Pain 102 (2003) 297–307

PAIN

www.elsevier.com/locate/pain

The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study

R.S.G.M. Perez[a,*], W.W.A. Zuurmond[a], P.D. Bezemer[b], D.J. Kuik[b], A.C. van Loenen[c], J.J. de Lange[a], A.J. Zuidhof[d]

[a]*Department of Anesthesiology, Vrije Universiteit Medical Center, P.O. Box 7057, 1007 MB, Amsterdam, The Netherlands*
[b]*Department of Clinical Epidemiology and Biostatistics, Vrije Universiteit Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands*
[c]*Department of Pharmacy, Vrije Universiteit Medical Center, P.O. Box 7057,1007 MB Amsterdam, The Netherlands*
[d]*Department of NDDO Oncology, Vrije Universiteit Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands*

Received 6 December 2001; accepted 11 October 2002

Abstract

To compare the effects of two free radical scavengers, dimethylsulfoxide 50% (DMSO) and *N*-acetylcysteine (NAC), for treatment of complex regional pain syndrome I (CRPS I), a randomized, double-dummy controlled, double-blind trial was conducted. Two outpatient clinics of two university hospitals in The Netherlands participated in the study and 146 patients, were included over a period of 24 months. Patients were randomized into two treatment groups, one was instructed to apply DMSO 50% five times daily to the affected extremity, the second was treated with NAC 600 mg effervescent tablets three times daily, both combined with placebo. Interventions were accompanied by pain medication, occupational therapy for upper extremity CRPS I and physical therapy for lower extremity CRPS I in specific circumstances. Treatment was given for 17 weeks, with a possibility to continue or switch medication after this period, up to 1 year following the onset of treatment. An impairment level sum score was the primary outcome measure. Upper and lower extremity skills and functions, and general health status were also evaluated. Overall, no significant differences were found between NAC and DMSO after 17 and 52 weeks on impairment level and general health status. Significant differences were found for subscores of lower extremity function, in favor of DMSO-treatment. Subgroup analysis showed more favorable results for DMSO for warm CRPS I and significantly better performance of NAC for patients with a cold CRPS I. Results tended to be negatively influenced if the duration of the complaint was longer. Treatment with DMSO and NAC are generally equally effective in treatment of CRPS I. Strong indications exist for differences in effects for subgroups of patients with warm or cold CRPS I: for warm CRPS I, DMSO-treatment appears more favorable, while for cold CRPS I, NAC-treatment appears to be more effective.

Keywords: Complex regional pain syndrome type I; Free radical scavengers; Randomized clinical trial

1. Introduction

Complex Regional Pain Syndrome type I (CRPS I), formerly known as reflex sympathetic dystrophy, is a poorly understood and hard to treat clinical complaint. It is characterized by various autonomic and vasomotor disturbances, of which diffuse pain, spreading edema, temperature disturbances and limitations in active range of motion are the most prominent (Veldman et al., 1993; Galer et al., 2000). Various treatment methods have been proposed, of which only a few have proven effective to a certain extent. In a meta-analysis, Kingery (1997) found support for analgesic effectiveness of corticosteroids, topical dimethylsulfoxide (DMSO), epidural clonidine and intravenous regional blocks with bretylium and ketanserin. In addition, findings from a meta-analysis conducted by our group (Perez et al., 2001a), suggested analgesic effectiveness for calcitonin treatment. Both studies concluded that intravenous regional blocks with guanethidine were ineffective in reducing pain in CRPS I. The latter findings link up with the doubts raised about the role of the sympathetic nervous system in the pathophysiological mechanism of CRPS I (Stanton-Hicks et al., 1995; Schott, 1995).

In the Netherlands, free radical scavengers such as DMSO and *N*-acetylcysteine (NAC), are widely applied in treatment of CRPS I. This scavenger therapy is based on the assumption that CRPS I is induced by an exaggerated inflammatory response to tissue injury, mediated by an excessive production of toxic oxygen radicals (Oyen et al., 1993). Support for the role of free radicals in CRPS I

* Corresponding author. Tel.: +31-204444386; fax: +31-204444385.
E-mail address: rsgm.perez@azvu.nl (R.S.G.M. Perez).

0304-3959/02/$20.00
doi:10.1016/S0304-3959(02)00414-1

was found in several studies (Goris et al., 1987; Van der Laan et al., 1997a, 1998). Van der Laan and Goris, (1997) describe evidence of tissue hypoxia combined with high oxygen supply, increased vascular permeability and increased acid phosphatase activity. Also, the positive results for corticosteroid treatment (Christensen et al., 1982) and prophylactic effect of vitamin C on occurrence of CRPS I after wrist fractures (Zollinger et al., 1999), sustain the idea of an inflammatory origin of CRPS I.

The efficacy of the free radical scavenger DMSO on CRPS I has been investigated in a number of studies (Goris et al., 1987; Langendijk et al., 1993; Geertzen et al., 1994; Zuurmond et al., 1996). In a blinded placebo-controlled study, Zuurmond et al. (1996) found that patients treated with DMSO 50% in a fatty cream improved significantly more on a general CRPS score than the placebo group. Other studies (Goris et al., 1987; Langendijk et al., 1993; Geertzen et al., 1994) have reported positive results for DMSO application as well. Although promising results have been described (Veldman and Dunki Jacobs, 1994), and NAC has been found to successfully reduce soft tissue damage in an animal model of inflammation (Van der Laan et al., 1997b), no studies have been performed to test the effectiveness of NAC in CRPS I patients.

Since both substances are regularly applied and provide a substantial burden on health care costs, a comparative investigation seems appropriate. Therefore, the aim of the present study was to compare the effects of DMSO and NAC for treatment of CRPS I.

2. Methods

2.1. Study design

Patients were included from the outpatient clinics of two medical centers in the Netherlands (VU medical center in Amsterdam and Nijmegen medical center in Nijmegen). To participate in the study patients had to meet the criteria for CRPS I according to Veldman et al, (1993) and the Netherlands WHO collaborating center (CBO) (Reflex sympathetic dystrophy guideline panel, 1993): (1) presence of four out of the following five symptoms: unexplained diffuse pain, difference in skin temperature relative to the other limb, diffuse edema, difference in skin color relative to the other limb, limited active range of motion; (2) aggravation of symptoms during or after exercise; (3) symptoms present in an area larger than and distal to the primary injury.

Patients had to be over 18 years of age; CRPS limited to one extremity; CRPS I shorter than 1 year; no prior treatment with NAC, DMSO or sympathectomy, and patients had to give informed consent. Patients were excluded if: the contralateral limb was impaired; the patient had to undergo surgery to the affected limb on short term; and in case of pregnancy.

