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Topical review

Anti-inflammatory treatment of Complex Regional Pain Syndrome

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1. CRPS-1 – definition, pathophysiology, treatment

Complex Regional Pain Syndrome type 1 (CRPS-1) is a disabling condition characterized by sensory, autonomic, (vaso)motor and trophic disturbances, of which pain, swelling, color changes, limited mobility and change in temperature of the affected extremity are the most predominant [4,33]. CRPS-1 mainly develops after fractures, operations or a small trauma but also occasionally develops without a triggering event [26].

Different mechanisms are thought to play a role in the development of CRPS-1, providing a possible explanation for the heterogeneity seen within this patient population. One of the mechanisms proposed to be involved in the origin and maintenance of CRPS-1 is an exaggerated inflammatory response to tissue injury [2]. Scientific evidence supports the involvement of inflammatory processes in CRPS-1, whereby elevated cytokine levels [17], elevated activity of mast cells, neurogenic inflammatory reactions, [2,18] and markers of oxidative stress [6] were found.

Systematic reviews addressing anti-inflammatory therapy provide limited evidence and contradictory conclusions [7,20,27]. However, in recent years additional studies have been published targeting the inflammatory component of CRPS-1. In light of the changing views about the involvement of inflammation, a comprehensive assessment of anti-inflammatory treatment approaches of CRPS-1 is warranted. The goal of the present topical review is to evaluate the effect of anti-inflammatory therapy on prevention, pain, range of motion and overall clinical improvement in CRPS-1.

2. Retrieving studies of anti-inflammatory CRPS-1 treatment

The Embase, Cochrane, Medline and Pubmed databases were scanned for relevant literature up to December 2009 (for search string, see Appendix 1). Reference lists of retrieved articles were screened for additional articles. Methodological quality of the articles was rated by two reviewers using the Delphi list [34]. Scores $\geqslant 7$ indicate high quality, scores $4 \leqslant 6$ indicate moderate quality and scores $\leqslant 3$ indicate poor quality. Included articles were evaluated on outcome (pain, range of motion and clinical improvement) and type of medication. A distinction was made between articles reporting about CRPS-1 after peripheral trauma (PT), and those evaluated about CRPS-1 after central nervous trauma (CNT), as different diagnostic criteria for the latter have been used in literature.

3. Results

Twenty-four eligible articles were found. Data for two clinical trials were reported in four separate articles and were therefore analyzed as two independent studies [29,32,35,37]. In total, 22 independent studies were analyzed in this review [1,3,5,8–12,14,19,21–24,28,29,31,32,35,37–40], 16 of which were not evaluated in previous reviews [1,9–11,19,21–24,28,29,31,32,36]. The anti-inflammatory modalities found in our search were corticosteroid treatment [1,3,5,9,10,14,19,21,22,24,31,39], free radical scavengers, [8,11,12,23,28,29,32,35–38] and the combination of corticosteroids and free radical scavengers [40]. Characteristics of included studies are presented in Table 1.

3.1. Pain

Twelve studies evaluated pain reduction following anti-inflammatory treatment [1,8,11,19,21,24,28,29,31,32,38–40].

3.1.1. Free radical scavengers

No effect of DMSO on pain reduction was found in a randomized placebo- controlled trial (RCT) of high quality (PT) [38], however a case series showed DMSO to significantly reduce pain (PT) [23]. Mannitol showed no significant pain reduction compared to placebo in a high quality RCT (PT) [28]. No significant differences were found in pain reduction between *N*-Acetylcysteine and DMSO in a high quality RCT (PT), however there was significant improvement for both interventions over the course of the trial [29,32].

3.1.2. Corticosteroids

One RCT of high quality revealed significantly more pain reduction for oral prednisolone than the prostaglandine inhibitor piroxicam (CNT) [19]. In addition, significant pain reduction was reported in two case series after treatment with prednisolone (PT, CNT) [1,21]. Furthermore, a case series showed 73% of patients experiencing pain reduction and 18% remaining pain free 1 year after treatment with intravenous blocks with lidocaine and methylprednisolone (PT) [39].

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Table 1
Study characteristics.

