed with CRPS after myocardial infarction, following stroke, or after traumatic brain injury (Braus et al., 1994; Eun Young et al., 2016; Kalita et al., 2016, 2006; Kim et al., 2016; Park et al., 2020; Russek et al., 1953; Sussman, 1952). The duration of CRPS symptoms from diagnosis to start of treatment was variable, with the shortest duration being 7 days and the longest being 4 years. However, CRPS duration was less than 1 year in 22 articles (i.e. so-called 'acute CRPS'). Seven articles included patients with a duration longer than 1 year (chronic CRPS), and the duration was unknown in 12 articles.

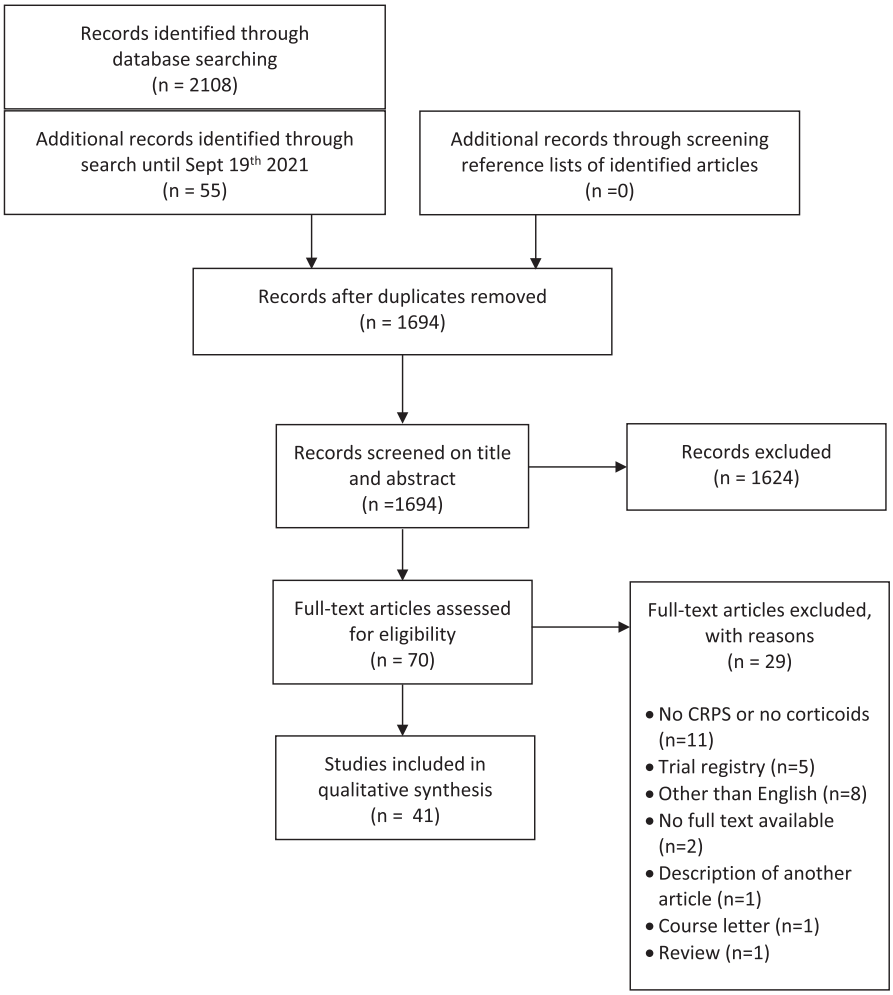

FIGURE 1 Flowchart showing the process of article selection

3.4 | Dose and drug administration

Table 3 presents the various routes of glucocorticoid treatment used. Oral was mainly applied, as well as intravenous (IV), intramuscular, regional block, local application and more invasive intrathecal. We describe the results of included studies based on administration route (see Table 1).

3.5 | Oral administration

Twenty-two studies used oral glucocorticoids. A variable duration of oral therapy was used with the shortest duration being 3 days (Kumowski et al., 2019) and the longest of 9–12 months (Mowat, 1974). Nonetheless, most studies treated patients for 2–4 weeks. Four older studies from the 1950s used oral cortisone, occasionally in combination with adrenocorticotropic hormone (ACTH). At least 1 g cortisone was administered in these studies, and the duration of therapy was 10–18 days. All studies described pain relief and improvement of range of motion (Dwyer, 1952; Rosen & Graham, 1957; Sigler & Ensign, 1951; Sussman, 1952). The other 18 studies used oral prednisone or equivalents with a daily dose range between 5 and 80 mg. One study used a low-dose prednisone (<7.5 mg/day), six studies used a moderate dose (between 7.5 and 40 mg/day) and 11 studies used high doses (>40 mg/day). Using low-dose prednisone causes improvement in pain level (i.e. on the visual analogue scale [VAS]) and signs of inflammation, but there were no significant differences between daily 5 mg prednisone and placebo (Lukovic et al., 2006). When using moderate prednisone doses, clinical improvement was evident, although not in all patients (Atalay et al., 2014; Glick, 1973; Okada et al., 2002; Park et al., 2020). However, comparing the moderate dose with placebo resulted in a significant improvement in signs and symptoms (Christensen et al., 1982) and shoulder-hand syndrome score (Braus et al., 1994). A high dose of oral prednisone showed improvement in pain relief, all signs and symptoms and CRPS score. For pain control, IV bisphosphonates were as effective as oral prednisone, but prednisone proved better for hand swelling (Eun Young et al., 2016). A significantly greater improvement in signs and symptoms of CRPS was shown among patients receiving glucocorticoids compared to those receiving Piroxicam (Kalita et al., 2006).

Three studies compared different dose regimens. Statistically significant differences in both severity score and Kozin's classification regardless of steroid dose were found when comparing a total dose of 450 mg prednisone with a total dose of 200 mg for 14 days (Park et al., 2020). Contrary to this effectiveness, a limited efficacy was shown in treating CRPS of more than 3 months, even with higher doses prednisone (i.e. 1 g in 16–22 days; Barbalinardo et al., 2016). When continuing with 10 mg of prednisone for 2 months, after 2 weeks with a tapered prednisone dose, no recurrence of CRPS occurred. Fifty percent of the patients in whom the prednisone was stopped after the 2-week period showed recurrence of symptoms (Kalita et al., 2016). Continuation of low-dose prednisone thus seems to be safe and effective.