Patients were stratified according to center and to the affected limb (i.e. upper or lower) and randomized into one of two treatment modalities in blocks of four. Based on a clinically significant difference op 6 (SD: 10) points on the primary effect measure (see below), using standard power analysis (Altman, 1999), the appropriate sample size was established at 45 patients per treatment per limb. Patients were treated for 17 weeks in two groups: one group was instructed to apply DMSO 50% in cremor vaselini cetomacrogolis five times daily to the affected extremity, in combination with three placebo effervescent tablets daily, patients in the second were treated with NAC (Fluimucil®) 600 mg effervescent tablets three times daily combined with application of placebo cream (cremor vaselini cetomacrogolis) to the affected limb five times daily, all in neutral packaging. Both interventions were (if necessary) accompanied by analgesics according to a strict protocol, starting with paracetamol 500 mg, followed by naproxen 250/500 mg and tramadol in progressive doses. Standardized occupational therapy was given to patients with upper extremity CRPS 1, and physical therapy for the lower extremity in specific circumstances, both according to evaluated guidelines (Oerlemans et al., 2000b).

Patients, researchers and physicians were blind to the interventions given, only the pharmacist was in possession of the allocation code. In order to mask the distinct odor of DMSO (onion- or garlic-like), the scent was artificially distributed in the research chamber. Placebo effervescent tablets were provided, by the manufacturer, with identical flavor and appearance as the real medication. Success of blinding was evaluated for participating physicians and patients at the end of treatment. Based on a strict protocol concerning the results on the primary effect measure, treatment could be stopped, continued or switched after 17 weeks. For those patients who continued or switched, the allocation code was broken.

2.2. Measurement of effects

Measurements took place prior to treatment and after 6 and 17 weeks (double-blind phase), with a follow up at 32 and 52 weeks. Measurement points at 17 and 52 weeks were considered to be most informative. Assessments were performed by two independent researchers in both participating institutions under environmentally stable conditions. Also, the time of measurement (i.e. morning or afternoon) was the same for all consecutive measurements. The primary effect measure was the impairment level SumScore (ISS), in which four aspects are incorporated: pain, as measured by visual analogue scale (VAS) (Scott and Huskinsson, 1979; Revill et al., 1979) and McGill pain questionnare (Vanderiet et al., 1987); temperature, measured with a Diadek® 9000 infrared thermometer (Oerlemans et al., 1999); volume, measured with a hand or foot volumeter (Smith, 1963); and active range of motion (AROM) measured with hand held goniometers. Results on

these individual measurements were converted into a sumscore, ranging from 5 to 50 (Oerlemans et al., 1998) (see Appendix A).

Secondary effect parameters were obtained at disability and handicap level. At disability level, the Radboud skills questionnaire (Oerlemans et al., 2000a) and modified Green test (Green, 1974; Buurke et al., 1999) were measured for patients with upper extremity CRPS I, and lower extremity function by two questionnaires (walking stairs questionnaire (WSQ) and questionnaire rising and sitting down (QRSD)) (Roorda 1996a,b) and gait analysis[1] using Penny and Giles™ electrogoniometers (Wagenaar and van Emmerik, 1994). The EuroQol (EuroQol group, 1990), COOP/WONCA (Scholten and Van Weel, 1992) and Short Form-36 (SF-36) (Brazier, 1993) were assessed as indicators for quality of life.

In order to be able to establish relevant subgroups, demographic and prognostic variables were gathered, such as age, sex, affected extremity, dominant extremity, initial trauma, time between initial trauma and CRPS I onset, smoking habits and type of CRPS I (i.e. primarily warm or cold). The classification into warm or cold CRPS was made by infrared thermometer at first visit, where patients showing a temperature difference relative to the unimpaired limb of −0.4°C or lower were classified as cold, and difference of +0.4°C or higher as warm (Uematsu et al., 1988; Bruehl et al., 1996; Oerlemans et al., 1998; Perez et al., 2001b). Furthermore, patient's history concerning temperature differences was taken into account, in order to eliminate the possibility of a chance finding. Temperature measurements took place under stable room temperature after approximately 10 min of acclimatization, in which both extremities were held in equal, comfortable position. The co-interventions were registered.

2.3. Analysis of data

Treatment effects were expressed as the difference scores (improvement) between measurements (baseline vs. 17 weeks and baseline vs. 52 weeks). Statistical analyses were performed blind to the treatment given, with SPSS 9.0 and BMDP 7.0 software. Prognostic comparability of both treatment groups was checked using χ^2-test, paired Student t test and Mann–Whitney–U test when appropriate. Possible influence of prognostic variables and effect modification (interaction) was analyzed using stepwise regression.

[1] Measurement of gait took place on a smooth surface. Changes in joint-angles during gait were measured in the saggital plane with electrogoniometers attached to hip, knee and ankle joints of both legs. Goniometer placement was based on an antropometric measurement protocol. Goniometers were attached to a small amplifier (weight 0.1 kg), which patients carried on their backs, connected to a mobile computer. Patients had to walk 6 m indicated by start and stop markers, which automatically triggered the beginning and end of the measurement. Patients walked at a maximum walking speed. Phase angles measured, are expressed in the mean relative phase between two joints in one leg. The difference between the unaffected and the score of the affected leg was presented.

The primary effect measure was analyzed according to intention to treat as well as per protocol principles. Differences between treatment effects were analyzed using four-way analysis of variance (ANOVA). Relevant subgroups were analyzed using three- or two-way ANOVA. Blinding was evaluated using the Sign test. For all outcome measures the two sided significance level was set at 5%.

3. Results

3.1. Patients

From April 1997 to 1999, 146 patients were recruited in both participating institutions, from a total of 159 patients fulfilling the inclusion criteria (see Fig. 1). The number of patients included with lower limb CRPS I was less than expected ($n = 41$). Thirteen patients refused participation, predominantly due to lack of time. One patient failed to show up for baseline measurement after randomization for unknown reasons. This patient was left out of the analysis. Of the remaining 145 patients, 71 were allocated to DMSO and 74 to NAC treatment. In the first 17 weeks, 33 patients did not complete the full research protocol, 14 of whom completed all measurements in the double-blind phase, 19 of whom missed one or more measurements. Reasons for drop out were: side effects (DMSO) ($n = 3$), side effects (NAC) ($n = 5$), interfering pathology ($n = 3$), non-compliance ($n = 3$), discontentment with treatment/research ($n = 3$), amelioration of complaints ($n = 4$), intervention physician ($n = 1$), other treatment ($n = 3$), no known reason ($n = 4$), other reasons ($n = 4$). For patients with missing measurements whose reasons for quitting were related to change in the complaint (i.e. amelioration, no change or deterioration), scores for the primary effect measure (ISS) were imputed. Amelioration was assigned a 6 point decrease at 17 weeks. In case no change or deterioration was reported, pretreatment scores were imputed at 17 weeks. If reasons for quitting were not related to changes in the course of the complaint, subsequent measurements were regarded as missing. Intention to treat analysis was based on 145 patients, per protocol analysis was based on 112 patients.

