

## Original Reports

# Treatment of Patients With Complex Regional Pain Syndrome Type I With Mannitol: A Prospective, Randomized, Placebo-Controlled, Double-Blinded Study

Roberto S. Perez,<sup>\*,†,‡</sup> Elien Pragt,<sup>§</sup> José Geurts,<sup>†,||</sup> Wouter W. Zuurmond,<sup>\*,†</sup> Jaap Patijn,<sup>||</sup> and Maarten van Kleef<sup>†,§,||</sup>

<sup>\*</sup>VU University Medical Center, Department of Anesthesiology, Amsterdam, The Netherlands.

<sup>†</sup>Research Consortium Trauma RElated Neuronal Dysfunction (TREND), Delft, The Netherlands.

<sup>‡</sup>Research Institute for Extramural Medicine (EMGO), Amsterdam, The Netherlands.

<sup>§</sup>University Hospital Maastricht, Department of Anesthesiology, Maastricht, The Netherlands; and

<sup>||</sup>Pain Knowledge Center Maastricht, Maastricht, The Netherlands.

**Abstract:** To assess the effects of intravenous administration of the free radical scavenger mannitol 10% on complaints associated with complex regional pain syndrome Type I (CRPS I), a randomized, placebo-controlled, double-blinded trial was performed. Forty-one CRPS I patients according to the Bruehl et al diagnostic criteria, were included in 2 outpatient pain clinics of 2 university medical centers and randomly assigned to receive either 10% mannitol iv in 1 L 0.9% NaCl in 4 hours for 5 consecutive days or equal volumes of 0.9% NaCl (placebo). Patients in both groups received physical therapy according to protocol and rescue pain medication if required. Complaints on impairment and disability level and quality of life were assessed up to 9 weeks after baseline, with primary measurement points at 2, 6, and 9 weeks. Monitoring of pain using the visual analogue scale took place continuously during the course of the trial. Except for a significant improvement on a subscale of the Jebsen-Taylor hand function test, no significant differences were found between mannitol and placebo treatment. Changes in both groups in the course of the trial were small and clinically irrelevant on all measurement indices. We conclude that intravenous administration of 10% mannitol is not more effective than placebo in reducing complaints for CRPS I patients and provides no addition to already-established interventions for CRPS I. Whether 10% mannitol can provide beneficial effects for subgroups of CRPS I patients with a pathophysiological profile more closely fitting the presumed mode of action for this intervention remains to be established.

**Perspective:** This article addresses the efficacy of the intravenous administration of the free radical scavenger mannitol for treatment of CRPS type 1. This intervention is not more effective than placebo in reducing complaints for CRPS I patients and provides no addition to already-established interventions for CRPS I.

© 2008 by the American Pain Society

**Key words:** Complex regional pain syndrome, mannitol, scavengers.

Received September 27, 2007; Revised February 6, 2008; Accepted February 12, 2008.

Supported by Pain Knowledge Center Maastricht.

Address reprint requests to Dr. Robert S. Perez, VU University Medical Center, Department of Anesthesiology, PO Box 7057, 1007 MB, Amsterdam, The Netherlands. E-mail: [rsgm.perez@vumc.nl](mailto:rsgm.perez@vumc.nl)

1526-5900/\$34.00

© 2008 by the American Pain Society

doi:10.1016/j.jpain.2008.02.005

Complex regional pain syndrome type I (CRPS I), formerly known as reflex sympathetic dystrophy or posttraumatic dystrophy, is a painful, potentially disabling syndrome that usually affects the distal part of the extremity (eg, feet and hands). The disorder is characterized by a variety of autonomic and vasomotor disturbances, of which diffuse pain, spreading edema, temperature disturbances, and functional impairment are the most prominent.<sup>13,15,34</sup> Occurrence of CRPS I differs

**Table 1. Patient Characteristics of the Study Sample**

	TOTAL SCORE	PLACEBO	MANNITOL	T	DF	P VALUE
Gender (n)	41	19	22			1*
Male, mean (%)	8 19.5%	4	4			
Female, mean (%)	33 80.5%	15	18			
Age, mean (SD)	45.3 (12)	43.9 (12.9)	46.5 (11.5)	-0.7	39	.513
Average number of patients using pain medication in week 0 (baseline), mean (SD)		10.2 (0.9)	10.8 (1.2)	-1.1	10	.310
Of which acetaminophen		1.0 (0.8)	0.7 (0.5)			
NSAIDS		2.5 (0.5)	3.3 (1.0)			
Anticonvulsants/antidepressants		4.3 (1.2)	4.5 (0.5)			
Weak/strong opioids		2 (0.6)	2.1 (0.7)			
Education						.538*
†Elementary (n)	20	11	9			
‡Vocational (n)	21	8	13			

Abbreviation: NSAIDS, nonsteroidal anti-inflammatory drugs.

\*Fisher exact test.

†≤10 years of education.

‡>10 years of education.

with the initiating event, whereby incidences up to 37% have been reported after wrist fractures.<sup>5</sup> Various underlying mechanisms have been suggested for CRPS I, none of which are able to completely explain the variety of clinical features exhibited by CRPS I patients. A recent hypothesis suggests that multiple mechanisms could be working in CRPS I, whereby the predominance of 1 mechanism may lead to a distinct clinical phenotype.<sup>8</sup>

One of these proposed mechanisms is an inflammatory response, in which an unknown stimulus induces an excessive production of inflammatory mediators,<sup>18,19</sup> leading to an imbalance in production and clearance of toxic oxygen radicals.<sup>29</sup> An excessive production of oxygen radicals subsequently results in destruction of healthy tissue. Besides positive results found for the use of free radical scavengers dimethyl sulfoxide (DMSO) and *n*-acetylcysteine for CRPS I treatment in controlled studies,<sup>14,16,31,36</sup> the use of intravenous mannitol, a known oxygen radical scavenger, has been suggested in the literature as a possible treatment for CRPS I.<sup>16,37</sup>

However, the efficacy of this treatment method has not been investigated in a controlled trial. Therefore, the aim of the present study was to determine whether intravenous mannitol infusion is an effective treatment in reducing pain and improvement of function of CRPS I by determining its effects compared with those of placebo.