Two studies using oral prednisone reported other outcome measures in addition to clinical symptoms (Kumowski et al., 2019; Park et al., 2020). One study investigated perfusion parameters before and after glucocorticoid treatment in addition to clinical symptoms. Twelve patients with CRPS duration of more than 1 year showed decreased blood flow and increased oxygen extraction fraction (OEF) after 3 cycles of remote ischaemic conditioning (RIC). In all patients, glucocorticoid pulse treatment with a total prednisone dosage between 180 and 360 mg led to significant changes in the microcirculatory response. Neither the blood flow was decreased nor was the OEF increased after RIC (Kumowski et al., 2019). Another study compared the treatment effects of high- and low-dose oral prednisone on changes in observed radioisotope uptake ratio (RUR) observed from three-phase bone scintigraphy. While the average ratio decreased in both groups when comparing the RUR before and after treatment, the difference was not significant when using high and low steroid doses (Park et al., 2020).

3.6 | Systemic infusion

In one study, IV treatment with 10% mannitol and 8 mg dexamethasone was applied daily for 1 week (Zyluk & Puchalski, 2008). Pain, CRPS score and finger flexion improved significantly.

3.7 | Regional intravenous blocks

Six studies used regional IV blocks (i.e. bier blocks). The dose administered varied between 80–125 mg methylprednisolone per block. Additionally, the number of given blocks was variable, with a range from 1 to 6 blocks per patient. One study gave 1–5 bier blocks per patient, repeated at 48–72 h intervals (Duncan et al., 1988), whereas another study used three sessions of bier blocks over a 2-day interval (Zyluk, 1998), and another study showed 3–6 sessions of IV regional blocks were needed (Varitimidis et al., 2011). All studies showed improvement in pain after treatment despite the variable regimens. Comparing methylprednisolone bier block with the placebo showed a significant improvement in pain severity before and after treatment in both groups. No long-term benefit in CRPS was provided (Ali Taskaynatan et al., 2004).

3.8 | Intramuscular administration

Using intramuscular 80 mg depomedrol injections in CRPS patients resulted in an improvement in both pain and swelling. Each patient received an average of 2.3 injections with a maximum of four injections (Grundberg, 1996). Moreover, a case report combining intramuscular tenoxicam with betamethasone periarthricular described a positive effect (Kinov, 2001).

3.9 | Epidural or intrathecal administration

A case report described a women with CRPS after surgery who showed improved functioning, reduced trophic changes and pain relief after receiving a cervical epidural methylprednisolone injection weekly for 4 weeks (Dirksen et al., 1987). Munts et al. (2010) studied patients with long-standing CRPS with a mean duration of 4.5 years (SD 2.2). This RCT comparing intrathecal corticosteroids and placebo was stopped prematurely due to a lack of effect on pain after the interim analysis.

3.10 | Local administration

A 40 mg triamcinolone injection at the tendon sheath of the extensor digitorum communis caused an improvement in the pain and swelling of the affected wrist (Kim et al., 2016).

3.11 | Cutaneous application

A case report described that local application of dexamethasone spray in combination with oral meloxicam effective and ensures that all clinical symptoms disappeared within a few weeks (Zych-Litwin & Litwin, 2019).

TABLE 1 Characteristics of included studies

First author, year, and country	Type	No. Patients	Mean age (range)	CRPS criteria	Initiating event	Location of CRPS
Oral administration						
Sigler and Ensign (1951), USA	CS	7 ♀ 4 ♂ 3	61 (54–71)	Shoulder hand syndrome by Steinbrocker	Various (trauma, myocardial infarction, cervical osteoarthritis)	Upper extremity
Dwyer (1952), Australia	CS	♀ 2	52 and 65	Unknown	Trauma	Upper extremity
Sussman (1952), USA	CR	♀ 1	71	Unknown	Myocardial infarction	Upper extremity
Rosen and Graham (1957), Canada	PS	73 Sex unknown	63 (31–80)	Shoulder hand syndrome by Steinbrocker	Various (trauma, myocardial infarction, lesion of central nervous system)	Upper extremity
Glick (1973), UK	PS	17 ♀ 11 ♂ 6	43 (17–63)	Unknown	Trauma or surgery	Upper (16) and lower extremity (1)
Kozin et al. (1976), USA	PS	11 ♀ 7 ♂ 4	56 (36–69)	Criteria for reflex sympathetic dystrophy syndrome	Various (trauma, cervical osteoarthritis, myocardial infarction, carcinoma, and unknown)	Upper (10) and lower extremity (2); one case with both)
Christensen et al., 1982, Denmark	RCT	23 ♀ 20 ♂ 3	66 (56–83)	Unknown	Trauma	Upper extremity
Braus et al. (1994), Germany	RCT	36 Sex unknown	Unknown	Shoulder hand syndrome by Steinbrocker and classification criteria by Kozin	Stroke	Upper extremity
Okada et al. (2002), Japan	CR	♀ 1	84	Criteria by Gibbons and Wilson	Surgery	Upper and lower extremity