Except for the number of smokers among patients with upper extremity CRPS I in Amsterdam, which was significantly higher in the DMSO group than in the NAC group (χ^2 test; $P = 0.01$), no significant differences on prognostic indicators (Table 1) or baseline levels of effect measures (Table 2) were found between DMSO and NAC or between both institutions. No differences were found between patients with upper or lower extremity CRPS I and participating centers on baseline and course of the ISS and were therefore pooled together.

Based on stepwise regression analysis with the change in ISS as dependent variable, duration of the complaint since initial trauma (expressed as duration, longer or shorter than 90 days) proved to be a significantly related to the change in

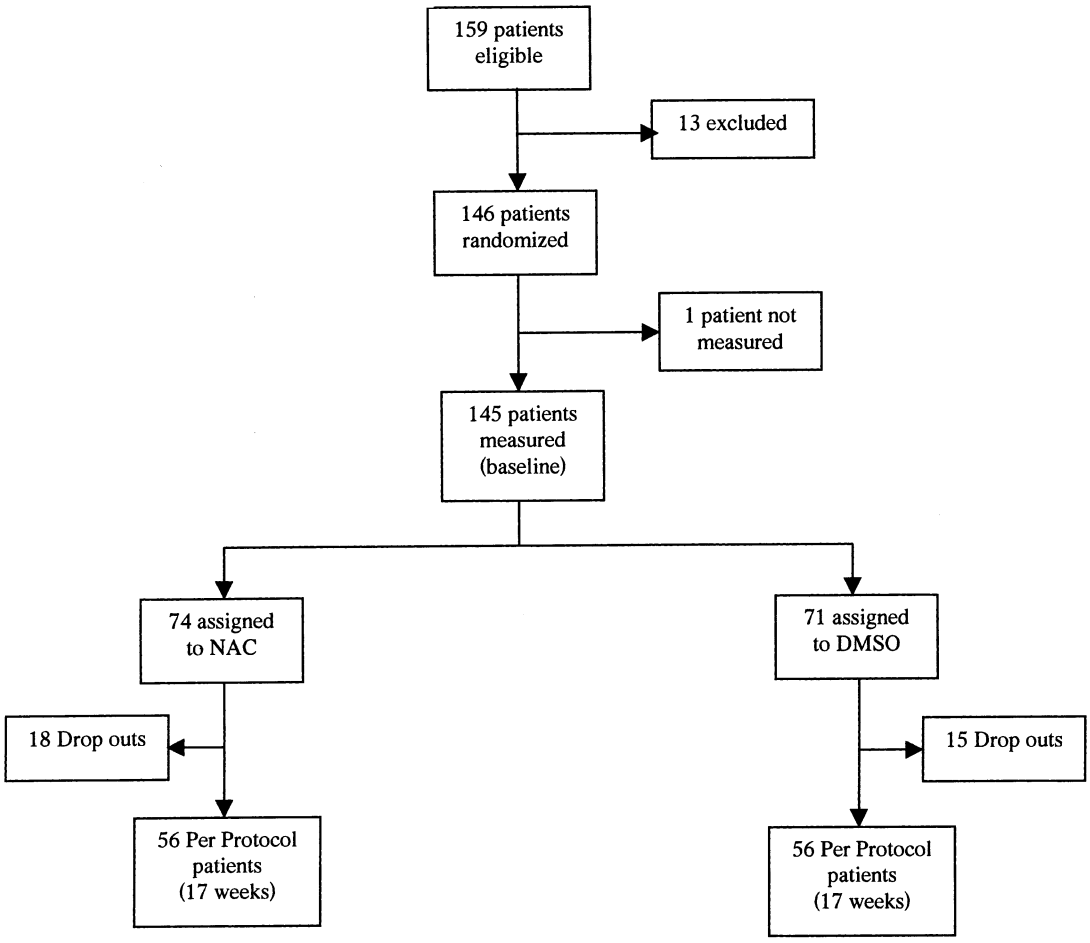

Fig. 1. Participating patients.

ISS ($P = 0.007$). The decrease in ISS was significantly greater for patients with a shorter duration. CRPS I type (i.e. primarily warm or cold) showed to be a significant modifier ($P = 0.003$) of the change in ISS. Both variables were therefore incorporated as factors in the analysis, and separate subgroup analyses were performed for warm (CRPS I-warm) and cold CRPS I (CRPS I-cold). The affected extremity (upper or lower) was also incorporated as a factor in the analysis for clinical and design reasons, leading to four factors in the ANOVA (i.e. treatment, extremity, CRPS I type and duration).

Table 1
Patient characteristics

	DMSO	NAC
N	71	74
Upper/lower extremity[a]	51/20	52/22
Female/male[a]	42/29	54/20
Smoking, yes/no[a]	25/46	29/45
Dominant side affected, yes/no[a]	36/35	35/39
Initially warm/cold CRPS I[a]	55/16	56/18
Age (years)[b]	50.08 (13.28)	48.94 (15.39)
Duration since trauma (days)[c]	86 (54, 116)	102 (64.5, 164.5)

[a] Counts.
[b] Mean (SD).
[c] Median (interquartile range).

3.2. Blinding

Blinding was evaluated in 85 patients and their physicians at the outpatient clinic. The assumptions of the patients about the received treatment were correct in 40 cases (47%), and incorrect in 28 (33%) cases. Physicians' assumptions were correct in 15 (18%) cases and incorrect in 12 (14%). The remaining numbers of patients and physicians had 'no idea'. In both evaluations, no significant differences were found between correct and incorrect assumptions (Sign Test: $P = 0.182$ and 0.701, respectively).

3.3. Main effects double-blind phase

No significant differences were found between DMSO and NAC on the primary effect measure in the first 17 weeks on intention to treat analysis ($F = 1.23$, $P = 0.270$) (Table 3). Both treatment groups showed a clinically relevant (27) decrease in ISS: the DMSO group decreased 9.05 (SD: 6.97) points, the NAC group decreased 8.31 (SD: 8.13)

Table 2
Baseline values effect measures

	DMSO ($n = 71$)		NAC ($n = 74$)	
ISS[a]	29.42	(6.67)	29.08	(6.50)
Radboud skills questionnaire[b]	2.95	(2.46, 3.78)	3.25	(2.2, 3.63)
Green test[b]	65	(34, 82)	59	(26, 90)
WSQ[a]				
Climbing stairs	4.22	(2.06)	4.88	(1.34)
Walking in home	3.03	(1.86)	3.50	(1.89)
Walking outside	5.50	(2.72)	5.24	(2.19)
Walking speed	4.56	(2.11)	3.75	(2.16)
QRSD[a]				
High seat	3.93	(3.29)	3.61	(2.83)
Low seat	5.56	(3.43)	5.29	(3.31)
Gait analysis[a]				
MRP[c] knee–ankle	24.4	(22.8)	6.9	(13.6)
MRP hip–ankle	37.0	(36.8)	17.7	(57.8)
MRP hip–knee	− 5.1	(28.6)	− 0.3	(20.7)
EuroQol[a]	0.533	(0.273)	0.535	(0.282)
COOP/WONCA[b]	2.83	2.17, 3.17	2.92	2.33, 3.33
SF-36[b]				
Phys. comp. sc.[d]	34.08	(29.71, 40.30)	36.06	(29.83, 41.28)
Ment. comp. sc.[e]	53.33	(42.59, 60.38)	48.70	(38.42, 58.06)

[a] Mean (SD).
[b] Median (interquartile range).
[c] Mean relative phase.
[d] Physical composite score.
[e] Mental composite score.

points (see Fig. 2). This decrease was statistically significant (Paired t test: intention to treat and per protocol for DMSO and NAC $P < 0.001$).