## Methods

### Sample and Data Collection

A prospective, randomized, placebo-controlled study was performed in 2 outpatient clinics for pain management of the university hospitals in Amsterdam and Maastricht in The Netherlands. To participate in the study, patients had to meet the Bruehl et al<sup>9,17</sup> criteria for CRPS I: (1) Report of at least 1 symptom of sensory, vasomotor, sudomotor/edema, and motor/trophic nature and dis-

play at least 1 sign in 2 of these categories; (2) continuing pain, which is disproportionate to any inciting event should be present. The patients had to be older than 18 years of age and younger than 75. Pain as measured on a 10-cm visual analog scale (VAS) had to be more than 4 cm on average in the preceding week, based on a single rating.<sup>12</sup> Radical scavengers such as DMSO and *n*-acetylcysteine had to be stopped for more than 1 week before the beginning of the trial. No specific inclusion criteria with respect to CRPS I subgroups,<sup>8</sup> patient profile, or duration of CRPS I was used. Patients were excluded in the case of pregnancy or lactation; known severe kidney, liver, heart, or lung disease; known nerve damage in the affected area; active infection; mental retardation; involvement in a legal procedure because of CRPS I; the use of a pacemaker or defibrillator and in the case another (second) complaint interfering with the functional tests and VAS ratings was present. The medical ethics committee of both participating institutions approved the study. All patients gave written informed consent.

After inclusion in the study, the patients were randomly assigned to receive either 10% mannitol, administered over 4 hours by an intravenous infusion of 1 L each day for a period of 5 days, or 1 L 0.9% NaCl (placebo), administered in the same fashion, using a computer-generated table of random numbers. The intravenous cannula was inserted into the unaffected extremity to prevent further increase of complaints in the affected extremity. Patients in both groups received standardized physical therapy according to an evaluated treatment protocol.<sup>28</sup> Continued use or use of rescue pain medication according to the WHO pain ladder (ie, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDS], anticonvulsants/antidepressants, weak/strong opioids) was allowed during the course of the trial. Patients, researchers, and physicians administering the treatment were blinded until the end of the trial.

**Table 2. Baseline Values of the Outcome Measurements**

		PLACEBO	MANNITOL	T	DF	P VALUE
VAS, mean (SD)		48 (23.6)	53.1 (17.5)	-0.8	39	.431
Duration of symptoms months, median (IQR)		14 (5-30)	6.5 (4-29)			.401†
Duration of symptoms <12 mo (n)	29	13	16			1*
Duration of symptoms >12 mo (n)	12	6	6			
CRPS side left, n (%)	24	12	12			.752*
CRPS side right, n (%)	17	7	10			
Temperature diff in °C, median (IQR)	39	0.5 (0.1-1.8)	0.5 (0.4-1.3)			.593†
CRPS warm (n)	8	2	6			.419*
CRPS cold (n)	18	8	10			
Volumetry (diff in mL), median (IQR)	39	25 (9.3-53.7)	35 (16-60)			.414†
Hand function tests						
Jebsen-Taylor hand function test (n)	22	10	12			
Turning cards diff, median (IQR)		3.8 (1.5-12.2)	2.5 (1.3-5.5)			1†
Moving small objects diff, median (IQR)		2.3 (1.2-7.1)	3.8 (2.8-4.9)			.254†
Simulated feeding diff, median (IQR)		2.6 (-0.4-12.1)	1.6 (0.5-3.7)			.683†
Stacking checkers diff, median (IQR)		1.6 (0.2-3.4)	1.1 (0.8-1.9)			.970†
Moving empty cans diff, median (IQR)		2.4 (0.7-7.9)	0.9 (0.4-1.2)			.079†
Moving full cans diff, median (IQR)		2.7 (0.6-4.3)	2.1 (1.3-3.5)			1†
Dynamometer (n)	20	8	12			
Force diff (kg), median (IQR)		14 (11.6-20.0)	17.8 (13.1-34.7)			.305†
Active range of motion (AROM) (n)	22	10	12			
Max. abduction DIG1-DIG5 (cm), diff median (IQR)		2.0 (1.6-5.5)	3.8 (1.7-6)			.456†
Foot function tests						
Foot function test board (n)	19	9	9			
Forward and backward shifting diff, median (IQR)		0.5 (-0.1-1.6)	0.5 (-0.5-1.0)			.916†
Lateral shifting diff, median (IQR)		0.9 (0.1-1.4)	0.6 (0.3-0.9)			.355†
Alternately touching diff, median (IQR)		0.8 (0.1-3.0)	0.2 (-0.8-0.8)			.163†
Depressing a pedal diff, median (IQR)		1.2 (0.7-12.3)	2.0 (0.8-3.3)			.606†
Rand-36 (n)	39	18	21			
Physical functioning, mean (SD)		45.8 (22.0)	54 (21.8)	-1.2	37	.254
Social functioning, mean (SD)		57.6 (27.5)	61.3 (21.3)	-0.5	37	.641
Role limitations physical, median (IQR)		0 (0-6.25)	0 (0-0)			.178†
Role limitations emotional, mean (SD)		57.4 (44)	57.1 (46.1)	0.0	37	.986
Mental health, mean (SD)		63.3 (18.4)	71 (14.9)	-1.4	36	.165
Vitality, mean (SD)		49.2 (23.2)	53.3 (15.8)	-0.7	37	.512
Bodily pain, median (IQR)		27.5 (11.7-47.5)	32.6 (21.4-44.9)			.865†
General health, mean (SD)		57.2 (22.5)	60 (23.2)	-0.4	37	.708

Abbreviations: CRPS, complex regional pain syndrome; IQR, interquartile range; diff, difference nonaffected-affected; VAS, visual analog scale.