Duration of CRPS (mean)	Medication, dose, and route	Primary outcome measure	Outcome	Side effects
7 d–10 mo	ACTH average 1020 mg (345–2320 mg) and additional cortisone 1175 mg in one case Duration of therapy: 10–99 days (average 30.1 days)	Clinical improvement (pain relief and range of motion)	Pain relief and re-establishment of satisfactory range of motion	No information
3 and 6 months	1 g cortisone given in 10–18 days, combined with 60–120 units ACTH in 2–7 days	Clinical effect (pain relief and range of motion)	Pain relief and improvement in movement	No side effects
4–18 weeks ($\bar{x}$: 6.9 weeks)	Oral cortisone 100 mg/day for 10 days and then gradually reduced dose	Clinical improvement	Pain subsided sufficiently, swelling subsided considerably, hand and shoulder mobility increased	Hyperglycaemia
24 h–4 years	Cortisone (100–200 mg/day for 14 days) or ACTH (dose unknown) in addition to routine physical measures ($n = 15$)	Pain relief and range of motion	Pain relief and improvement of movement within ≥80% of normal ($n = 10$)	No information
Unknown	Prednisolone 15–40 mg/day (14–70 weeks)	Clinical improvement; no improvement, poor, good, very good, excellent	15 derived any benefit, three showed no benefit	Dyspepsia, weight gain, and moon face
4–60 weeks	Prednisone 60–80 mg/day for 2 weeks and tapered to 5–10 mg every other day for a maximum of 14 weeks	Measurement of shoulder range of motion, swelling (ring size), tenderness (dolorimeter), and functional capacity (grip strength)	Improvement in all measurements on affected side in all but one patient; significant improvement in swelling and tenderness	No information
50–194 d ($\bar{x}$: 92 d)	Oral prednisone 3 days 10 mg. Medication continued until clinical remission was obtained, maximally 12 weeks ($n = 13$) Placebo ($n = 10$)	Activity of RDS (pain, oedema, volar sweating, and finger-knitting ability) and resting blood flow	Prednisone: all patients showed >75% improvement Placebo: only two reported improvement	No information
Unknown	Oral methylprednisolone 32 mg/day for 14 days before being tapered in 14-day period Placebo for 4 weeks and if no visible improvement, the same methylprednisolone regimen was applied	Shoulder-hand syndrome score	31 of 34 patients treated with methylprednisolone became and remained symptom free during hospital stay and for up to 6 months after discharge. Placebo without clinical improvement	Sleeping problems, hyperglycaemia, slight hypertension, and reversible steroid acne
3 months	Oral methylprednisolone 16 mg/day and neurotropin 12 U/day. Dose methylprednisolone gradually tapered until no longer needed by 2 months	Clinical symptoms	Clinical symptoms improved	No information

(Continues)

TABLE 1 (Continued)

First author, year, and country	Type	No. Patients	Mean age (range)	CRPS criteria	Initiating event	Location of CRPS
Bianchi et al. (2006), Italy	PS	31 ♀ 24 ♂ 7	58 (20–81)	Classification criteria by Kozin	Trauma	Upper (25) and lower extremity (6)
Kalita et al. (2006), India	RCT	60 ♀ 20 ♂ 40	56 (40–70)	Unknown	Stroke	Upper extremity
Lukovic et al. (2006), Former Serbia and'Montenegro	RCT	60 ♀ 45 ♂ 15	47 (34–62)	Unknown	Trauma	Upper extremity
Atalay et al. (2014), Turkey	RS	45 ♀ 25 ♂ 20	44 (22–67)	Former IASP criteria	Trauma	Upper extremity
Barbalinardo et al. (2016), The Netherlands and UK	CA	31 ♀ 18 ♂ 13	47 (19–70)	Budapest criteria	Trauma, surgery, and spontaneous	Upper (18) and lower extremities (13)

Duration of CRPS (mean)	Medication, dose, and route	Primary outcome measure	Outcome	Side effects
10–204 days	Prednisone: 4 days maximum dose 40–60 mg/day, tapered by 10 mg/day. Daily dose of 10 mg for 3 days and 5 mg for 2 days (Length of treatment 17–25 days)	VAS and clinical severity of CRPS (0–22)	Significant reduction in VAS levels, significant improvement in score of clinical severity of CRPS; 1-year follow-up showed the outcome for all clinical variables persisted	No side effects
Unknown	Prednisolone 40 mg/day for 14 days tapered by 10 mg/week versus Piroxicam 20 mg/day	CRPS score (scoring the sensory, autonomic and motor symptoms on a 0–14 scale). Improvement significant if the score was reduced by ≥2. Improvement in activity of daily living by Barthel index (BI)	Improvement in symptoms and signs observed in 25 (83.8%) patients in prednisolone group and in five (16.7%) patients in Piroxicam group Both drugs improve the activity of daily living as assessed by BI score	Gastritis and upper respiratory tract infection
Unknown	Oral prednisone 5 mg/day versus placebo, both in combination with physical procedures; interference currents with 60–100 Hz, magnetic therapy, and physical treatment	VAS and changes in swelling, functional improvement, skin colour, and reduction in overall treatment duration	Improvement in VAS, local swelling, skin colour, and functional status. No significant differences between groups	No information
Unknown	Oral prednisolone, starting at 30 mg and tapered by 5 mg every 3 days until discontinuation after 3 weeks	Clinical symptoms, pain severity (VAS, measured in rest and activity), grip strength, functional assessment Quick-Disabilities of the Arm, Shoulder and Hand (Q-DASH) score; quality of life with Short Form-36 (SF-36)	Significant improvements in clinical symptoms and functional assessment; VAS scores, grip strength, Q-DASH scores and SF-36 sub scores improved significantly	No side effects
4–317 mo ($\bar{x}$: 15 mo)	Oral prednisolone in both centres: *UK*: 100 mg daily tapered by 25 mg every 4 days to 0 (total 1 g in 16 days) *NL*: 60 mg daily for 2 weeks lowered 20 mg every 4 days to 0 (total 1.08 g in 22 d)	Pain rating *UK*: completed daily brief pain inventory *NL*: 3/d NRS scale	In maximally four (13%) patients, an important analgesic effect was observed. Low efficacy of oral steroids in the treatment of CRPS with >3 months pain duration was found	Euphoria, psychological 'high', malaise, depression, 'violently sick', stomach-ache, and fatigue

(Continues)

TABLE 1 (Continued)

First author, year, and country	Type	No. Patients	Mean age (range)	CRPS criteria	Initiating event	Location of CRPS
Eun Young et al. (2016), Korea	RCT	21 ♀ 10 ♂ 11	65 (44–77)	Budapest criteria	Stroke	Upper extremity
Kalita et al. (2016), India	RCT	52 ♀ 23 ♂ 29 Only CRPS score ≥8 included	55 (35–85)	Unknown	Stroke	Upper extremity
Winston (2016), Canada	CS	3 ♀ 2 ♂ 1	50, 50, and 78	Budapest criteria	Trauma	Upper extremity
Zanotti et al. (2017), Argentinia	CS	♂:3	25, 26, and 28	Unknown	Total hip replacement	Lower extremity
Kumowski et al. (2019), Germany	PS	12 ♀ 5 ♂ 7	48 (38–57)	Budapest criteria	Trauma or surgery	Upper extremity
Park et al. (2020), Korea	RS	34 ♀ 20 ♂ 14	63 (58–69)	Budapest criteria	Traumatic brain injury or stroke	Upper extremity