The results for the per protocol analysis were comparable (DMSO: 9.45 (SD: 7.49); NAC: 8.33 (SD: 7.75); $F = 0.92$, $P = 0.340$). In this analysis, CRPS I-warm improved significantly more ($F = 5.90$, $P = 0.017$) than CRPS I-cold.

Patients in both treatment groups improved on disability level, with the exception of a few items on the gait analysis (Table 3). Differences between both groups were not significant (Radboud skills questionnaire: $F = 0.19$, $P = 0.662$; Green test: $F = 0.62$, $P = 0.432$; walking ability questionnaires: F range 3.78–0.16, P range 0.061–0.687; gait analysis: F range 0.17–0.03, P range 0.684–0.959).

No significant differences were found between DMSO and NAC for the EuroQol ($F = 0.27$, $P = 0.602$), COOP/WONCA ($F = 0.03$, $P = 0.856$) and SF-36 (physical: $F = 1.32$, $P = 0.252$; mental: $F = 0.51$, $P = 0.475$). All effect measures on handicap level improved over a period of 17 weeks (Table 3).

3.4. Subgroup analysis double-blind phase

3.4.1. CRPS I-warm versus CRPS I-cold

Because CRPS I type proved to be a significant modifier in the main analysis, separate subgroup analyses were performed for CRPS-warm and -cold. A greater improvement was found in the CRPS I-warm group for DMSO than for NAC (Table 4). This difference was, however, not significant (intention to treat: $F = 3.24$, $P = 0.075$; per protocol: $F = 3.25$, $P = 0.075$). A significant difference in favor of NAC was found for patients with CRPS I-cold (intention to treat: $F = 8.12$, $P = 0.009$; per protocol: $F = 4.79$, $P = 0.040$). Patients in this subgroup seem to have minimal benefit from DMSO treatment.

No significant differences were found between DMSO and NAC on any effect measure on disability level for CRPS I-warm (Radboud skills questionnaire: $F = 2.72$, $P = 0.104$; Green test: $F = 0.67$, $P = 0.417$; walking ability questionnaires: F range 2.74–0.02, P range 0.115–0.891; gait analysis: F range 0.24–0.05, P range 0.631–0.741) and CRPS I-cold (Radboud skills questionnaire: $F = 0.06$, $P = 0.806$; Green test: $F = 3.46$, $P = 0.088$; walking ability questionnaires: F range 3.90–0.01, P range 0.070–0.936; gait analysis: F range 0.51–0.43, P range 0.490–0.524).

For the CRPS I-warm improvement on the physical composite score of the SF-36 was significantly greater for DMSO than NAC ($F = 11.93$, $P = 0.001$). No significant differences between DMSO and NAC were found for other effect measures on handicap level (EuroQol: $F = 0.01$, $P = 0.939$; COOP/WONCA: $F = 0.57$, $P = 0.452$; SF-36 mental: $F = 1.48$, $P = 0.228$).

No significant differences were found between DMSO and NAC on handicap level for CRPS I-cold (EuroQol:

Table 3
Intention to treat analysis: difference scores for effect measures

	Improvement at 17 weeks				Improvement at 52 weeks			
	DMSO ($n = 71$)		NAC ($n = 74$)		DMSO ($n = 71$)		NAC ($n = 74$)	
ISS[a]	9.05	(6.97)	8.31	(8.13)	11.77	(8.66)	10.56	(8.88)
Radboud skills[b]	0.92	(0.37, 1.32)	0.62	(0.13, 1.16)	1.26	(0.41, 1.71)	1.22	(0.36, 1.63)
Questionnaire								
Green test[b]	13.55	(−7.73, 84.35)	10.70	(−23.05, 79.92)	31.79	(5.77, 46.83)	28.49	(−0.1, 55.53)
WSQ[a]								
Climbing stairs	0.76	(3.39)	− 0.27	(2.83)	3.24	(4.45)	1.7	(4.61)
Walking in home	1.53	(2.39)	0.37	(1.59)	5.29	(4.34)	0.95	(4.07)
Walking outside	2.16	(3.16)	0.77	(1.72)	6.47	(5.89)	1.80	(3.59)
Walking speed	1.66	(1.66)	0.65	(1.84)	1.94	(2.41)	0.25	(1.97)
QRSD[a]								
High seat	1.70	(3.05)	0.87	(1.87)	4.23[c]	(4.05)	0.85	(2.66)
Low seat	0.8	(3.38)	0.0	(4.78)	2.88	(2.85)	0.45	(2.11)
Gait analysis[a]								
MRP[d] knee–ankle	10.7	(26.8)	− 1.2	(26.1)	4.5	(18.4)	− 11.6	(23.4)
MRP hip–ankle	38.0	(47.6)	23.9	(37.5)	36.6	(39.6)	7.4	(61.7)
MRP hip–knee	− 11.8	(46.5)	− 5.8	(20.0)	0.5	(35.9)	6.5	(28.2)
EuroQol[a]	0.159	(0.256)	0.077	(0.245)	0.198	(0.243)	0.101	(0.322)
COOP/WONCA[b]	0.33	(0, 0.83)	0.33	(−0.17, 0.71)	0.50	(0, 1.00)	0.33	(0, 0.71)
SF-36[b]								
Phys. comp. sc.[e]	6.28	(−0.65, 10.45)	2.17	(−2.03, 6.35)	10.56	(3.42, 16.22)	4.69	(−3.04, 11.62)
Ment. comp. sc.[f]	0.76	(−7.43, 6.25)	2.44	(−2.01, 8.05)	0.55	(−4.98, 6.22)	3.43	(−3.07, 11.91)

[a] Mean (SD).
[b] Median (interquartile range).
[c] Significant at $P = 0.05$.
[d] Mean relative phase.
[e] Physical composite score.
[f] Mental composite score.

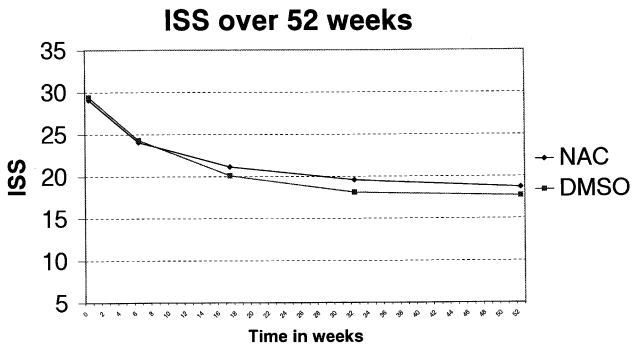

Fig. 2. Course of the ISS over 52 weeks. Reference points at 0, 6, 17, 32 and 52 weeks.