\*Fisher exact test.

†Mann-Whitney U test.

## Measurement of Effects

The primary effect measure was the influence of treatment on the intensity of pain using the VAS. Pain at the present time was measured 3 times daily for 1 week before treatment and after the treatment for 9 weeks continuously, using a paper pain diary. Secondary effect measurements were obtained at impairment, disability, and handicap level before treatment and after 2, 6, and 9 weeks. Two independent researchers tested the patients in both the participating institutes under environmentally stable conditions. Consecutive measurements were performed at the same time for each patient to control for circadian influences. Both researchers followed a rigid written assessment protocol for each assessment instrument. Range of movement of the hands was expressed by measuring the maximum abduction dig 1-5 distance for the hand and total range of motion

of the ankle for the foot. Muscle strength was tested with a Jamar dynamometer (Jackson, MI).<sup>1,6</sup> Temperature of the hands or feet was measured with a Diatek 9000 infrared thermometer (San Diego, CA).<sup>25</sup> Volume differences were assessed with the use of water displacement volumeters.<sup>24,30</sup> For measurements of hand function, the Jebsen-Taylor test<sup>21</sup> was performed for patients with upper extremity CRPS I, and lower extremity function was measured with the Foot Function.<sup>22</sup> Quality of life measured by the Dutch Rand-36 questionnaire (at 0, 6, and 9 weeks).<sup>1</sup> For measurements at impairment (except for pain) and disability level, results of the measurements were expressed as differences between the affected and unaffected extremity. Possible side effects were registered weekly from the onset of the interventions for the duration of the trial. Use of rescue pain medication was registered weekly in the pain diary.

**Table 3. VAS Pain Scores in the Course of the Trial**

	T2		T6		T9	
	PLACEBO	MANNITOL	PLACEBO	MANNITOL	PLACEBO	MANNITOL
VAS (n)	18	22	18	22	18	22
VAS max (mm), mean (SD)	71.1 (21.0)	68.5 (21.1)	63.3 (27.0)	67.8 (24.5)	62.2 (29.6)	63.3 (28.3)
VAS mean (mm), mean (SD)	46.2 (22.2)	50.6 (20.2)	45.1 (24.9)	47.3 (26.5)	45.1 (31.8)	49.7 (25.3)
Average number of patients using rescue pain medication per week, mean (SD)	10.4 (2.4)	10.4 (2.4)	9.2 (1.6)	10.2 (2.1)	7.2 (1.8)	7.7 (1.3)
Of which						
Acetaminophen	2.2 (0.8)	1.2 (0.5)	1 (0.6)	1.3 (0.5)	1.6 (0.5)	0.4 (0.5)
NSAIDS	1.9 (0.4)	2.6 (0.8)	1.9 (0.4)	2 (1.0)	1.9 (0.9)	1 (0.6)
Anticonvulsants/antidepressants	3.6 (1.6)	4.9 (0.9)	3 (1.0)	3.9 (0.4)	2.7 (1.0)	4.3 (0.5)
Weak/strong opioids	2.6 (0.5)	1.6 (0.8)	2.6 (0.5)	2.3 (0.8)	1.6 (0.5)	1.9 (0.4)
VAS diff (mm), mean (SD)	T0 vs T2		T0 vs T6		T0 vs T9	
	-1.1 (9.5)	2.5 (10.8)	0.0 (15.5)	5.8 (20.3)	-0.1 (22.2)	3.4 (19.1)

Abbreviations: IQR, interquartile range; diff, difference nonaffected-affected; NSAIDS, nonsteroidal anti-inflammatory drugs; VAS, visual analog scale.

### Analysis of Data

Standard power calculation based on the primary effect measure revealed that 21 patients per group were necessary to establish a difference of 2 cm on the VAS (SD = 2) with a power of 90% and a significance level of .05. Treatment effects were expressed as mean and median values for different measurement points and as difference scores (improvement) between measurements. Baseline versus 1, 2, 3, 4, 5, 6, 7, 8, and 9 weeks (ie, difference scores) was used for the outcome parameters of pain and baseline versus 2, 6, and 9 weeks for the secondary outcome parameters, except for the RAND-36.

Data gathered in the diary (ie, pain scores and quality-of-life assessments) were controlled at each patient visit. Missing values for quality-of-life assessments were corrected if the patient was able to recall the missing value. Because VAS scores were considered to be specifically time related, individual missing scores were not corrected to avoid recall bias. In the case of missing VAS scores (daily and weekly), sum score calculations were corrected for fewer observations. In the case of inability to perform clinical tests (due to severity of complaints of fear of exacerbation of complaints by the patient), data were handled as missing. No data imputation techniques were applied.