Duration of CRPS (mean)	Medication, dose, and route	Primary outcome measure	Outcome	Side effects
Unknown	Oral prednisolone 1 mg/kg body weight, dose was tapered over 2 week ($n = 10$) IV bisphosphonate (Pamidronate), total 180 mg delivered via 3 infusions every other day ($n = 11$)	Pain (VAS) and hand oedema (circumference of the middle finger and wrist)	Pamidronate was as effective as a steroid for pain control, but less effective than a steroid for hand swelling	No steroid-induced side effects
Unknown	*Pre-randomization* ($n = 58$) Oral prednisolone 40 mg/day for 14 days tapered to 10 mg by 30 days Non-responders excluded *Randomization* ($n = 52$) 1: Prednisolone 10 mg/day for 2 months 2: treatment stopped if recurrence of CRPS after 1 month: crossover and prednisolone 10 mg/day for 1 month ($n = 13$)	CRPS severity scale (0–14), Visual Analogue Scale (VAS), modified Rankin Scale (mRS), and BI scores	Improvement in CRPS score and VAS scores at all time points. The mRS and BI scores improved at the end of the standard treatment. Continuation of 10 mg prednisolone for a further 2 months resulted in no recurrence of CRPS-1, whereas 50% had a recurrence in the group in which prednisolone was stopped	Hyperglycaemia, weight gain, and gastrointestinal symptoms
Unknown	Oral prednisone 60 mg, taper of 5 mg/day until 20 mg Dose was weaned as symptoms subsided, treatment <1 month in all cases	Clinical symptoms	Resolution of pain, swelling, and disability in all three patients	No information
1–2 mo	All cases received 80 mg 1–2 dehydrocortisol once daily for 7 days. One case also received a sympathetic block using 8 mg dexamethasone and bupivacaine	Clinical symptoms, VAS, and modified Harris Hip Score (mHHS)	Symptoms decreased progressively until disappearing in 8–9 months and complete pain relief. Long-term follow-up (3–6 years) showed mHHS 88–95, meaning good to excellent results after total hip replacement	No information
3–47 weeks ($\bar{x}$: 25 wk)	Corticoid pulse treatment with oral prednisolone: 3 days: 90, 60, 30 mg ($n = 5$) 6 days: 90, 90, 60, 60, 30, 30 mg ($n = 7$)	Perfusion parameters induced by RIC: blood flow, O_2-saturation, and OEF	All parameters were significantly different from pre-treatment values. The correlation of the blood flow differences and OEF disappeared after treatment	No information
Unknown	High dose oral prednisolone for 14 days, total dose: 450 mg ($n = 14$) versus low dose oral prednisolone for 14 days, total dose: 200 mg ($n = 20$)	Severity scores, Kozin's classification scores and RUR observed from three-phase bone scintigraphy prior to treatment and within 5 days of treatment	Difference in RUR was not significant, but patient's severity score and Kozin's classification score were statistically significant regardless of steroid dose	Stomach-ache

(Continues)

TABLE 1 (Continued)

First author, year, and country	Type	No. Patients	Mean age (range)	CRPS criteria	Initiating event	Location of CRPS
Jamroz et al. (2020), Canada	RS	39 ♀ 26 ♂ 13	52 (11–85)	Budapest criteria	Trauma, surgery or idiopathic	Upper (29) and lower (10) extremity
Systemic infusion						
Zyluk and Puchalski (2008), Poland	PS	75 ♀ 68 ♂ 7	58 (38–82)	Unknown	Trauma or surgery	Upper extremity
Regional intravenous blocks						
Poplawski et al. (1983), Canada	PS	27 ♀ 14 ♂ 13	Mean unknown (31–81)	Unknown	Trauma	Upper (20) and lower extremity (7) Bilateral: 1
Duncan et al. (1988), USA	RS	20 ♀ 13 ♂ 7	55 (31–81)	Unknown	Trauma	Upper extremity
Tountas and Noguchi (1991), Canada	RS	17 ♀ 13 ♂ 4	55 (44–70)	Unknown	Trauma or surgery	Upper (12) and lower extremity (5)

Duration of CRPS (mean)	Medication, dose, and route	Primary outcome measure	Outcome	Side effects
$\bar{x}$: 81 d ± 67.7 d	Oral prednisone started with 60 mg followed by tapering to 20 mg/day; then 15 mg for 1 week, 10 mg for 1 week and 5 mg for 1 week	Signs and symptoms. Pain stratified into no longer present, decreased pain, or'not improved. Range of motion stratified into fully restored, functionally restored, or not restored	All symptoms and signs decreased significantly. Complete pain resolution reported in 48.7% of patients, another 19 patients reported decreased pain and one patient showed no improvement in pain. Over 90% of patients reported functional improvement in range of motion	In 71.8%, no side effects. Sleeping disorder, anxiety, headache, weight gain, nausea, vomiting, hyperglycaemia, hypertension, and osteopenia
<4 mo	IV treatment with 10% mannitol 2× 250 ml and dexamethasone 8 mg/day for 1 week	Severity of pain (VAS), loss of finger flexion, grip strength, and CRPS score	Decrease in mean VAS score, mean loss of finger flexion, and mean CRPS score; all were statistically significant ($p < 0.05$)	No side effects
2–36 mo	Regional IV block utilizing a mixture of lidocaine and methylprednisolone 2–5 blocks per patient	Results of treatment were graded excellent (little to no pain or swelling and full ROM), very good, good, fair, or poor (little or no response to treatment)	21 of 28 extremities (17 hands and 4 feet) improved significantly following treatment	Tinnitus, dizziness, low-grade superficial infection, superficial thrombophlebitis
Unknown	Bier block composed of lidocaine, 80–120 mg methylprednisone and reserpine or guanethidine Blocks were repeated at 48–72h intervals. 1–5 blocks per patient, average 2.3	Range of motion and improvement in pain	Patients noted a 50%–100% improvement in pain, mean pain reduction of 79.5%. Range of motion improved from a pre-block mean of 46% to 81% normal following the blocks	Hypotensive episode in patient receiving antihypertensive drugs
2–6 mo	Regional IV block 80 mg Solumedrol in combination with xylocaine without epinephrine 1–4 blocks per patient, average 2.4	Clinical symptoms graded as excellent (little or no pain, swelling or stiffness), good, fair, or poor (symptoms were unaltered or worse)	Overall late results: excellent in nine, good in two and fair in four patients	No information