$F = 0.34$, $P = 0.563$; COOP/WONCA: $F = 0.04$, $P = 0.849$; SF-36 physical: $F = 0.84$, $P = 0.368$, mental: $F = 0.01$, $P = 0.941$).

3.4.2. Influence of duration

In general, the ratio CRPS I-warm to -cold patients in CRPS I of short duration did not differ significantly from this ratio in longer duration CRPS I (χ^2 test: $P = 0.073$). Patients with CRPS I-warm shorter than 90 days improved more on the COOP/WONCA and the mental composite score of the SF-36 (res. $F = 7.51$, $P = 0.008$; $F = 14.99$, $P < 0.001$). This difference was more prominent for longer duration CPRS I patients treated with DMSO, which scored significantly lower ($F = 11.28$, $P = 0.001$).

Patients with CRPS I-cold longer than 90 days scored significantly lower on the EuroQol ($F = 5.74$, $P = 0.024$), COOP/WONCA ($F = 4.64$, $P = 0.041$) and physical composite score of the SF-36 ($F = 5.18$, $P = 0.032$). On the EuroQol, patients with a short duration of CRPS I of the lower extremity improved significantly more ($F = 5.93$, $P = 0.022$). Furthermore, a significant interaction was found between treatment effect and duration for the SF-36 mental composite score ($F = 15.06$, $P < 0.001$); the highest improvement was obtained by patients with CRPS I shorter than 90 days treated with DMSO.

3.4.3. Influence of localization

A significant interaction was found on the ISS between treatment effect and affected extremity ($F = 4.02$, $P = 0.048$). Table 4 shows that in the DMSO group lower extremity CRPS I patients improve more, and in the NAC group upper extremity CRPS I patients show a greater improvement.

3.5. Main effects follow up

In the second phase of the study, eight additional patients dropped out due to interfering pathology ($n = 2$), discontentment with treatment/research ($n = 3$) and other reasons ($n = 3$).

No statistical differences were found between DMSO and NAC on change in ISS over 52 weeks (intention to treat; $F = 0.78$, $P = 0.380$). The decrease in ISS in the follow up period was moderate in both groups (DMSO: 2.89 (SD: 6.26); NAC: 2.71 (SD: 6.07)) (Table 3).

On disability level, a significant difference was found at 52 weeks on the item 'rising and sitting down – high seat' of the QRSD ($F = 6.94$, $P = 0.013$). No other significant differences on other effect measures on disability level (Table 3).

We found no significant differences between DMSO and NAC on the EuroQol, COOP/WONCA and SF-36 at 52 weeks (Table 3).

3.5.1. Influence of duration

In general, patients with CRPS I shorter than 90 days improved significantly more on the COOP/WONCA and the physical and mental composite score of the SF-36 (res. $F = 9.32$, $P = 0.003$; $F = 4.35$, $P = 0.04$; $F = 10.09$, $P = 0.002$). Also, interaction between treatment effect and duration revealed patients treated with DMSO with CRPS I longer than 90 days to score significantly lower on the SF-36 mental composite score: ($F = 7.68$, $P = 0.007$).

3.5.2. Influence of localization

Patients with lower extremity CRPS I scored significantly lower on the COOP/WONCA ($F = 7.67$, $P = 0.007$) and the physical composite score of the SF-36 ($F = 3.97$,

Table 4
Intention to treat analysis at 17 and 52 weeks. ISS score for warm and cold subgroups

	Improvement at 17 weeks				Improvement at 52 weeks			
	DMSO		NAC		DMSO		NAC	
Warm CRPS I[a]	$n = 55$		$n = 56$		$n = 55$		$n = 56$	
Upper extremity	11.47	(8.61)	8.97	(8.26)	13.32	(10.10)	10.76	(9.15)
Lower extremity	13.40	(8.02)	6.41	(7.22)	17.11	(7.94)	10.75	(8.96)
Cold CRPS I[a]	$n = 16$		$n = 16$		$n = 16$		$n = 16$	
Upper extremity	1.37	(4.80)	9.87	(9.49)	1.75	(6.92)	12.75	(6.43)
Lower extremity	3.00	(4.34)	6.63	(7.52)	9.75	(10.47)	7.50	(9.01)

[a] Mean (SD).

$P = 0.049$). An interaction between treatment effect and affected extremity was found for the COOP/WONCA, where lower extremity CRPS I patients treated with DMSO performed significantly better ($F = 5.74$, $P = 0.018$).

3.6. Subgroup analysis follow up

3.6.1. Treatment after 17 weeks

Based on individual results on the ISS, 32 patients were able to stop treatment (i.e. ISS $\leq$ 15 points), 46 patients could continue (improvement ISS $\geq$ 6 points) the medication received in the double-blind phase and 34 had to switch from one experimental treatment to the other (improvement ISS $\leq$ 5 points). No significant differences were found between the number of patients treated with NAC or DMSO among 'stoppers', patients continuing medication or 'switchers'. Significant differences ($F = 7.99$; $P = 0.006$) were found in improvement on the ISS after 17 weeks (stop: −0.79 (SD: 6.30); continue: 3.93 (SD: 5.49); switch: 3.55 (SD: 6.12)).

3.6.2. CRPS I-warm vs. CRPS I-cold

No significant differences (intention to treat analysis) were found between DMSO and NAC for CRPS I-warm ($F = 1.36$, $P = 0.248$) and CRPS I-cold ($F = 3.60$, $P = 0.070$) subgroups on the ISS at 52 weeks. For CRPS I-warm, patients treated with DMSO (14.18 (SD: 8.83) points) improved more than NAC patients (10.76 (SD: 9.10) points), whereas for CRPS I-cold patients improved more with NAC (9.94 (SD: 7.57) points) than DMSO (5.75 (SD: 8.20) points).

Patients with lower extremity CRPS I-warm treated with DMSO improved significantly more on all items of the WSQ and QRSD (except for 'climbing stairs') than patients treated with NAC (F range 7.43–5.57, P range 0.014–0.031). No additional significant differences were found on any of the effect measures on disability level for CRPS I-warm or -cold.

A significantly greater improvement on the physical composite score of the SF-36 was found for DMSO than NAC for CRPS I-warm ($F = 4.77$, $P = 0.032$).

For CRPS I-cold, no significant differences were found between DMSO and NAC on any of the quality of life charts.

3.6.3. Influence of duration

Patients with CRPS I-warm shorter than 90 days, improved significantly more on the COOP/WONCA ($F = 4.47$, $P = 0.038$). Patients treated with DMSO with CRPS I-warm longer than 90 days, however, obtained the lowest scores ($F = 4.09$, $P = 0.047$) on the mental composite score of the SF-36.