Statistical analyses were performed blinded for the treatment given, with the use of SPSS 12 software (SPSS, Inc., Chicago, IL). Prognostic comparability and treatment effect were assessed by using the independent Student *t* test, Mann-Whitney *U* test,  $\chi^2$  test, and Fisher exact test when appropriate. Possible influence of prognostic variables and effect modification (interaction) was analyzed by using stepwise regression. Success of blinding was tested for patients and researchers at the end of the trial period, using the binomial test. For all outcome measures, the 2-sided significance level was set at 5%.

### Results

From March 2002 until November 2004, 297 patients were considered for this trial, of which 42 patients were

considered eligible and agreed to participate (Fig 1). Sociodemographic characteristics of both remaining patient groups are summarized in Table 1. All included patients had CRPS I affecting either 1 arm ( $n = 23$ ) or 1 leg ( $n = 19$ ). Of these 42 patients, 1 (CRPS I affecting the arm and assigned to the placebo group) was not included in the analysis group. The patient did not receive study medication because of a painful unaffected hand, so no intravenous cannula could be placed. The randomization was carried out successfully; no significant differences ( $P > .10$ ) were found between the placebo and mannitol groups in sociodemographic features and baseline values (Table 2).

### Outcomes and Estimation

#### Pain

No significant differences were found between mannitol and placebo for weeks 1 to 9 for the maximum and mean VAS per week or VAS difference compared with baseline on intention-to-treat analysis (Table 3). No significant differences were found between both groups in the number of patients requesting rescue pain medication (Table 3) or the amount or strength of pain medication used.

The mean VAS for each week is shown for both interventions in Fig 2. The mean values in both groups showed no improvement in the course of the trial.

#### Impairment and Function Level

Except for a significant improvement at T9 in the "stacking checkers" subscale of the Jepsen-Taylor test in favor of mannitol treatment, no significant differences were found on impairment and function level measurements in this study. The changes in the course of the study were, on average, small and clinically irrelevant on all indices.

#### Quality of Life

Changes in quality of life on the 9 domains of the RAND-36 questionnaire are displayed in Table 4. There

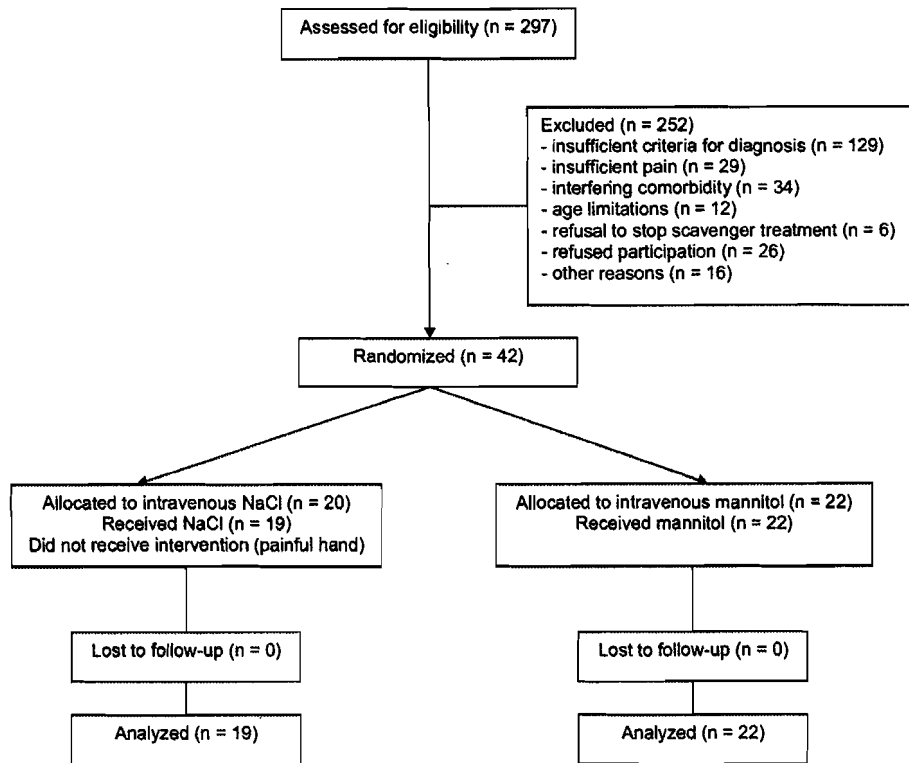


Figure 1. Flow diagram of patient inclusion.

are no significant differences between the effects of the 2 interventions at 6 and 9 weeks after treatment. As was the case on impairment and function level, the changes in the course of the study were small.

**Adverse Events and Side Effects**

Patients in both groups had mild side effects. No significant differences were found with respect to the number of patients reporting side effects or the nature of the side effects experienced between both groups. The most frequently reported side effects are presented in Table 5 for the major measurement points. No serious adverse events occurred during the course of the trial.

**Success of Blinding**

Success of blinding was evaluated in all patients and in 34 instances by the treating physician. Blinding was considered successful for physicians, whereby in 22 of 34 cases, physician guesses were accurate, which was not significantly different from chance ( $P = .123$ ). However, 27 of 41 patients correctly identified whether they had received placebo or mannitol, which was statistically significant ( $P = .015$ ).