References	Diagnostic term/ included patients	Design	Quality score[a]	Intervention	N	Main outcome measurements	Results
Glick ('73) [9]	Reflex dystrophy syndrome	Case series	3 (0, 0, 0, 1, 0, 0, 0, 1, 1)	Prednisolone during 10–70 weeks, dosages from 15 to 40 mg/day	17	Clinical improvement: (graded as: excellent–very good–good–fair–poor–no improvement)	Results: excellent ($N = 4$), good very ($N = 3$), good ($N = 3$), fair ($N = 2$), poor ($N = 2$), no improvement ($N = 2$), withdrawal because of side-effects ($N = 1$)
Glick and Helal ('76) [10]	Post-traumatic neurodystrophy (SHS included)	Case series	2 (0, 0, 0, 0, 0, 0, 0, 1, 1)	Prednisolone for 3–4 months starting at 15–40 mg/day, individual increase of dosage (total dosages not reported)	21	Clinical improvement (graded as: very good–good–fair–poor)	Results: very good ($N = 10$), good ($N = 3$), fair ($N = 5$), poor ($N = 3$)
Kozin et al. ('76) [21]	Reflex sympathetic dystrophy (SHS and development of RSD after MI and cancer included)	Case series	3 (0, 0, 0, 1, 0, 0, 0, 1, 1)	Prednisone dose and period of time dependent on patient, ranging from 2 to 14 weeks, dosages from 60 to 80 mg/day	11	Grip strength, swelling by ring size, joint tenderness by dolorimeter score (per joint: max. score of 20, measured joints: 7–15)	Significant improvement in ring size (mean change −2.6% (range −7.7% to +3.0%); $P < 0.05$), dolorimeter score (mean change −78 (range −3 to −224; $P < 0.02$)
Kozin et al. ('81) [22]	Reflex sympathetic dystrophy (nerve injury included)	Comparative non-randomized study	3 (0, 0, 0, 1, 0, 0, 0, 1, 1)	Stellate ganglion blockade versus 60–80 mg of prednisone for 2–4 days (occasionally up to 2 weeks), where after rapidly tapered	55	Subjective response (excellent, good, fair, poor, fair).	Prednisone: excellent 40%, good 23%, fair 9%, poor 29%. Stellate ganglion blockade: fair 15%, poor 85%
Christensen et al. ('82) [5]	Reflex sympathetic dystrophy	Randomized placebo-controlled trial	5 (1, 0, 1, 1, 0, 0, 0, 1, 1)	Prednisone orally, 10 mg three times/day until clinical remission, maximum of 12 weeks	23	Clinical improvement score consisting of pain, oedema, volar sweating and finger knitting ability (max. score 20)	Significant better clinical improvement for prednisone (prednisone: mean score from 8.5 (range 4–18) to 0.7 (range 0–3), placebo: (mean score from 8.2 (range 6–11) to 5.9 (range 0–9); $P < 0.01$)
Goris ('85) [11]	Reflex sympathetic dystrophy	Non-randomized comparative trial	2 (0, 0, 0, 1, 0, 0, 0, 1, 0)	Topical DMSO 50% five times/day for 2 weeks or mannitol 10% iv 1 l/day during 1 week or mannitol 10% 20 ml oral five times/day for 2 weeks	9	Pain, oedema, hyperhydrosis. Function	Full pain relief in 8/9 patients, full recovery of function in 6/9 patients, all treated with DMSO