TABLE 1 (Continued)

First author, year, and country	Type	No. Patients	Mean age (range)	CRPS criteria	Initiating event	Location of CRPS
Zyluk (1998), Poland	PS	36 ♀ 23 ♂ 13	54 (44–73)	Unknown	Trauma or surgery	Upper extremity
Ali Taskaynatan et al. (2004), Turkey	RCT	♂ 22	22 (20–25)	Former IASP criteria	Trauma	Upper extremity
Varitimidis et al. (2011), Greece	PS	168 ♀ 91 ♂ 77	53 (19–78)	Unknown	Trauma or surgery	Upper extremity
Intramuscular administration						
Grundberg (1996), USA	PS	47 ♀ 31 ♂ 16	54	Unknown	Trauma or surgery	Upper extremity
Kinov (2001), Bulgaria	CR	♀ 1	51	Unknown	Trauma	Upper extremity
Epidural or intrathecal administration						
Dirksen et al. (1987), The Netherlands	CR	♀ 1	50	Unknown	Surgery	Upper extremity

Duration of CRPS (mean)	Medication, dose, and route	Primary outcome measure	Outcome	Side effects
1–8 mo	Regional IV blocks 80 mg methylprednisolone in combination with lidocaine and heparin. 3 blocks in 2-day interval	Overall results at 12 mo graded as good (relief of spontaneous pain, no limitation in finger movement), moderate, or poor (symptoms unaltered or worse)	Late results described good treatment response in 25 patients (69%), in eight as moderate (22%) and in three (9%) as poor	Superficial thrombophlebitis
3.1 mo	Bier block once a week, 3 sessions • Study group: 40 mg methylprednisolone and lidocaine • Placebo group: saline	Pain severity, range of motion, oedema measured with a volumeter, and satisfaction	Significant improvement in pain severity before and after treatment in both groups; no long-term benefits were provided	Nausea, dizziness, tinnitus, flushing, and pruritus
2–6 weeks	Regional IV blocks 125 mg methylprednisolone and lidocaine; 1–2 blocks a week, 3–6 sessions per patient, average 4.8	Severity of pain (VAS), signs and symptoms, and a score based on criteria by Zyluk (2003)	148 (88%) patients reported minimal or no pain (0–2) at end of their treatment At final follow-up, 134 (92%) patients reported no pain'	No side effects
8–36 wk ($\bar{x}$: 15 wk)	Intramuscular Depo-medrol 80 mg injection. Max. 4 injections at 2-wk interval, average: 2.3	Pain, swelling, grip strength, pinch strength, and PIP motion	All patients were relieved of night and rest pain; motion in PIP joint and swelling improved in all	Mild depression fluid retention, insomnia, hypomania, hyperglycaemia
5 mo	Intramuscular tenoxicam combined with three betamethasone periarticular applications to the shoulder every 3 days	Clinical symptoms	Marked improvement at day 12 with no pain at rest and slight tenderness during passive and active movements.' On the third month of discharge patient was asymptomatic and range of motion was within normal limits except shoulder abduction	No information
1 mo	Cervical epidural injection with 60 mg methylprednisone, once a week for 4 weeks	Clinical signs	Improved functioning, pain relief, increase in hand temperature, and reduced muscular contracture and trophic changes	Spontaneous contractions neck muscles

(Continues)

TABLE 1 (Continued)

First author, year, and country	Type	No. Patients	Mean age (range)	CRPS criteria	Initiating event	Location of CRPS
Munts et al. (2010), The Netherlands	RCT	21 ♀ 16 ♂ 5	46 (35–57)	Former IASP criteria	Trauma and surgery	Upper and lower extremity 12 patients had ≥2 affected extremities
Local administration						
Kim et al. (2016), Korea	PS	23 ♀ 11 ♂ 12	64	Budapest criteria	Stroke	Upper extremity
Cutaneous application						
Zych-Litwin and Litwin (2019), Poland	CR	♂ 1	67	Unknown	Trauma	Lower extremity
Combined types of administration						
Russek et al. (1953), USA	PS	17 ♂ 3 (Sex unknown for 14)	56 (48–62)	Unknown	Myocardial infarction	Upper extremity
Steinbrocker et al. (1953), USA and Canada	PS	27 Sex unknown	Unknown	Unknown	No information	Upper extremity

Duration of CRPS (mean)	Medication, dose, and route	Primary outcome measure	Outcome	Side effects
x̄: 4,5 y sd: 2.2	Single 60 mg methylprednisolone bolus intrathecal ($n = 10$) versus placebo, 1.5 ml sodium chloride 0.9% ($n = 11$)	Pain: NRS and McGill pain questionnaire Movement: Burke-Fahn-Marsden dystonia rating scale, unified myoclonus rating scale, tremor research group rating scale CRPS signs and symptoms	The interim analysis showed no effect on pain, therefore the study ended prematurely	Only post lumbar puncture side effects mentioned (postdural puncture headache and backache)
90 d (26–536 days)	Injection of 40 mg triamcinolone at tendon sheath of extensor digitorum communis (EDC)	Range of motion, manual muscle test, pain (VAS) and cross-sectional area (CSA) of both (EDC) tendon sheaths. 13 patients were not able to answer properly due to aphasia or severe neglect	After steroid injection, significant decrease in CSA and swelling of the affected wrist and VAS score declined significantly	No side effects
12 days	Local application of dexamethasone spray, 0.28 mg/g for 10 days and oral meloxicam 15 mg/day for 20 days	Clinical symptoms	Within a week, all symptoms disappeared except oedema, which resolved after the next 4 weeks	No information
3–20 weeks (x̄: 6.5 wk)	Oral or intramuscular cortisone; starting dose 200–300 mg first 2 days. Following this, reduced to 50 mg daily through the third week	Clinical improvement	Five cases experienced complete relief of signs and symptoms, eight marked improvement, three moderate improvement, and one had no response.	No side effects
Unknown	Corticotropin, cortisone, or both ($n = 13$). versus Stellate ganglion block ($n = 14$)	Clinical features (i.e. pain, signs, and symptoms) graded as complete recovery, greatly improved, slightly improved, or no improvement	Stellate blocks gave somewhat better results. In the cortisone/corticotropin group all symptoms and signs were abolished in four, great improvement in four, and one patient failed to respond	Sudden occlusion of arteries below femoral in both legs and manic psychosis