**Discussion**

Based on the results of the present study, treatment with intravenous 10% mannitol does not appear to be

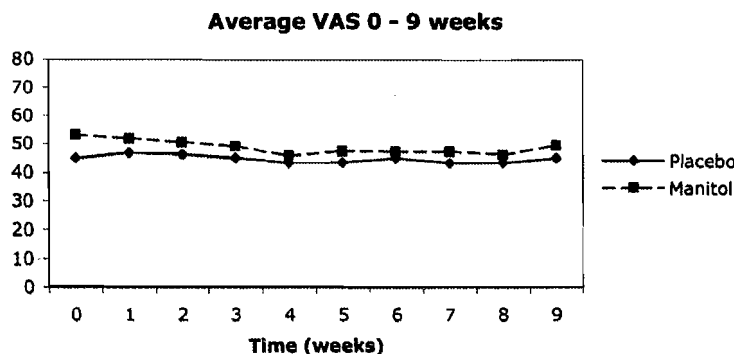


Figure 2. Average pain scores over a period of 9 weeks. VAS, visual analog scale.

**Table 4. Secondary Outcomes in the Course of the Trial**

	T0 vs T2		T0 vs T6		T0 vs T9	
	PLACEBO	MANNITOL	PLACEBO	MANNITOL	PLACEBO	MANNITOL
Volume and temperature (n)	19	20	19	20	18	19
Temperature diff in °C, median (IQR)	0.1 (-0.7-0.3)	0.2 (-0.5-1.8)	0.4 (-0.3-0.8)	-0.1 (-0.6-0.7)	0.0 (-0.3-0.4)	-0.1 (-0.5-0.8)
Volumetry (diff in mL), median (IQR)	-1.5 (-20.0-25.3)	-4.0 (-30.0-15.0)	1.5 (-16.3-15.3)	-15 (-25-5)	-5.5 (-13.8-8.8)	-10 (-29.3-22.5)
Hand function tests						
Jebsen-Taylor hand function test (n)	10	10	10	12	10	11
Turning cards diff (sec), median (IQR)	0.6 (0.2-3.8)	0.7 (0.2-2.5)	1.7 (0.3-2.7)	0.8 (-1.4-2.1)	0.5 (-0.5-2.6)	0.6 (-0.2-2.9)
Moving small objects diff (sec), median (IQR)	0.3 (-2.0-2.4)	0.7 (-0.1-2.9)	1.0 (-1.2-1.7)	2.0 (0.7-2.9)	0.2 (-3.1-0.9)	1.6 (0.1-3.1)
Simulated feeding diff (sec), median (IQR)	0.1 (-2.7-2.7)	0.9 (-2.0-1.9)	1.0 (-1.6-2.1)	0.4 (-1.2-1.0)	1.2 (-0.6-3.7)	0.4 (-1.0-2.9)
Stacking checkers diff (sec), median (IQR)	0.0 (-1.5-0.8)	0.6 (-0.1-1.3)	0.1 (-0.3-1.4)	0.2 (-0.5-0.8)	-0.5 (-3.2-0.4)	0.6 (0.3-1.0)*
Moving empty cans diff (sec), median (IQR)	0.8 (0.0-2.1)	0.1 (-0.5-0.3)	0.9 (-0.1-2.6)	0.3 (-0.3-2.1)	0.8 (-0.4-2.0)	0.1 (-0.6-1.0)
Moving full cans diff (sec), median (IQR)	0.5 (-0.6-2.0)	1.0 (-0.1-1.3)	0.3 (-0.3-0.6)	0.6 (-0.4-1.3)	0.8 (-0.4-2.6)	0.8 (0.3-2.1)
Dynamometer (n)	7	9	7	10	7	9
Force diff, median (IQR)	-3.3 (-6.0-0.3)	-0.3 (-3.3-5.7)	-3.6 (-6.3-1.3)	-2.2 (-5.5-3.7)	-3.7 (-5.0-0.7)	-1.3 (-8.6-2.7)
Active range of motion (AROM) (n)	10	11	10	11	10	12
Abduction DIG1-DIG5 (cm) diff, median (IQR)	0.8 (-0.5-1.6)	1.0 (0.2-1.5)	-0.1 (-1.1-1.5)	-0.1 (-1.0-1.5)	-0.4 (-0.9-0.8)	-0.5 (-1.2-2.2)
Foot function tests						
Foot function test board (n)	8	8	7	7	8	7
Forward and backward shifting diff, median (IQR)	0.5 (-0.8-0.8)	0.3 9-0.6-0.7)	-0.1 (-0.7-1.1)	-0.1 (-0.2-0.6)	-0.4 (-1.2-1.6)	0.3 (-0.6-1.0)
Lateral shifting diff, median (IQR)	-0.2 (-0.7-0.4)	-0.5 (-0.6-0.0)	0.1 (-0.5-0.2)	-0.3 (-0.5-0.1)	-0.4 (-0.5-0.0)	-0.2 (-0.5-0.0)
Alternately touching diff, median (IQR)	-0.3 (-1.1-0.3)	0.2 (-0.3-0.9)	0.1 (-0.9-0.8)	0.0 (-1.1-0.6)	-0.1 (-0.5-0.4)	0.8 (-0.4-0.9)
Depressing a pedal diff, median (IQR)	-0.1 (-0.8-1.7)	-0.5 (-3.5-1.2)	-0.7 (-2.4-0.0)	-1.1 (-1.6-0.1)	-0.7 (-1.8-0.1)	-1.3 (-2.2-0.1)
Rand-36 (n)			18	21	18	21
Physical functioning, median (IQR)	—	—	0.0 (-11.3-1.3)	0.0 (-10.0-7.5)	-5.0 (-10.0-15)	10 (-5.0-20.0)
Social functioning, median (IQR)	—	—	0.0 (0.0-15.6)	0.0 (-25.0-6.3)	0.0 (-25.0-12.5)	0.0 (-12.5-12.5)
Role limitations physical, median (IQR)	—	—	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Role limitations emotional, median (IQR)	—	—	0.0 (0.0-66.7)	0.0 (-33.0-0.0)	0.0 (0.0-0.0)	0.0 (-33.0-0.0)
Mental health, median (IQR)	—	—	-2.0 (-9.0-9.0)	0.0 (-8.0-3.0)	-4.0 (-16.0-4.0)	-4.0 (-9.0-4.0)
Vitality, median (IQR)	—	—	2.5 (-10.0-12.5)	-5.0 (-15.0-2.5)	0.0 (-15.0-0.0)	-5.0 (-10.0-0.0)
Bodily pain, median (IQR)	—	—	0.0 (-12.3-10.7)	0.0 (-17.3-0.0)	10.2 (-22.4-10.2)	-10.2 (-12.5-0.0)
General health, median (IQR)	—	—	5.0 (-11.3-15.0)	0.0 (-13.8-10)	5.0 (-10.0-10.0)	0.0 (-5.0-20.0)