In the cold subgroup, patients with a duration of CRPS I longer than 90 days scored lower on the physical composite score of the SF-36 ($F = 4.70$, $P = 0.041$) and the COOP/WONCA ($F = 5.05$, $P = 0.034$).

3.6.4. Influence of localization

In general, patients with CRPS I-warm with lower extremity CRPS I showed a greater improvement on the COOP/WONCA than patients with upper extremity CRPS I ($F = 5.99$, $P = 0.017$). A significant interaction was found for the cold subgroup between treatment effect and affected extremity; patients with upper extremity CRPS treated with NAC obtained the highest scores, and patients treated with DMSO the lowest ($F = 5.52$, $P = 0.027$)

3.7. Co-interventions and side effects

Medicinal consumption was equally distributed over both treatment groups. In the blinded phase, however, patients in the NAC groups used more paracetamol 500 mg than the DMSO group (mean 6.1 vs. 0.78 per patient). On the other hand, tramadol consumption was higher in the DMSO group (mean 4.4 mg in drops/5.82 in capsules vs. 0 mg in drops/1.9 in capsules). These differences were, however, not significant. Most prominent side effects were the distinct odor and skin reactions of DMSO, and sulfur-like taste and stomach reactions of NAC. In eight cases, three in the DMSO group due to severe skin reactions and five in the NAC group due to severe stomach complaints, these side effects were reason for dropping out.

4. Discussion

The results of the present study show that DMSO 50% and *N*-acetylcysteine are, overall, equally effective in treatment of CRPS I. For both interventions a clinically relevant improvement on the primary effect measure is seen, in keeping with the ISS responsiveness found by Oerlemans et al. (1998). They found a decrease of 4.8 points to be in agreement with an overt decrease of symptoms based on clinical observation.

Although no significant differences were found on the primary effect measure in the main analysis, DMSO 50% generally showed more improvement. The latter was emphasized by a few significant differences in favor of DMSO 50% on disability level for lower extremity CRPS I. These findings support the results found in other studies (Goris et al., 1987; Langendijk et al., 1993; Geertzen et al., 1994; Zuurmond et al., 1996) concerning the effectiveness of DMSO in CRPS I. The fact that both DMSO and *N*-acetylcysteine provided a clinically relevant and statistically significant improvement over 17 weeks, may render further support for a possible inflammatory mechanism is CRPS I.

Subgroup analysis revealed that differences in effectiveness of both interventions were present, attributable to CRPS I type. Warm CRPS I patients seem to benefit more from DMSO 50% treatment, whereas *N*-acetylcysteine is more effective in the cold CRPS I subgroup. No unambig-

uous explanation for this difference is available at present due to uncertainty concerning the pathophysiological mechanism involved in CRPS I and lack of fundamental data of DMSO 50% and *N*-acetylcysteine in CRPS I. These differences in effect may be related to pharmacological and physiological properties of both substances. DMSO 50% is a particular scavenger for the hydroxyl radical. Besides that, anti-inflammatory, local anesthetic, weakly bacteriostatic and diuretic effects have been reported (Reilly et al., 1991; Yu and Quinn, 1994). *N*-acetylcysteine on the other hand has been shown to directly reduce hydroxyl radicals, hydrogen peroxide and hypochlorus acid, and anti-inflammatory activity is reported by diminishing the release of the pro inflammatory mediator TNF-α. Furthermore, the cysteine group of the molecule detaches in the intestinal tract, and serves as a prodrug for the development of glutatione (GSH), and thus could provide indirect antioxidant effects (Reilly et al., 1991; Cotgreave, 1997). As the possibility of more than one mechanism involved in pathogenesis of CRPS I (Schott, 1995) has been reported, possibly the appearance of warm and cold CRPS I could be attributed to a two different underlying mechanisms. A speculative hypothesis could therefore be that the different effects found for both substances for either warm or cold CRPS I, are due to differences in modes of action of both medications interacting with different pathological mechanisms. A chance finding, however, cannot be ruled out at this point. Additional prospective research based on groups matched according to CRPS I type is warranted in order to confirm these findings. The cold CRPS I group in particular, which was small ($n = 34$), should be investigated more extensively. Since treatment effects were generally lower in this subgroup (see also Table 4), other interventions for this subgroup should be considered, for instance, vasodilatatory medication to enhance circulation in the affected area.

Longer duration of the complaint tended to have a negative influence on treatment outcome. Similar results were found by Muizelaar et al. (1997) when investigating the effects of nifedipine and phenoxybenzamine, and underline the general opinion that early intervention is preferable in treatment of CRPS I (Birklein et al., 2000). Also for this specific subgroup, other treatment methods should be considered and investigated. However, research on CRPS I appears to be focused either on early intervention or chronic CRPS I. No guidelines could be found in literature specifically addressing treatment of patients of 'medium' duration (i.e. 4–12 months).

It should be noted, however, that in general longer duration of CRPS I is considered to be associated with a cold temperature of the affected extremity (Birklein et al., 1998), and thus it might be argued, whether the duration or the CRPS I type is responsible for the effects found. In our sample, however, the number of patients with CRPS I-warm exceeded that of CRPS I-cold in the subgroup of patients with longer (i.e. 90 days or more) duration of CRPS I. Furthermore, the ratio CRPS I-warm to -cold patients in CRPS I of short duration did not differ significantly from this ratio in longer duration CRPS I. These findings are in keeping with those by Bruehl et al. (2002) who found no evidence for temporally derived staging of CRPS based on clinical features of the complaint.

Also, influence of the affected extremity was found for some effect measures. Although this difference was not found for the primary effect measure in the main analysis, and the number of patients with lower extremity CRPS I was small, the differences found in secondary effect measures suggest that upper and lower extremity CRPS I react differently to the interventions in the present study. As no scientific medical explanation for this can be provided, these findings should be considered as artifacts at this point. Future research should control for both the duration and the affected extremity.

One point of discussion is the lack of a placebo-control group in this study. Four studies (Goris et al., 1987; Langendijk et al., 1993; Geertzen et al., 1994; Zuurmond et al., 1996), three of which were blinded RCT's, showed positive results with respect to DMSO 50% treatment. Significant differences in favor of DMSO treatment compared to placebo were found in three of these studies (Goris et al., 1987; Langendijk et al., 1993; Zuurmond et al., 1996). DMSO is regarded as standard therapy for CRPS I in the Netherlands since 1993 (Reflex Sympathetic dystrophy guideline panel, 1993). We therefore decided to, in the patients' best interest, not to apply placebo control. We do

Table A1
Conversion of the VAS, McGill – number of words chosen total, AROM, temperature and volume into the impairment level sumscore (ISS)[a]

VAS (mm)	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–100
McGill – NWCT	0–2	3–4	5–6	7–8	9–10	11–12	13–14	15–16	17–18	19–20
AROM[b]	5–6	7–8	9–10	11–12	13–14	15–16	17–18	19–20	21–22	23–25
Temperature difference (°C)	0–0.3	0.4–0.5	0.6–0.7	0.8–0.9	1.0–1.1	1.2–1.3	1.4–1.5	1.6–1.7	1.8–1.9	≥ 2.0
Volume difference (ml)[c]	3.5%	5%	6.5%	8%	9.5%	11%	12.5%	14%	15.5%	> 15.5%
ISS	1	2	3	4	5	6	7	8	9	10

[a] VAS, visual analogue scale; NWCT, number of words chosen total; AROM, active range of motion; Temp, temperature.