Goris et al. ('87) [12]	Reflex sympathetic dystrophy	Randomized controlled cross-over study	3 (1, 0, 0, 1, 0, 0, 1, 0, 0)	Topical DMSO 50% in water versus placebo (plain water) five times a day, 1 week of DMSO and one week placebo	20	Subjective clinical evaluation by patient and researcher and range of motion (ROM)	Subjective clinical improvement for DMSO: 13/20 patients (patient-based) and 16/20 (researcher-based), $P < 0.001$. ROM improvement: 15/17 patients, average improvement of 100° for DMSO: 8/17 patients, average improvement of 41° for placebo, $P = 0.035$.
Langendijk et al. ('93) [23]	Reflex sympathetic dystrophy	Case series	3 (0, 0, 0, 1, 0, 0, 0, 1, 1)	Topical DMSO 50% cream, five times a day, until RSD score <10	38	RSD score[b](on a 0–100 scale), VAS pain score[c]	Significant improvement of RSD score (mean 83.5; SD 13.2 to $\leqslant 10$; $P < 0.01$) and VAS pain score (mean 5.3; SD 2.9 to 0.9; SD 1.3); $P < 0.01$)
Braus et al. ('94) [3]	SHS in hemiplegic patients after stroke	Randomized placebo-controlled trial	4 (1, 0, 1, 1, 0, 0, 0, 1, 0)	Methylprednisolone 32 mg during 14 days and a 14 day tapering period. Placebo group continued as open study after 14 days (except 2)	36	SHS-score[b] (on a 0–14 scale)	Relevant improvement (SHS-score <4) for 31/34 patients treated with methylprednisolone. 17/34 were first treated with placebo and physical therapy resulting in temporary relief
Geertzen et al. ('94) [8]	Sympathetic reflex dystrophy of the hand	Randomized actively controlled trial	5 (1, 0, 1, 1, 0, 0, 0, 1, 1)	DMSO lotion 50% in water applied three times/day for 3 weeks versus regional intravenous ismelin blocks 2/week during 3 weeks	26	VAS pain score[c], VAS daily activities, oedema, discoloration, ROM, abduction/adduction of fingers and a total score of all above (on a 0–70 scale, shown in figure) during 9 weeks	Patients treated with DMSO improved more on mean total score (42–15) then ismelin blocks (43–27) (information derived from figure)
Grundberg ('96) [14]	Reflex sympathetic dystrophy	Case series	3 (0, 0, 0, 1, 0, 0, 0, 1, 1)	Intramuscular methylprednisolone 80 mg every 2 weeks, with a maximum of four injections, average 2.3 injections	47	Grip strength, pinch strength, PIP motion, swelling (graded as: no-moderate-severe)	Average grip strength improvement of 22 lbs, pinch grip 4 lbs; average improvement of PIP motion from 39° to 75°. Swelling decreased in all patients (base line; 47 patients with moderate to severe swelling; after treatment: no swelling in 26 patients and mild swelling in 21 patients)
Zuurmond et al. ('96) [38]	Reflex sympathetic dystrophy	Randomized controlled trial	7 (1, 1, 1, 1, 0, 1, 1, 1, 0)	DMSO 50% in fatty cream versus placebo fatty cream during 2 months (times/day not reported)	30	RSD score[b] (on a 0–5 scale), VAS pain score[c]	Significant improvement of RSD score (DMSO: median improvement 4 (range 0–5), placebo: median improvement of 3 (range 0–5), $P < 0.01$). No significant improvement of VAS pain score (DMSO: median improvement 2.9; (range −2.8 to 7.0), placebo: 1.0 (range −3.9 to 9.0))