Abbreviations: IQR, interquartile range; diff, difference affected-nonaffected.

\*Mann-Whitney *U* test, *P* < .05.

**Table 5. Side Effects in the Course of the Trial**

	T1		T2		T6		T9	
	PLACEBO	MANITOL	PLACEBO	MANNITOL	PLACEBO	MANNITOL	PLACEBO	MANNITOL
Side effects (n)	13	16	7	6	4	3	3	3
Headache (n)	5	9	4	1	0	1	0	0
Dizziness (n)	0	2	0	1	0	0	0	0
Fatigue (n)	2	2	0	1	0	0	0	0
Increased urination (n)	1	3	0	1	0	0	0	0
Miscellaneous	11	12	7	7	4	3	3	3

\* $\chi^2$  test, <.05.

effective in the treatment of CRPS I. Except for a significant improvement on a subscale of the Jebsen-Taylor hand function test, no significant differences were found between mannitol and placebo treatment. Considering the overall lack of significant differences between both groups and the chance of a type 1 error when performing multiple statistical comparisons, the significant difference found for the Jebsen-Taylor test can in all likelihood be regarded as a chance finding, in absence of a sound explanation for this difference. Furthermore, the changes in both groups in the course of the trial were small and clinically irrelevant. This lack of effect found for mannitol treatment is in contrast with the positive effects consistently found for other free radical scavengers in the treatment of CRPS I. For both 50% DMSO<sup>14,16,36</sup> and *n*-acetylcysteine<sup>31</sup> positive effects have been found in (randomized) controlled clinical trials. Both 50% DMSO, mannitol, and, to a lesser extent, *n*-acetylcysteine, are particular scavengers for the hydroxyl radical and poses diuretic properties. However, besides these properties, DMSO exhibits other anti-inflammatory, local anesthetic, and (weakly) bacteriostatic properties,<sup>32,35</sup> whereas *n*-acetylcysteine is reported to reduce the release of the proinflammatory mediator TNF- $\alpha$ <sup>10</sup> and improve vascular function by promoting endothelium derived vasodilation.<sup>4</sup> Possibly, the difference in effectiveness may be explained by difference in mode of action between these substances. However, in view of the fact that multiple mechanisms have been suggested to underlie CRPS I<sup>20</sup> and identification of a specific mechanism explaining CRPS I signs and symptoms in an individual patient is not yet possible, explaining the lack of effect of mannitol by using a mechanistic approach remains speculative.

Another possible explanation for the lack of effect in this study might be the duration of the complaints of the patients in the present study sample. Compared with previous studies evaluating the effects of free radical scavengers, which incorporated patients with a short duration on the complaints (ie, 1 year or less), the present sample contained 12 patients with a CRPS I duration of more than 1 year. Although the value of early intervention has yet to be established for CRPS I, the general opinion<sup>7</sup> as well as results of subgroup analyses from other studies<sup>23,31</sup> appear to be in favor

of early intervention. It is therefore possible that patients with a shorter duration of complaints might respond more favorably to mannitol treatment than the population in this study. The fact that for the majority of the patients in the present study the duration of complaints was shorter than 1 year and the median duration of the complaints in the mannitol group was 6.5 months makes the results more promising for mannitol treatment for patients with a shorter CRPS I duration less likely.

A point of discussion with respect to the present study might be that the severity of the complaints experienced by the patients was limited; differences between the affected and unaffected extremity with respect to temperature, volume, and foot function for the lower extremity were small. This might have accounted for limited improvement on these indices in both groups. This, however, does not apply to the intensity of pain (VAS) experienced by patients in both groups, which was moderate to severe, and the RAND-36 scores, which were poorer on all indices compared with Dutch reference data<sup>2</sup> and other disease populations.<sup>1,11</sup> Change over time on both measurement indices was small in this study.

With respect to the VAS ratings, it should be noted that the reported severity in our sample was still lower compared with data on CRPS I in an identical fashion in one of our institutions<sup>12</sup> (VAS, 6.9 [SD 1.4]; *n* = 54). Although lower pain scores are more difficult to improve and may have limited the possibility to show a beneficial effect of mannitol, we do believe that a (moderately) effective intervention should have been able to reduce pain scores more than we found in our study.