TABLE 1 (Continued)

First author, year, and country	Type	No. Patients	Mean age (range)	CRPS criteria	Initiating event	Location of CRPS
Mowat (1974), UK	CS	3 ♀ 2 ♂ 1	56 (51–65)	Shoulder hand syndrome by Steinbrocker	Trauma, cerebrovascular accident, and spontaneous	Upper extremity
Glick and Helal (1976), UK	PS	21 Sex only known for 7 cases: ♀ 5 ♂ 2	Only known for 7 cases: 48 (25–67)	Unknown	Trauma	Only known for 7 cases: upper (5) and lower extremity (2)
Kozin et al. (1981), USA	PS	55 Sex only known for whole study population ($n = 64$, ♀ 36, ♂ 18)	48.3	Criteria for reflex sympathetic dystrophy syndrome	Various (trauma, peripheral nerve injury, myocardial infarct, cerebral disease or hemiplegia, idiopathic, and spinal cord injury)	Upper (46) and lower extremity (18)
Lee et al. (2012), Korea	RS	59 ♀ 38 ♂ 21	48 (21–78)	Budapest criteria	Trauma or surgery	Upper extremity

Duration of CRPS (mean)	Medication, dose, and route	Primary outcome measure	Outcome	Side effects
2–7 months	Soluble prednisolone 60 mg for 4 days, reintroduce 10 mg/day after 4 days. Over the following 9–12 months the prednisolone dose was steadily reduced and stopped. In one case, also injection of hydrocortisone in subacromial bursa	Hand volume (measured in beaker of warm water), grip strength, movement restrictions	Beneficial effects in all patients: reduction in hand volume and improvement in all other symptoms and signs	No information
Unknown	Oral prednisolone 15–40 mg/day for 3–4 months (18) Intramuscular methylprednisolone (2) Adrenocorticotropic hormone (A.C.T.H) (1)	Relief of pain and improvement of movement and power graded as very good, good, fair, or poor	Relief of pain and > 50% of improvement of function in 10 cases; reduction of pain and 20% improvement in three cases; five cases showed relief of pain without improvement; and three cases showed no significant change'	No information
8–143 weeks ($\bar{x}$: 75.9 weeks)	Stellate ganglion blockade ($n = 20$) Oral corticosteroid (varying dosages for 3–4 weeks starting with higher dosages and gradually decreasing dose; $n = 35$)	Subjective estimate of patient's pain response graded as excellent (>75% relief), good (50%–75%), fair (25%–50%), or poor (<25%). Objective measurement of grip strength, tenderness, and ring size	Stellate blockade: 0% good, 85% poor, and 15% fair response Corticosteroids: 63% good to excellent response; objective improvement was present in all but one patient who received corticosteroids	No information
1–149 d ($\bar{x}$: 91 d)'	Four treatment modalities A: oral diclofenac for 1 month ($n = 10$) B: oral gabapentin for 1 month ($n = 12$) C: IV 10% mannitol and 7 mg dexamethasone, once daily for 7 days ($n = 11$) D: IV 20% mannitol and 7 mg dexamethasone, once daily for 7 days in combination with gabapentin for 1 month ($n = 26$)	Pain levels (VAS), finger joint range of motion, grip strength, pinching, swelling, sweating, and skin colour	Combination D (mannitol, dexamethasone, and gabapentin) led to improvement in pain level, finger ROM, swelling, and grip strength	No side effects

(Continues)

TABLE 1 (Continued)

First author, year, and country	Type	No. Patients	Mean age (range)	CRPS criteria	Initiating event	Location of CRPS
Vas and Pai (2012), India	CS	5 ♀ 1 ♂ 3 (Sex unknown for one patient)	51, 52, 60, and 72 (Age unknown for one patient)	Budapest criteria	Trauma	Upper extremity, all bilateral

Abbreviations: CA, Clinical audit; x̄, mean; CR, Case report; CS, Case series; d, days; IV, intravenous; mo, months; PS, prospective study; RCT, randomized controlled trial; RS, retrospective study; wk, weeks; y, year.

TABLE 2 Criteria sets used to diagnose CRPS

	No. of studies (% of total)
Used CRPS criteria set[a]	
No. criteria sets described	21 (51)
Criteria for RSD	2 (5)
Shoulder hand syndrome by Steinbrocker[a]	4 (10)
Classification criteria by Kozin[a]	2 (5)
Criteria by Gibbons and Wilson	1 (2.5)
Former IASP criteria	3 (7.5)
Budapest criteria	9 (22)

Abbreviations: IASP, International Association for the Study of Pain; RSD, reflex sympathetic dystrophy syndrome.

[a]Because one study used two criteria sets (shoulder hand syndrome by Steinbrocker and classification criteria by Kozin), the percentage of studies does not sum to 100.