Zyluk ('98) [39]	Post-traumatic reflex sympathetic dystrophy	Case series	2 (0, 0, 0, 1, 0, 0, 0, 1, 0)	Single intravenous block of 80 mg methylprednisolone and 20 ml 1% lidocaïne	36	Pain (severe/moderate), swelling, discoloration, temperature, hyperhidrosis, loss of finger flexion, summarized in total score (graded as poor–moderate–good)	Pain relief in 73% of patients, 18% of the patients pain free. Clinical improvement qualified as good in 69%, moderate in 22% and poor in 9% of patients
Zollinger et al. ('99) [37] Zollinger et al. ('00) [35]	Wrist fractures, conservatively treated	Randomized controlled trial	8 (1, 1, 0, 1, 1, 1, 1, 1, 1) 9 (1, 1, 1, 1, 1, 1, 1, 1, 1)	Vitamin C 500 mg/day versus placebo during 50 days after trauma	115	Development of reflex sympathetic dystrophy	Significantly lower ratio of RSD (vitamine C: 7%, placebo: 22%, $P < 0.04$)
Perez et al. ('03) [29]	Complex regional pain syndrome type 1	Randomized actively controlled trial	8 (1, 1, 0, 1, 1, 1, 1, 1, 1)	Topical DMSO 50% cream five times/day, versus *N*-Acetylcysteïne (NAC) 600 mg three times/day	146	ISS[d], WSQ, QRSD, gait analysis, EuroQol, COOP/WONCA, SF-36	DMSO and NAC equally effective. Both resulted in decrease of ISS (reduction DMSO: 9.05; SD 6.97, NAC: 8.31; SD 8.13)
van Dieten et al. ('03) [32]	Reflex sympathetic dystrophy according to the Veldman criteria	Randomized comparitive controlled trial	8 (1, 1, 0, 1, 1, 1, 1, 1, 1)	Topical DMSO 50% cream five times per day, versus NAC 600 mg three times/day	131	Cost-effectiveness, ISS[d], mean utility	DMSO provides the best cost effectiveness profile, see Perez et al. ('03)
Taskaynatan et al. ('04) [31]	Complex regional pain syndrome type I	Randomized placebo-controlled trial	7 (1, 1, 0, 1, 1, 1, 1, 1, 0)	Bier block with lidocaïne 10 ml 2% and methylprednisolone 40 mg once a week versus 100 ml saline, three times in total	22	VAS pain[c], ROM (distance between finger tip and distal palmar crease in cm), oedema (measured by a volumeter in grams)	No significant difference in improvement of: mean VAS pain (active treatment: 5.7; SD 1–4.2; SD 1.3, placebo: 4.8; SD 1.1–3.5; SD 0.9), mean ROM (active treatment: 2.8; SD 0.3–2.7; SD 0.4, placebo: 2.5; SD 0.6–2.5; SD 0.6), mean oedema (active treatment: 1522; SD 134–1516; SD 133, placebo: 1522; SD 137–1520; SD 137).
Bianchi et al. ('06) [1]	CRPS according to criteria of Kozin, not reacting on regular physiotherapy	Case series	3 (0, 0, 0, 1, 0, 0, 0, 1, 1)	Prednisone 60 mg ($N = 2$), 50 mg ($N = 1$) or 40 mg ($N = 28$) for 2–4 days tapered to 30–40 mg for 2–4 days and at last tapered to 5–10 mg for 2–3 days. Two cycles in patients with poor results ($N = 4$)	31	Pain: VAS scale[c]. Swelling, function (on a 0–2 scale). Clinical severity (on a 0–22 scale)	Improvement after 1 year for all measured variables after 1 cycle (upper limb: median VAS 9 (range 3–10) to 0 (range 0–1), functional ability 2 (range 1–2) to 0 (range 0–0), lower limb: VAS median 7.5 (range 6–9) to 0 (range 0–1), functional ability 1 (range 0–2) to 0 (range 0–2), $P < 0.001$). Clinical severity score for affected limb: 16.8 (range 10.1–22) to 2.0 (range 0–4.5). Clinical improvement after 1 year and two cycles of treatment (median score 19 (range 18–21) to 8 (1–10), $P < 0.01$).
Kalita et al. ('06) [19]	Complex regional pain syndrome developed after stroke	Randomized actively controlled study	8 (1, 1, 0, 1, 1, 1, 1, 1, 1)	Prednisolone oral 40 mg/day versus piroxicam oral 20 mg/day for 14 days	60	CRPS score[b] (on a 0–14 scale): sensory aspects separately described (on a 0–5 scale), Barthel index (daily activity scale ranging from 0 to 20)	Significant improvement of: CRPS score (prednisolone: mean 10.73; SD 1.95–4.27; SD 2.83, piroxicam: mean 9.83; SD 2.34–9.37; SD 2.89, $P < 0.0001$), sensory component (prednisolone: mean 3.98; SD 0.85–1.13; SD 1.31; piroxicam: mean 4.00; SD 0.87–3.67; SD 1.35; $P < 0.0001$). No significant difference in Barthel index (prednisolone: mean 1.97; SD 4.94–9.87; SD 4.43; piroxicam: 2.57; SD 4.32–7.07; SD 5.56) after 1 month
Lukovic et al. ('06) [24]	Complex regional pain syndrome type I (first stadium)	Randomized placebo-controlled trial	3 (0, 0, 0, 1, 0, 0, 1, 1, 0)	Oral prednisone 5 mg + diverse physical agents versus placebo + diverse physical agents, until stable remission	60	Treatment duration, VAS pain scores[c], swelling (severe, moderate, absent), skin color (normal, pale, cyanotic), motor function (1st–3rd degree functional impairment)	No significant difference for VAS pain (prednisone: 6.0; SD 1.5–0.2; SD 0.4, placebo: 5.9; SD 1.5–0.3; SD 0.7), severe swelling (prednisone: 12/30 to 0/30, placebo:13/30 to 0/30), function (prednisone: 29/30 patients with 1st degree impairment after treatment; placebo: 27/30 patients with 1st degree)
Zollinger et al. ('07) [36]	Wrist fractures	Randomized controlled trial (comparative and placebo)	9 (1, 1, 1, 1, 1, 1, 1, 1, 1)	Vitamin C 200 mg, 500 mg, 1500 mg or placebo during 50 days after the trauma	416	Development of CRPS-1	Significant lower ratio of CRPS-1 (vitamin C (all dosages): 2.4%, placebo: 10%; $P = 0.002$, vitamin C 500 mg 2%: placebo 10%; $P = 0.007$, vitamin C 1500 mg 2%, placebo: 10%; $P = 0.005$). Vitamin C 200 mg is not significantly more effective then placebo (vitamin C 200 mg: 4%, placebo: 10%)