Related to this issue is the accuracy of the sample size calculation used in this study. To establish the required sample size, a power calculation was performed using a more conservative standard deviation (*n* = 2) compared with the abovementioned study by Forouzanfar et al.<sup>12</sup> The actual standard deviation in the present sample was, however, slightly higher (SD = 2.1), which would have lead to a slightly larger sample size. Also, as higher levels of variance for present pain VAS ratings have been reported in literature,<sup>27</sup> one cannot exclude sampling error on this point in our trial. In addition, one could argue that a smaller difference between groups could have been chosen in this study,

as chronic CRPS I patients might also welcome a less substantial reduction in pain. Again, this would have led to a larger sample size. Whether we would have been able to establish clinically relevant and statistically significant differences in favor of mannitol using a larger sample size remains questionable, in our opinion. The VAS scores for mannitol changed for only a few millimeters (with stable SDs) in the course of the trial, which is clinically irrelevant by any standard. Furthermore, when we consider the stability of the VAS scores, we believe it to be unlikely that these would increase substantially with a larger sample size.

However, choosing a patient population with a profile more favorable to mannitol intervention might well have resulted in a better response to this intervention. Because mannitol is a free radical scavenger, it is possible that a subgroup of patients with inflammatory signs and symptoms predominating would benefit more from mannitol treatment. Because we did not apply a specific focus based on pathophysiological or clinical appearance in our inclusion, this aspect has to be established in a future study. Again, we would like to stress that a mechanistic approach, in the absence of an established pathophysiological mechanism for CRPS I, must be interpreted with caution.

Another issue related to sampling error is the fact that patients in both groups received rescue medication and physical therapy according to protocol.<sup>26,28</sup> As favorable results for this specific physical therapy protocol have been established (albeit in combination with DMSO and/or *n*-acetylcysteine), one might expect more progress in both groups than found in the present study. Notwithstanding the fact that some CRPS complaints were mild in this sample, it is possible that patients in this study were more refractory to treatment than patients in earlier studies.

No serious adverse events occurred during mannitol administration, and side effects were mild in nature and comparable in both study groups. Patients in this study were screened for relevant comorbidity, such as preexistent renal dysfunction. However, physicians should be aware of possible deleterious effects of mannitol accumulation in patients with (moderate) re-

nal failure, for which transient adverse events have been described.<sup>33</sup>

A further point of discussion is the success of the blinding procedure applied in this study. Although both the appearance of the containers of the administered substances as the manner in which in they were administered was identical in both groups, significantly more patient (placebo: *n* = 13; mannitol: *n* = 13) correctly indicated which treatment they had received. This, in our opinion, further underlines the poor results for mannitol treatment, as in general patient awareness of the received intervention is considered to be a guiding factor in patient appreciation and judgment of effect of the received intervention.<sup>3</sup> In the case of this study, the most probable effect of this knowledge would have been that patients treated with placebo would have scored worse (while knowing that the intervention is regarded ineffective) and that patients treated with mannitol would have scored better (knowing that they had received the active substance). The fact that this did not lead to substantial differences between both groups can therefore be regarded as a further indication of the lack of effect of mannitol in the current CRPS I sample. The blinding procedure was successful for the treating physicians in this trial, reducing subjectivity on the conducting side of the trial.

In summary, we conclude that intravenous administration of 10% mannitol is not more effective than placebo in reducing complaints for CRPS I patients and provides no addition to already-established interventions for CRPS I. Whether 10% mannitol can provide beneficial effects for subgroups of CRPS I patients with a pathophysiological profile more closely fitting the presumed mode of action for this intervention remains to be established.

## Acknowledgments

This study forms a part of TREND (Trauma RElated Neuronal Dysfunction), a knowledge consortium that integrated research on Complex Regional Pain Syndrome type I (CRPS I).

## References

1. Aaronson NK, Acquadro C, Alonso J, Apolone G, Bucquet D, Bullinger M, Bungay K, Fukuhara S, Gandek B, Keller S: International Quality of Life Assessment (IQOLA) Project. *Qual Life Res* 1:349-351, 1992
2. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te VA, Verrips E: Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 51:1055-1068, 1998
3. Altman DG. *Practical Statistics for Medical Research*. London, UK, Chapman & Hall/CRC, 1999
4. Andrews NP, Prasad A, Quyyumi AA: N-acetylcysteine improves coronary and peripheral vascular function. *J Am Coll Cardiol* 37:117-123, 2001
5. Atkins RM, Duckworth T, Kanis JA: Algodystrophy following Colles' fracture. *J Hand Surg [Br]* 14:161-164, 1989
6. Beaton DE, O'Driscoll SW, Richards RR: Grip strength testing using the BTE work simulator and the Jamar dynamometer: a comparative study: Baltimore Therapeutic Equipment. *J Hand Surg [Am]* 20:293-298, 1995
7. Birklein F, Riedl B, Claus D, Neundorfer B: Pattern of autonomic dysfunction in time course of complex regional pain syndrome. *Clin Auton Res* 8:79-85, 1998
8. Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stan-