[b] Points for the percentage of affected range/unaffected range: 1 point for >95%; 2 points for 94–85%; 3 points for 84–64%; 4 points for 64–25%; 5 points for <25%.

[c] Volume difference relative to the unaffected limb, based on volume classes. The percentage expresses the average difference with respect to the volume class concerned.

recognize, however, that since only a few placebo controlled studies on DMSO 50% have been performed, the possibility exists that the results found in these studies might be artifacts, which cannot be excluded in the present study due to lack of placebo control. However, additional analysis of the results show that the percentage of patients benefiting from both therapies is well over that considered to be attributable to placebo response (i.e. 30% (Beecher and Boston, 1955)), even while taking into account the possibly higher placebo response rate reported for CRPS patients (up to 57.7% (Verdugo and Ochoa, 1991; Ochoa et al., 1994; Verdugo and Ochoa, 1994)). In our study, 80.7% of patients showed improvement at 17 weeks, of which 70.9% showed a clinically relevant improvement (improvement ISS $\geq$ 6 points). At 52 weeks 85.6% of patients showed improvement on the ISS.

A problem closely related to the issue of placebo response is the question of bioavailability of both substances in CRPS I patients. DMSO is known for it's carrier properties and is rapidly absorbed through the intact dermis and other membranes, and is reported to retain a constant plasma concentration up to 3 days following initial application (David, 1972). Follow up of one CRPS I patient revealed plasma blood concentrations varying from 1.40 ml/l at 12 h to 1.14 ml/l at 20 h after last application of one daily dose (i.e. five times application of DMSO 50% to the extremity) as used in the present study. No such data are available for *N*-acetylcysteine in CRPS I patients. Bioavailability in healthy humans has been reported to be 4–10% for oral administration. *N*-acetylcysteine does not accumulate in plasma after repeated 200 mg (Cotgreave, 1997) or 600 mg doses (Borstrom and Kagedal, 1990). Judging from single dose studies carried out for 400 and 800 mg *N*-acetylcysteine (Pendyala and Creaven, 1995), we estimate the plasma concentration for the 600 mg dose used in our study to lie between 2 and 5 mg/l at 1 h after administration. Although low doses of *N*-acetylcysteine have been reported to work effectively as a scavenger (Bast et al., 1991), further research into the pharmacokinetics and pharmacodynamics of *N*-acetylcysteine in CRPS I patients is warranted to clarify relationship between bioavailability and effectiveness of this substance. However, it is possible that not the pure form of N-acetylcysteine, but it's deacetylated form provides the primary mode of action in restoring the oxidant–antioxidant balance. In that respect, the effects of liberated cysteine and it's function as a GSH precursor should be investigated further in CRPS-I patients

We conclude that both DMSO 50% and *N*-acetylcysteine are equally effective in treatment of CRPS I. Treatment for cold CRPS I with DMSO 50% seems unadvisable, and *N*-acetylcysteine would be the preferred treatment. Warm CRPS I patients benefit more from DMSO 50% treatment. Physicians and researchers should take into account the possible disadvantageous influence of longer duration of CRPS I, and be aware of differences in treatment effect between upper and lower extremity CRPS I.

Acknowledgements

This study was supported by a research grant from the Dutch National Health council (College voor Zorgverzekeringen), the Netherlands. The authors would like to thank Mr P.E.T. Burm for his assistance with data collection, Professor Dr R.J.A Goris and Dr L. van der Laan for screening potential patients and supervising this research in Nijmegen, and the staff of the occupational therapy departments of the Vrije Universiteit medical center and Nijmegen medical center for their treatment of participating patients.

Appendix A

The conversion of the VAS, McGill is given in Table A1.

References

Altman DG. Practical statistics for medical research, New York, NY: Chapman and Hall, 1999.

Bast A, Haenen GRMM, Doelman CJA. Oxidants and antioxidants: state of the art. Am J Med 1991;91(Suppl 3c):2s–13s.

Beecher HK, Boston MD. The powerful placebo. J Am Med Assoc 1955;159:1602–1606.

Birklein F, Riedl B, Claus D, Neundorfer B. Pattern of autonomic dysfunction in time course of complex regional pain syndrome. Clin Auton Res 1998;8:79–85.

Birklein F, Riedl B, Sieweke N, Weber M, Neundorfer B. Neurological findings in complex regional pain syndromes – analysis of 145 cases. Acta Neurol Scand 2000;101:262–269.

Borstrom L, Kagedal B. Dose dependent pharmacokinetics of *N*-acetylcysteine after oral dosing to man. Biopharm Drug Dispos 1990;11:131–136.

Brazier J. The SF-36 health survey questionnaire – a tool for economists. Health Econ 1993;2:213–215.

Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? Pain 2002;95:119–124.

Bruehl S, Lubenow TR, Nath H, Ivankovich O. Validation of thermography in the diagnosis of reflex sympathetic dystrophy. Clin J Pain 1996;12:316–325.

Buurke JH, Grady JH, de Vries J, Baten CTM. Usability of thenar eminence orthosis: report of a comparative study. Clin Rehabil 1999;13:288–294.

Christensen K, Jensen EM, Noer I. The reflex sympathetic dystrophy: response to treatment with systemic corticosteroids. Acta Chir Scand 1982;148:653–655.

Cotgreave IA. N-acetylcysteine: pharmacological considerations and experimental and clinical applications. Adv Pharmacol 1997;38:205–227.

David NA. The pharmacology of dimethyl sulfoxide. Annu Rev Pharmacol 1972;12:353–742.

EuroQol group. EuroQol – a new facility for measuring health related quality of life. Health Policy 1990;16:199–208.

Galer BS, Henderson J, Perander J, Jensen PM. Course of symptoms and quality of life measurement in complex regional pain syndrome: a pilot survey. J Pain Symptom Manage 2000;20:286–292.

Geertzen JHB, de Bruijn H, de Bruijn-Kofman AT, Arendzen JH. Reflex sympathetic dystrophy: early treatment and psychological aspects. Arch Phys Med Rehabil 1994;75:442–446.

Goris RJA, Dongen LMV, Winters HAH. Are toxic oxygen radicals involved in the pathogenesis of reflex sympathetic dystrophy? Free Radic Res Commun 1987;3:13–18.