(*continued on next page*)

Table 1 (*continued*)

References	Diagnostic term/ included patients	Design	Quality score[a]	Intervention	N	Main outcome measurements	Results
Perez et al. ('08) [28]	Complex regional pain syndrome type I	Randomized placebo-controlled trial	9 (1, 1, 1, 1, 1, 1, 1, 1, 1)	Mannitol 10% 1 l iv or placebo (1 l NaCl 0.9% iv) every day during 5 days	41	VAS pain score[c] (range 0–100), function level, quality of life (QOL), hand function/ foot function, dynometer, AROM	No significant improvement of pain (mannitol: 53.1; SD 17.5–49.7; SD 25.3, placebo: 48; SD 23.6–45.1; SD 31.8), AROM (mannitol: −0.5 (IQR −1.2 to 2.2), placebo: −0.4 (IQR −0.9 to 0.8), QOL: physical functioning: mannitol: 10.0 (IQR −5.0 to 20), placebo: −5.0 (IQR −10.0 to 15.0), social functioning: mannitol: 0.0 (IQR −12.5 to 12.5), placebo: 0.0 (IQR −25.0 to 12.5)
Zyluk and Puchalski ('08) [40]	Complex regional pain syndrome type I, less then 4 months	Case series	2 (0, 0, 0, 1, 0, 0, 0, 1, 0)	Mannitol 10% iv 2 × 250 ml and 8 mg dexametason/day every day for 1 week	70	VAS pain score[c], finger flexion (distance in cm from finger tip to distal palmar crease), CRPS score[b] (on a 0–10 scale)	Significant improvement of: VAS pain score (mean 6.7 (range 5–9) to 2.3 (range 1–5), $P < 0.05$), finger flexion (6 cm (range 3–10) to 0.3 cm (range 0–5), $P < 0.05$), CRPS score (7.6–2.2, $P < 0.05$)

SHS = shoulder hand syndrome.

[a] Methodological quality is rated according to a Delphi list [34]. Studies receive score "0" or "1" on the following criteria: randomization, blinded medication, similar study groups, properly specified in- and exclusion criteria, blinded researcher, blinded care taker, blinded patient, clear purpose of the study and intention-to-treat analysis (e.g. 0, 0, 0, 1, 0, 0, 0, 1, 1 = quality score of 3). Scores ⩾ 7 indicate high quality, scores 4 ⩽ 6 indicate moderate quality and scores 3 or lower indicate poor quality.

[b] RSD score, SHS score and CRPS score are compound scores to assess disease severity, based on pain, temperature, colour, autonomic differences between the extremities and loss of function.

[c] VAS pain score is measured on a scale from 0 to 10.

[d] ISS is a validated compound score to assess the severity of symptoms of CRPS-1, based on pain, temperature and volume differences between the extremities and loss of function measured on a scale from 5 to 50.

In contrast, a placebo-controlled RCT of poor quality evaluating low dosages of oral prednisolone showed no effects on pain reduction (PT) [24]. Likewise, a high quality RCT on blocks with lidocaïne and prednisolone showed no effect on pain reduction compared to placebo (PT) [31].