- ton-Hicks M: Complex regional pain syndrome: Are there distinct subtypes and sequential stages of the syndrome? *Pain* 95:119-124, 2002
9. Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M: External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria: International Association for the Study of Pain. *Pain* 81:147-154, 1999
10. Cotgreave IA: N-acetylcysteine: Pharmacological considerations and experimental and clinical applications. *Adv Pharmacol* 38:205-227, 1997
11. Essink-Bot ML, Krabbe PF, Bonsel GJ, Aaronson NK: An empirical comparison of four generic health status measures: The Nottingham Health Profile, the Medical Outcomes Study 36-item Short-Form Health Survey, the COOP/WONCA charts, and the EuroQol instrument. *Med Care* 35:522-537, 1997
12. Forouzanfar T, Kemler M, Kessels AG, Koke AJ, van Kleef M, Weber WE: Comparison of multiple against single pain intensity measurements in complex regional pain syndrome type I: Analysis of 54 patients. *Clin J Pain* 18:234-237, 2002
13. Galer BS, Henderson J, Perander J, Jensen MP: Course of symptoms and quality of life measurement in complex regional pain syndrome: A pilot survey. *J Pain Symptom Manag* 20:286-292, 2000
14. Geertzen JH, de Bruijn H, Bruijn-Kofman AT, Arendzen JH: Reflex sympathetic dystrophy: Early treatment and psychological aspects. *Arch Phys Med Rehabil* 75:442-446, 1994
15. Geertzen JH, Dijkstra PU, Groothoff JW, ten Duis HJ, Eisma WH: Reflex sympathetic dystrophy of the upper extremity: A 5.5-year follow-up, I: Impairments and perceived disability. *Acta Orthop Scand Suppl* 279:12-18, 1998
16. Goris RJ, Dongen LM, Winters HA: Are toxic oxygen radicals involved in the pathogenesis of reflex sympathetic dystrophy? *Free Radic Res Commun* 3:13-18, 1987
17. Harden RN, Bruehl SP: Diagnostic criteria: The statistical derivation of the four criterion factors, in Wilson P, Stanton-Hicks M, Harden RN (eds): *CRPS: Current Diagnosis and Treatment*, Vol. 32. Seattle, WA, IASP Press, 2005
18. Huygen FJ, de Bruijn AG, De Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ: Evidence for local inflammation in complex regional pain syndrome type 1. *Mediators Inflamm* 11:47-51, 2002
19. Huygen FJ, de Bruijn AG, Klein J, Zijlstra FJ: Neuroimmune alterations in the complex regional pain syndrome. *Eur J Pharmacol* 429:101-113, 2001
20. Janig W, Baron R: Complex regional pain syndrome: Mystery explained? *Lancet Neurol* 2:687-697, 2003
21. Jepsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA: An objective and standardized test of hand function. *Arch Phys Med Rehabil* 50:311-319, 1969
22. Kemler MA, de Vet HC: An objective and standardized test of foot function: Normative values and validation in patients with reflex sympathetic dystrophy. *Arch Phys Med Rehabil* 81:1401-1407, 2000
23. Muizelaar JP, Kleyer M, Hertogs IA, DeLange DC: Complex regional pain syndrome (reflex sympathetic dystrophy and causalgia): Management with the calcium channel blocker nifedipine and/or the alpha-sympathetic blocker phenoxybenzamine in 59 patients. *Clin Neurol Neurosurg* 99:26-30, 1997
24. Oerlemans HM, Goris RJ, Oostendorp RA: Impairment level sum score in reflex sympathetic dystrophy of one upper extremity. *Arch Phys Med Rehabil* 79:979-990, 1998
25. Oerlemans HM, Graff MJ, Jkstra-Hekkink JB, de BT, Goris RJ, Oostendorp RA: Reliability and normal values for measuring the skin temperature of the hand with an infrared tympanic thermometer: A pilot study. *J Hand Ther* 12:284-290, 1999
26. Oerlemans HM, Oostendorp RA, de Boo T, Goris RJ: Pain and reduced mobility in complex regional pain syndrome, I: Outcome of a prospective randomised controlled clinical trial of adjuvant physical therapy versus occupational therapy. *Pain* 83:77-83, 1999
27. Oerlemans HM, Oostendorp RA, de Boo T, Perez RS, Goris RJ: Signs and symptoms in complex regional pain syndrome type I/reflex sympathetic dystrophy: Judgment of the physician versus objective measurement. *Clin J Pain* 15:224-232, 1999
28. Oerlemans HM, Oostendorp RA, de Boo T, van der LL, Severens JL, Goris JA: Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type I. *Arch Phys Med Rehabil* 81:49-56, 2000
29. Oyen WJ, Arntz IE, Claessens RM, Van der Meer JW, Corstens FH, Goris RJ: Reflex sympathetic dystrophy of the hand: An excessive inflammatory response? *Pain* 55:151-157, 1993
30. Perez R, Oerlemans HM, Zuurmond W, De Lange J: Impairment level Sum Score for lower extremity Complex Regional Pain Syndrome type I. *Disabil Rehabil* 25:984-991, 2003
31. Perez RS, Zuurmond WW, Bezemer PD, Kuik DJ, van Loenen AC, de Lange JJ, Zuidhof AJ: The treatment of complex regional pain syndrome type I with free radical scavengers: A randomized controlled study. *Pain* 102:297-307, 2003
32. Reilly PM, Schiller HJ, Bulkley GB: Pharmacologic approach to tissue injury mediated by free radicals and other reactive oxygen metabolites. *Am J Surg* 161:488-503, 1991
33. van Hengel P, Nikken JJ, de Jong GM, Hesp WL, van Bommel EF: Mannitol-induced acute renal failure. *Neth J Med* 50:21-24, 1997
34. Veldman PH, Reynen HM, Arntz IE, Goris RJ: Signs and symptoms of reflex sympathetic dystrophy: Prospective study of 829 patients. *Lancet* 342:1012-1016, 1993
35. Yu ZW, Quinn PJ: Dimethyl sulphoxide: A review of its applications in cell biology. *Biosci Rep* 14:259-281, 1994
36. Zuurmond WW, Langendijk PN, Bezemer PD, Brink HE, de Lange JJ, van Loenen AC: Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. *Acta Anaesthesiol Scand* 40:364-367, 1996
37. Zyluk A: [Clinical estimation of late treatment results in posttraumatic Sudeck's dystrophy treated with mannitol, calcitonin and exercise therapy]. *Ann Acad Med Stetin* 40:133-144, 1994