3.12 | Combined types of administration

Six studies combined or compared various types of glucocorticoid administration. Two studies compared oral corticosteroids with stellate ganglion blocks. Steinbrocker showed the stellate ganglion block to provide better results compared to oral corticoids, whereas Kozin et al. showed the opposite (Kozin et al., 1981; Steinbrocker et al., 1953). Two studies applied oral or intramuscular glucocorticoids. Russek described complete or marked improvement in 13 patients and moderate clinical improvement in three. However, one patient did not respond to the treatment (Russek et al., 1953). Moreover, a study comparing oral prednisone, intramuscular methylprednisolone and ACTH described eight patients with poor or fair treatment effect. In this study, 'fair' signified pain relief which still required analgesics and no improvement in movement or power (Glick & Helal, 1976). Furthermore, two studies studied different treatment modalities or combinations. A retrospective study conveyed advantages for IV 20% mannitol and steroid in combination with oral gabapentin in patients with CRPS 1 of the upper extremity in comparison to three other treatment options; diclofenac, gabapentin and IV 10% mannitol in combination with steroid. Pain level (VAS), finger range of motion, swelling and grip strength improved (Lee et al., 2012). Additionally, five cases described a complete resolution of CRPS using a multimodality treatment regimen. This treatment included amitriptyline, pregabalin, tramadol, continuous brachial plexus blockade for 4–5 weeks for the most affected side, stellate ganglion block with triamcinolone for the less affected side, dry needling and physiotherapy. These five patients suffered from bilateral CRPS (Vas & Pai, 2012).

Assessing all included studies, regardless of administration type, all except two studies described clinical improvement on various parameters. There was pain relief, as well as improvement in both range of motion and clinical symptoms of inflammation (e.g. swelling and skin temperature). However, when treating CRPS for a duration of more than 3 months, the efficacy of oral prednisone was found to be limited (Barbalinardo et al., 2016).

3.13 | Side effects

Glucocorticoid treatment is often associated with various side effects. However, these side effects are both dose and time-dependent (Ericson-Neilsen & Kaye, 2014;

Duration of CRPS (mean)	Medication, dose, and route	Primary outcome measure	Outcome	Side effects
4–14 mo	Multimodality treatment regimen (MMTR) consisting of amitriptyline, pregabalin, tramadol, dry needling, physical therapy, and • Continuous brachial plexus block (0.125% bupivacaine); one patient did not receive due to cost • Stellate ganglion block (40 mg triamcinolone, bupivacaine)	Pain severity on verbal rating scale (VRS), motor features, redness, temperature changes, range of motion, hand grip; DASH scale	MMTR was responsible for complete resolution of CRPS, including disability	No information

Huscher et al., 2009). Of the included studies 14 reported various side effects as specified in Table 1. Side effects were reported in eight studies using moderate to high daily doses of oral prednisone (Barbalinardo et al., 2016; Braus et al., 1994; Glick, 1973; Jamroz et al., 2020; Kalita et al., 2016, 2006; Park et al., 2020; Sussman, 1952). Furthermore, four studies applying regional IV blocks reported side effects, one using intramuscular depomedrol injection (Grundberg, 1996) and the study by Steinbrocker et al. comparing oral cortisone and stellate ganglion blocks (Steinbrocker et al., 1953).

3.14 | Risk of bias

Due to deviant study design or missing control group in most studies ($n = 33$), a qualitative bias assessment was not possible using the predefined tools (i.e. NOS and ROBINS-I). Therefore, the potential risk of bias was evaluated for the eight RCTs. The revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to judge five domains, by which an overall risk of bias judgement was made; low risk of bias, some concerns and high risk of bias are possible. Two RCTs were evaluated to have an overall low risk of bias (Kalita et al., 2006; Munts et al., 2010), one was judged to have some concerns (Ali Taskaynatan et al., 2004) and three studies were judged to have an overall high risk (Christensen et al., 1982; Eun Young et al., 2016; Lukovic et al., 2006; see Table 4). Two studies used a crossover design and therefore the Rob2 tool for crossover trials was used (Braus et al., 1994; Kalita et al., 2016). This tool contains an extra domain evaluating the risk of bias arising from period and carryover effects. Both studies were judged as high risk (see Table 5).

4 | DISCUSSION AND CONCLUSIONS

Using glucocorticoids appears to be natural in treating CRPS with a major role for inflammation in pathophysiology (Bruehl, 2010; Parkitny et al., 2013). To our knowledge, this is the first review which focuses specifically on glucocorticoid treatment in CRPS.

CRPS is known to affect both upper and lower extremities, but the upper extremity is more prone to become affected (de Mos et al., 2007; Ott & Maihöfner, 2018). Included studies reflect this, including 39 studies assessing upper extremity CRPS, of which 11 also studied lower extremity CRPS.

Tissue damage is the initial trigger for CRPS development. Most often, fracture, blunt trauma or surgery initiate CRPS (de Mos et al., 2007; Ott & Maihöfner, 2018; Sandroni et al., 2003). This is reflected in the included studies, with trauma and surgery being most frequently mentioned. However, there were eight studies including patients with CRPS after myocardial infarction (Russek et al., 1953; Sussman, 1952); following stroke (Braus et al., 1994; Eun Young et al., 2016; Kalita et al., 2016, 2006; Kim et al., 2016) and after traumatic brain injury (Park et al., 2020). CRPS is known to develop after an injury of the extremities (Birklein & Schlereth, 2015; Harden et al., 2010; Veldman et al., 1993), and it is doubtful whether CRPS may also be present after a heart attack or stroke without peripheral trauma. These eight articles therefore should be viewed with caution. Disuse of the affected extremity may play a role in the underlying pathophysiology of these patients.

Strikingly, only nine of 41 articles included used the new IASP clinical diagnostic criteria (i.e. the Budapest

TABLE 3 Summary of characteristics of included studies

	Number of studies (%)
Type of glucocorticoid administration	
Oral	22 (53.5)
Intravenous	7 (17)
Intramuscular	2 (5)
Epidural or Intrathecal	2 (5)
Cutaneous	1 (2.5)
Local application	1 (2.5)
Combined types of administration	6 (14.5)
Initiating event[a]	
Trauma	30 (73)
Surgery	13 (32)
Myocardial infarction	6 (15)
Cerebrovascular accident	8 (19.5)
Spontaneous	2 (5)
Other[b]	6 (15)
No information	1 (2.5)
More than one initiating event[c]	16 (39)
Location of CRPS	
Upper extremity	28 (68)
Lower extremity	2 (5)
Both upper and lower extremity	11 (27)
Duration of CRPS[d]	
Acute (<1 year)	22 (54)
Chronic (>1 year)	7 (17)
No information	12 (29)

Abbreviations: yr: year, %: percentage of total.