3.1.3. Combined free radical scavenger and corticosteroid treatment

In one case series a combination of intravenous mannitol and dexametason was reported to provide significant decrease in pain (PT) [40].

3.2. Range of motion

Ten studies addressed the effects of anti-inflammatory treatment on range of motion (ROM) [1,8,11,12,14,24,28,29,31,32,40]. The outcome was either reported as subjective improvement [1,11,12] or as objectively measured effects [8,14,24,28,31,40] (see Table 1).

3.2.1. Free radical scavengers

Treatment with DMSO provided a significant subjective improvement of ROM compared to placebo in one-randomized controlled cross-over study of poor quality (PT) [12]. In another non-randomized trial on topical DMSO compared to intravenous mannitol a decrease of subjective joint stiffness in both patient groups was found (PT) [11]. One high quality RCT showed no improvement of ROM between *N*-Acetylcysteine and DMSO (PT), however there was a significant improvement with both free radical scavengers over the course of the trial [29,32]. One RCT of high quality on intravenous mannitol did not show improvement of range of motion (PT) [28].

3.2.2. Corticosteroids

Improvement of ROM was reported in two case series. One or two treatment cycles of corticosteroids showed a significant improvement of ROM after 1 year (PT) [1]. Similarly, intramuscular corticosteroids (PT) [14] were reported to provide an increase in proximal interphalangeal joint movement in 68% of the patients at a one year follow-up. However, RCTs reported less positive effects for improvement in the range of motion, whereby only limited effects of oral prednisolone were observed when compared to piroxicam in a high quality RCT (CNT) [19]. Another high quality trial on bier blocks with lidocaine and prednisolone (PT) [31] and an RCT of poor quality on oral administration of low-dose corticosteroids (PT) showed no improvement on range of motion when compared to placebo [24].

3.2.3. Combined free radical scavenger and corticosteroid treatment

The combined treatment of patients with CRPS-1 with the scavenger mannitol and dexametason (PT) [40] yielded a significant improvement of finger flexion in a case series.

3.3. Overall clinical improvement: compound scores and subjective global assessment

Clinical improvement was studied in 13 studies [1,3,5,9,10,12,19,22,23,29,32,38–40], using either compound scores based on validated measurements of pain, range of motion, oedema and temperature difference between the affected and unaffected extremity, [1,3,5,19,23,29,32,38–40] and subjective assessment as outcome [9,10,12,22].

3.3.1. Free radical scavengers

One placebo-controlled cross-over RCT of poor quality reported overall clinical improvement for DMSO expressed as subjective clinical wellbeing by the patient and the physician (PT) [12].

Positive results for clinical improvement as determined with compound scores were found for topical DMSO in two RCTs of high quality compared to placebo (PT) [38] and in one RCT of moderate quality compared to regional intravenous ismelin blocks (PT) [8] as well as in one case series (PT) [23]. A high quality RCT comparing *N*-Acetylcysteine to DMSO (PT) [29,32] revealed significant improvements in clinical compound scores for both interventions, without significant differences between both arms of the study.

3.3.2. Corticosteroids

All studies evaluating the use of corticosteroids reported significant positive results on overall clinical improvement. This included three case series, of which one showed improvement of clinical scores after one or two cycles of corticosteroids (PT) [1], and two case series showed good to excellent clinical results in respectively 59% (PT/CNT) [9] and 62% of CRPS-1 patients (PT/CNT) [10]. Two RCT's of moderate quality comparing corticosteroids to placebo ((CNT) [3], (PT) [5]) and a high quality RCT comparing corticosteroids to piroxicam (CNT) [19] reported significant differences in favor of corticosteroid treatment.

3.3.3. Combined free radical scavenger and corticosteroid treatment

A case series evaluating the effect of a combination of mannitol and dexametason showed a significant improvement on a compound score (PT) [40].

3.4. Prevention of CRPS-1

Two RCTs addressed primary prevention of CRPS-1 using the free radical scavenger vitamin C (PT) [35–37]. A significant preventive effect of vitamin C was found in both studies. While 22% of the patients in the control group, only 7% of the patients in the vitamin C group, developed CRPS-1 [35,37]. Similar results were observed in another study (control 10.1%, vitamin C 2.4%) [36].

