

**Original Article**

# No Recovery of Cold Complex Regional Pain Syndrome After Transdermal Isosorbide Dinitrate: A Small Controlled Trial

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**Abstract**

*The microcirculation appears to be impaired in cold chronic complex regional pain syndrome (CRPS). This double-blind, placebo-controlled, randomized trial investigated the effect of the nitric oxide (NO) donor isosorbide dinitrate (ISDN) on the peripheral blood flow in patients with chronic CRPS. Twenty-four patients received 1% ISDN in Vaseline® or a placebo ointment applied to the dorsum of the affected hand four times daily for 10 weeks. The patients participated in a physical therapy program to improve activity. The primary outcome measure was blood distribution in the affected extremity, which was determined by measuring the skin temperature using videothermography. We also measured NO and endothelin-1 concentrations in blister fluid, pain using the visual analog scale, and activity limitations using an upper limb activity monitor and the Disabilities of Arm Shoulder and Hand Questionnaire. ISDN failed to produce a significant improvement in temperature asymmetry in chronic cold CRPS patients, and it did not result in the expected reduction in pain and increase in activity compared with placebo either. There may be other central or peripheral factors contributing to the disturbed vasodynamics in cold chronic CRPS that are not influenced by NO substitution. This study does not show an improvement of the regional blood distribution by ISDN in the involved extremity of patients with cold-type CRPS. J Pain Symptom Manage 2009;38:401–408. © 2009 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

**Key Words**

*Nitric oxide, isosorbide dinitrate, vasodilation, endothelial dysfunction, videothermography, CRPS*

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## Introduction

Complex regional pain syndrome (CRPS) is a painful disorder that usually occurs as a complication of surgery or trauma. There are two types — in CRPS Type 1, the focus of this study, no overt nerve lesion is detectable, whereas in CRPS Type 2, a nerve lesion is present.<sup>1,2</sup> Diagnosis is based mainly on consensus-derived clinical criteria.<sup>3,4</sup> The main characteristics of CRPS are continuous pain, sensory disturbances, marked changes in tissue blood flow and skin surface temperature, edema, sweating, movement disorders, and trophic changes of the skin; the severity of the symptoms is often disproportional to the initial event.<sup>5,6</sup> Activity limitations are common.<sup>7</sup> The symptoms may be related to exaggerated local inflammatory response mediated by cytokines,<sup>8–11</sup> neurogenic inflammation mediated by neuropeptides,<sup>10,12–14</sup> or both.<sup>5</sup> In the acute stage, this leads to a “warm dystrophy” with classic signs of inflammation, such as redness, increased skin temperature, edema, loss of function, and pain.<sup>15–17</sup>

During the chronic stage of the disease, inflammatory signs are replaced by atrophy, reduced regional blood flow, and consequently, reduced temperature.<sup>18,19</sup> These findings indicate impaired microcirculation, which affects temperature and nutritive blood flow in superficial and deep tissues.<sup>20–22</sup>

The microcirculation is regulated by neural and endothelial factors.<sup>23</sup> The neural factors were examined by Wasner et al., who induced whole-body temperature changes to study the sympathetic cutaneous vasoconstrictor activity in CRPS, and identified three vascular regulation patterns: the “warm,” the “intermediate,” and the “cold” type.<sup>24</sup> It was suggested that, in CRPS, unilateral inhibition of sympathetic vasoconstrictor neurons leads to a warmer affected limb in the acute stage, whereas secondary changes in neurovascular transmission would lead to vasoconstriction and cold skin in the chronic stage of the disease.<sup>24</sup>

With regard to the endothelial factors, we recently showed that, in patients with an intermediate type of CRPS Type 1, levels of endothelin-1 (ET-1) are increased in skin blister fluid from the affected extremities, whereas nitric oxide (NO) levels are reduced.<sup>25</sup> As a consequence, ET-1-related vasoconstriction is exaggerated and NO vasodilative activity is suppressed. A NO donor

might stimulate NO-related vasodilative function and counteract vasoconstriction by ET-1, thus leading to endothelium-derived vasodilation. In a pilot study with five patients,<sup>26</sup> we demonstrated an apparent vasodilative effect of transdermally-applied isosorbide dinitrate (ISDN), a NO donor.

The aim of this double-blind, placebo-controlled, randomized clinical trial was to determine whether ISDN ointment improves regional blood distribution in the involved extremity of patients with cold-type CRPS Type 1, and if so, whether this improves functioning.

## Methods

### Study Design

This was a double-blind, placebo-controlled, randomized study with 24 patients (12 per group). Patient inclusion took place from June 2005 to December 2006, and the final measurements were obtained in April 2007. Patients were randomized to receive 1% ISDN in Vaseline<sup>®</sup> or a placebo ointment. Three centimeters of ointment, corresponding to approximately 1 g ointment and 10 mg active ingredient, was applied to the dorsum of the affected hand four times daily for 10 weeks. Outcome measures were assessed at the start of the study (start) and after 10 weeks (end).

### Patient Recruitment

Potential patients were selected from Erasmus Medical Center outpatients, from patients responding to an announcement in the Dutch CRPS Patients Association's magazine and web site, and from patients referred by anesthesiologists at neighboring hospitals. Eligible candidates ( $n = 195$ ) were invited to visit our outpatient clinic, and F.W. and F.J.P.M.H. selected 47 patients with cold CRPS Type 1 according to the criteria described by Harden and Bruehl.<sup>3</sup> Inclusion criteria were: age between 18 and 60 years, and CRPS Type 1 limited to one upper extremity. Patients with cardiovascular or neurovascular disease, and patients hypersensitive to nitrates were excluded. Only 30 patients fully met these inclusion criteria, of which 24 agreed to participate in this trial.