[a]Because some studies met more than one initiating events, the percentage of studies does not sum to 100.

[b]Other initiating events: idiopathic, carcinoma, peripheral nerve injury, cervical osteoarthritis, total hip replacement, lesion of central nervous system, spinal cord injury and unknown.

[c]In some studies, multiple initiating events caused CRPS in included patients.

[d]Duration of CRPS from diagnosis to start of treatment.

criteria or Harden Bruehl criteria; Harden et al., 2010). These diagnostic criteria were adopted in 2012 as new international standard for diagnosing CRPS. Introducing these criteria reduced the CRPS diagnostic rates by approximately 50% (de Boer et al., 2011; Perez et al., 2007). It is thus questionable whether all patients in the included studies are, in fact, comparable.

The studies were also clinically diverse regarding the route of glucocorticoid administration, dosages used and duration of CRPS symptoms. As the diverse routes of administration are not comparable, we 'assessed the studies in groups based on the administration route, which makes this review more accessible for clinical practice. Almost all included studies reported a positive therapeutic effect on different parameters, with an improvement in pain relief and range of motion being the most mentioned.

Given the duration of CRPS symptoms in the included studies, it is relevant that 22 studies included patients with acute CRPS (<1 year). Especially in the early months (i.e. the acute stage), clinical signs of CRPS include peripheral inflammation such as pain, increase in temperature, swelling, redness and loss of function (Birklein & Schlereth, 2015; Bharwani, Dirckx, Stronks, et al., 2017). Therefore, glucocorticoids are considered a natural treatment in this phase. In longer-existing CRPS, it is likely that the active inflammation had extinguished and that there is residual damage which may be both peripheral and central. Therefore, we suspect that the anti-inflammatory effect of glucocorticoids will be less present in longer-existing CRPS. One study on longer-existing CRPS duration conveyed that the efficacy of oral steroids was limited when treating CRPS with a duration of more than 3 months (Barbalinardo et al., 2016). However, certain articles in which the CRPS duration was more than 1 year reported an improvement, and glucocorticoid treatment seem also appropriate for these patients (Kozin et al., 1981; Rosen & Graham, 1957). With current treatment based on the underlying pathophysiologic mechanism believed to be the most prominent in a specific case, it is sensible that only patients who present with inflammatory signs and symptoms are treated with glucocorticoids.

Using glucocorticoids causes side effects and many are both dose and time-dependent (Ericson-Neilsen & Kaye, 2014; Huscher et al., 2009). A short course of glucocorticoids usually causes no side-effects. However, it is known that up to 90% of patients using glucocorticoids for more than 60 days develop side effects, even when using a low dose (≤7.5 mg/day); Curtis et al., 2006). Dose and time dependence also play a clear role within the studies in this review. Of the eight studies reporting side effects when using oral prednisone in seven studies treatment duration was more than 2 weeks (Barbalinardo et al., 2016; Braus et al., 1994; Glick, 1973; Jamroz et al., 2020; Kalita et al., 2006, 2016; Sussman, 1952). It is of course also possible that the described side effects may be an isolated problem or occurred in combination with other medication and not as a specific side effect of the glucocorticoid treatment.

The extensive methodological heterogeneity of the included studies made it impossible to draw a clear conclusion on the efficacy of glucocorticoid treatment in CRPS. The study results would ideally be presented in forest plots, as such a visual representation is of great importance to clearly convey mutual effectiveness.

TABLE 4 Risk of bias assessment using RoB 2 tool

Study	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Christensen et al. (1982)	−	−	+	−	X	X
Ali Taskaynatan et al. (2004)	+	+	+	+	−	−
Kalita et al. (2006)	+	+	+	+	+	+
Lukovic et al. (2006)	−	−	+	X	−	X
Munts et al. (2010)	+	+	+	+	+	+
Eun Young et al. (2016)	−	−	+	X	+	X

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
− Some concerns
+ Low

TABLE 5 Risk of bias assessment using RoB 2 tool for crossover trials

Study	Risk of bias domains						
	D1	S	D2	D3	D4	D5	Overall
Braus et al. (1994)	+	X	+	+	−	−	X
Kalita et al. (2016)	+	X	−	+	X	+	X

Domains:
D1: Bias arising from the randomization process.
S: Bias arising from period and carryover effects.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
− Some concerns
+ Low

However, the studies differed too much from each other in several areas (e.g. dosage, treatment duration, CRPS duration and outcome parameters) to make this possible in a reliable manner. For this reason, only a narrative review was possible.

This lack of pooling of the data is a limitation of this review, as is the inclusion of articles. Our search included glucocorticoid and corticosteroid alongside descriptions of CRPS, algodystrophy, posttraumatic dystrophy and derivatives of these terms, which represent only a few of the many descriptions related to CRPS. Additionally, many names are used for glucocorticoids. For these reasons, publications may have been missed if the authors used another description. We attempted to avoid missing articles by checking the identified articles' reference lists for additional studies. Moreover, an additional search was performed for more recently published articles. Additionally, articles published in languages other than English were not included in our review, as a result of which eight potentially valuable articles were excluded. Both the search strategy and excluding other languages may have caused publication bias, which we consider to be a limitation of this review. Despite potential bias, including almost every study design provides a better insight into all that is known about glucocorticoid treatment in CRPS. However, it was not possible to assess the quality of all included studies, so only the RCTs were assessed. The quality assessment showed that all but two RCTS were judged as 'overall some concerns of bias' or 'overall high risk of bias'. This was partly due to the lack of published research protocols, whereby publication bias could not be ruled out. Both the lack of bias assessment and this relatively high risk of bias from the assessed articles reduced the review's reliability.

In conclusion, there is evidence to support the use of glucocorticoids in treating CRPS patients. In particular, this evidence applies to pain relief and improved range of motion. Future research should examine which administration route and dose of glucocorticoids are most optimal, preferably in high-quality intervention studies.

AUTHOR CONTRIBUTIONS

CB, JT and FH conceived and designed the study. CB was involved in performing the search. CB and PB selected the studies. CB drafted the manuscript. All authors were involved in revising and approving the manuscript.

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CONFLICT OF INTEREST

None declared.

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