Green M. Hand assessment. Br J Occup Ther 1974;37:215–218.
Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain. Pain 1997;73:123–139.
Langendijk PNJ, Zuurmond WWA, Apeldoorn HAC, van Loenen AC, de Lange JJ. Good results of treatment of reflex sympathetic dystrophy with a 50% dimethyl sulfoxide cream [Dutch]. Ned Tijdschr Geneesk 1993;137:500–503.
Muizelaar JP, Kleyer M, Hertogs IA, DeLange DC. Complex regional pain syndrome (reflex sympathetic dystrophy and causalgia) management with calcium channel blocker nifedipine and/or the alpha-sympathetic blocker phenoxybenzamine in 59 patients. Clin Neurol Neurosurg 1997;99:26–30.
Ochoa JL, Verdugo RJ, Campero M. Pathophysiological spectrum of organic and psychogenic disorders in neuropathic pain patients fitting the description of causalgia or reflex sympathetic dystrophy. In: Gebhardt GF, Hammond DL, Jensen TS, editors. Procedings of the 7th world congress of pain, Paris, France, Seattle, WA: IASP Press, 1994. pp. 483–494.
Oerlemans HM, Cup EHC, Boo de T, Goris RJA, Oostendorp RAB. The Radboud skills questionnaire: construction and reliability in patients with reflex sympathetic dystrophy of one upper extremity. Disabil Rehabil 2000a;22:233–245.
Oerlemans HM, Goris RJA, Oostendorp RAB. Impairment level sumscore in reflex sympathetic dystrophy of one upper extremity. Arch Phys Med Rehabil 1998;79:979–990.
Oerlemans HM, Graff MJL, Dijkstra-Hekking JBG, Boo de T, Goris RJA, Oostendorp RAB. Reliability and normal values for measuring the skin temperature of the hand with an infrared tympanic thermometer: a pilot study. J Hand Ther 1999;12:284–290.
Oerlemans HM, Oostendorp RAB, Boo de T, Laan van der L, Severens JL, Goris RJA. Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type1. Arch Phys Med Rehabil 2000b;81:49–56.
Oyen WJG, Arntz IE, Claessen RAMJ, van der Meer JWM, Corstens FHM, Goris RJA. Reflex sympathetic dystrophy of the hand: an excessive inflammatory response? Pain 1993;55:151–157.
Pendyala L, Creaven PJ. Pharmacokinetic and pharmacodynamic studies of *N*-acetylcysteine a potential chemopreventive agent during a phase I trial. Cancer Epidemiol Biomarkers Prev 1995;4:245–251.
Perez RSGM, Kwakkel G, Zuurmond WWA, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS): a research synthesis of 21 randomised clinical trials. J Pain Symptom Manage 2001a;21:511–526.
Perez RSGM, Burm PET, Rijnsburger ER, Zuurmond WWA, Lange de JJ. Predictive value of pain, temperature, volume and range of motion in complex regional pain syndrome type I. Anesthesiology 2001b;95:A803.
Reilly PM, Schiller HJ, Bulkley GB. Pharmacologic approach t tissue injury mediated by free radicals and other reactive oxygen metabolites. Am J Surg 1991;161:488–503.
Reflex sympathetic dystrophy guideline panel. Recommendations for the approach of reflex sympathetic dystrophy patients. Clinical practice guideline. The national project on quality assurance of invasive anesthesiological pain control. Utrecht: The Netherlands WHO collaborating center for quality assurance in health care (CBO); 1993.
Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of the linear analogue scale for evaluating pain. Anesthesia 1979;31:1191–1198.
Roorda RD, Roebroeck ME, Lankhorst GJ, van Tilburg T. De vragenlijst loopvaardigheid: hiërarchische schalen om beperkingen in het opstaan en lopen te meten [Dutch]. Revalidata 1996a;18:34–38.
Roorda LD, Roebroeck ME, Lankhorst GJ, Tilburg van T, Bouter LM. Measuring functional limitations in rising and sitting down: development of a questionnaire. Arch Phys Med Rehabil 1996b;77:663–669.
Scholten JHG, Weel van C. Functional status assessment in family practice. The Dartmouth coop functional assessment charts/wonca, Lelystad: Meditext, 1992.
Schott GD. An unsympathetic view of pain. Lancet 1995;345:634–636.
Scott J, Huskinsson EC. Graphic representation of pain. Pain 1979;2:175–184.
Smith CJ, Velayos EE, Hiad CJ. A method for measuring swelling of hands and feet: normal variation and applications in inflammatory joint disease. Acta Rheumatol Scan 1963;9:293–305.
Stanton-Hicks M, Jänig W, Hasselbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain 1995;63:127–133.
Uematsu S, Edwin DH, Jankel WR, Kozikowski J, Trattner M. Quantification of thermal asymmetry. J Neurosurg 1988;69:552–555.
Vanderiet K, Adriaensens H, Carton H, Vertommen H. The McGill pain questionnaire constructed for the Dutch language (MPQ-DV). Preliminary data concerning reliability and validity. Pain 1987;30:395–408.
van der Laan L, Goris RJA. Reflex sympathetic dystrophy, an exaggerated inflammatory response? In: Cooney WP, Schuind F, editors. Hand clinics, Philadelphia, PA: Saunders, 1997.
Van der Laan L, Kapitein PJC, Oyen WJG, Verhofstad AAJ, Hendriks T, Goris RJA. A novel animal model to evaluate oxygen derived free radical damage in soft tissue. Free Radic Res 1997a;26:363–372.
Van der Laan L, Oyen WJG, Verhofstad AAJ, Tan ECTH, Ter Laak HJ, Gabreëls-Festen AAWM, Hendriks T, Goris RJA. Soft tissue repair capacity after oxygen derived free radical induced damage in one hind limb of the rat. J Surg Res 1997b;72:60–69.
Van der Laan L, ter Laak HJ, Gabreëls-Festen AAWM, Goris RJA. Histopathological findings in chronic reflex sympathetic dystrophy. Neurology 1998;51:20–25.
Veldman PHJM, Dunki Jacobs PB. Reflex sympathetic dystrophy of the head; a case report and discussion of diagnostic criteria. J Trauma 1994;36:119–121.
Veldman PHJM, Reynen JAM, Arntz IE, Goris RJA. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;34:1012–1016.
Verdugo RJ, Ochoa JL. High incidence of placebo responders among chronic neuropathic pain patients. Ann Neurol 1991;30:229.
Verdugo RJ, Ochoa JL. Sympathetically maintained pain. Phentolamine blocks question the concept. Neurology 1994;44:1003–1010.
Wagenaar RC, van Emmerik RAE. Dynamics of pathological gait. Hum Mov Sci 1994;13:441–447.
Yu Z-W, Quinn PJ. Dimethyl sulpoxide: a review of its applications in cell biology. Biosci Rep 1994;14:259–281.
Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomized trial. Lancet 1999;345:2025–2028.
Zuurmond WWA, Langendijk PHJ, Bezemer PD, Brink HEJ, Lange de JJ, Loenen van AC. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. Acta Anesthesiol Scand 1996;40:364–637.