4. What to do now?

Our results suggest that anti-inflammatory therapy may be beneficial for CRPS-1. Pain reduction and improvement of range of motion were found after treatment with the free radical scavengers *N*-Acetylcysteine and DMSO, as well as after treatment with corticosteroids. In all evaluated studies both free radical scavengers (DMSO, *N*-Acetylcysteine) and corticosteroids showed improvement of clinical outcome. In addition, the free radical scavenger vitamin C showed substantial preventive effects. These results are in line with the current hypotheses about the involvement of an inflammatory process in CRPS-1 [2,17,30] and are comparable to other reviews evaluating anti-inflammatory interventions for CRPS-1 [7,20,27].

Glucocorticosteroids and free radical scavengers differ in pharmacological mechanism. Glucocorticosteroids reduce manifestations of inflammation by suppression of mediators, such as cytokines and chemokines. Furthermore, regulation of immune cells alters as a result of corticosteroid treatment, which may lead to reduction of phagocytosis, antigen response, cytokine production and cellular immune response. On the other hand, free radical scavengers reduce inflammatory reactions by neutralizing free radicals that are produced during the inflammatory cascade, thereby limiting ongoing tissue damage.

In the studies included in this review both pathways result in a decrease of symptoms in patients with CRPS-1, which is in line with the pathophysiological mechanisms proposed to be involved in CRPS-1. Aberrant and neurogenic inflammation after trauma associated with elevated cytokine levels [2,17], elevated activity of mast cells [18] and increased cell markers of oxidative stress have been reported [6]. Furthermore, ischemia–reperfusion injury leading to excessive free radical production has been proposed to play a role in CRPS-1 [13].

Interestingly, the effects of both interventions were not uniformly beneficial. Although significant pain reduction was observed for DMSO and *N*-Acetylcysteine in the course of treatment [29], no difference was found between both the interventions. In addition, DMSO exhibited no effects on pain reduction in another high quality placebo-controlled trial [38] and intravenous mannitol provided no effects on any outcome measurements [28]. Intravenous corticosteroids [31] and low-dose corticosteroids [24] also showed no effects on pain reduction or ROM. Our findings suggest that these treatment modalities may not be equally effective for all the features exhibited by CRPS-1 patients. Furthermore, the mode of administration (i.e. intravenous, oral, topical) may be of influence on the efficacy of the intervention. In addition, these treatments were applied in heterogeneous groups of CRPS-1 patients, without accounting for possible differences related to prevailing pathophysiological mechanisms in individual patients. Arguments in favor of a phenotype or mechanism-based approach to CRPS-1 have been made by some researchers [15,25]. Unfortunately, descriptions of clinical profiles of patients included in the studies were insufficient to allow for phenotype-based subgroup comparisons in the present review.

5. Restrictions

Studies of limited methodological strength were also included in the present topical review to obtain a comprehensive overview of effects of anti-inflammatory therapies. This may, however, have led to overestimation of the effects, because low quality studies tend to report more positive results. Different non-validated or subjective-measurement instruments were used in the evaluated studies, limiting the reliability and comparability of results.

Articles of our own group [28,29,38] were evaluated in the present review. To exclude bias the quality assessment was not performed by the authors involved in these studies. In addition, the applied methodological scoring list used left little room for interpretation bias. Furthermore, all evaluated studies addressing prevention of CRPS-1 were performed by the same research group, and the number of patients that actually developed CRPS-1 was limited. Replication of these findings in other settings may therefore be warranted.

6. Needs for the future

Further research on anti-inflammatory therapy in patients with CRPS-1 is clearly indicated. Inclusion of homogeneous patient groups using internationally accepted diagnostic criteria [16] and the use of standardized measurement-instruments for pain, physical function as well as for quality of life may help improve the interpretation and comparability. Research targeted at well-defined subgroups of CRPS-1 patients with a clear inflammatory profile may add to a more mechanism-based approach.

Considering the positive results for both free radical scavengers and corticosteroids, studies comparing both treatment modalities as well as combining free radical scavengers and corticosteroids may be of interest. Further research may explore other forms of anti-inflammatory therapy, for instance anti-TNF-α and immunoglobulins.

7. Conflict of interest

There are no conflicts of interest to report for this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2010.07.020.

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