### Randomization

Randomization was performed by the Erasmus MC pharmacy according to the research policy of the Erasmus MC, using a computerized randomization list. Patients, researchers, and physicians were blind to the intervention administered; only the pharmacist had the allocation code.

### Physiotherapy

Patients in both treatment groups received a modified version of a physiotherapy program,<sup>27</sup> which consisted of exercises based on a graded activity approach and intended to improve functioning, strength, and mobility of the affected extremity. The patients received one therapy session a week by a local physiotherapist and performed daily exercises at home.

### Outcome Measures

The primary outcome measure was temperature. The secondary outcome measures were levels of NO and ET-1 in blister fluid, pain, and level of activity.

Temperature was measured using videothermography. A decrease in local skin temperature, as observed in chronic CRPS Type 1, is directly related to diminished tissue blood distribution.<sup>28</sup> Videothermography has been shown to be an effective means to monitor near-surface blood flow in the limbs.<sup>29,30</sup> A standard protocol was used to measure the skin temperature of both hands, compare the thermographic images and calculate the mean difference in temperature ( $^{\circ}\text{C}$ ).<sup>29,31</sup> In healthy subjects under normal conditions, the skin temperature difference detected between sides using computerized thermography is less than 1% or 0.25 $^{\circ}\text{C}$ .<sup>29,32,33</sup>

Artificial blisters were induced using a suction method,<sup>34–36</sup> and nitrate and nitrite concentrations in the blister fluid were determined.<sup>8,16,25,37,38</sup> The sample concentrations were expressed as total NO<sub>x</sub> (nmol/mL). If sufficient blister fluid remained, ET-1 concentrations were determined (pg/mL).

Pain is often described as the most prominent feature of CRPS Type 1.<sup>39</sup> The patients used a diary to record daily pain intensity according to a visual analog scale (VAS) scale (0–100 mm). The mean of three measurements daily during seven days preceding the hospital visit was used.

To determine the possible differences between perceived changes in activity (limitations) and actual activity, the Disabilities of the Arm, Shoulder and Hand Questionnaire (DASH) and the upper limb activity monitor (ULAM) were used. The ULAM is based on ambulatory accelerometry and enables long-term objective determination of actually performed upper limb activity in different postures and motions during everyday functioning. It is increasingly used in research involving a variety of patient groups,<sup>40,41</sup> including acute<sup>7</sup> and chronic<sup>42–44</sup> CRPS Type 1 patients. The signal analysis and its output were described previously.<sup>41,42,45,46</sup> The ULAM was fit to each patient after all measurements in the hospital at the start and end of the study. The patients were instructed to continue their normal activities while wearing the ULAM, with the exception of swimming, bathing, or showering. The following ULAM outcome measures for activity limitations were calculated for a 24-hour period: the intensity of activity of the CRPS limb, expressed as the mean motility value ( $\text{ms}^{-2}$ ); the duration of activity of the CRPS limb, expressed as the percentage of time that the activity exceeded predefined motility thresholds; percent bimanual, the percentage of time during which both upper limbs were active; and percent bimanual/contra, which is the percent bimanual divided by the percentage of time during which the contralateral limb was active. For these ULAM outcome measures, a higher value indicates a higher level of activity during daily functioning.

The DASH was developed to determine perceived changes in activity limitations of the entire upper limb during daily functioning.<sup>47,48</sup> The DASH Dutch Language Version<sup>49</sup> has been used before in CRPS patients.<sup>43</sup> The total score for 30 items was transformed into one score ranging from 0 to 100, and lower score indicates a higher perceived activity level.

### Statistical Analysis

Differences in patient characteristics between the treatment groups were analyzed using the Student's *t*-test for independent samples, the Mann-Whitney *U* test, the Chi-squared test, and Fisher's exact test when appropriate. Differences in mean subjective and objective parameters between treatment groups and across time, as well as the interaction between treatment and time were analyzed using a multivariate

repeated-measurements design, with group (ISDN or placebo ointment) and time (start and end) as independent variables.

The multivariate repeated-measurements analysis was used, despite the skewed distribution of the outcome measures, because of the robustness of analysis of variance. (Multivariate analyses of variance require that each dependent variable entered into the analysis be normally distributed. Nevertheless, we used this statistical model because it has been shown in Monte Carlo experiments that even with markedly skewed distributions, the empirically determined rejection region of the F-distribution is no larger than  $\alpha = 0.08$  when the usual 5% rejection region is used.<sup>50</sup>) Alpha was set at the traditional 0.05 level. Analyses were performed using the Statistical Package for the Social Sciences version 14.02 (SPSS Inc., Chicago, IL).

#### Statement of Compliance with Ethical Regulations

The Medical Ethics Committee of the Erasmus MC approved the study protocol (MEC 2004-159). The research was performed in accordance with the Declaration of Helsinki (2000) of the World Medical Association, and written informed consent was obtained from all participants. The trial registration number is ISRCTN60226869.

## Results

Twenty-four patients participated; all of them completed the study. The baseline characteristics of the ISDN and placebo groups are shown in Table 1. There were no significant

differences between the groups, except that the contralateral hands in the placebo group were significantly warmer. The temperature asymmetry between the CRPS and contralateral hands at baseline was equivalent for the two groups. As shown in Table 2, the interaction between treatment and time for temperature asymmetry was not significant.

For the sample as a whole, pain intensity was significantly reduced after treatment, but as Table 2 shows, there was no significant improvement in the VAS as a result of ISDN treatment.

Although the blistering suction method was applied to all patients, because of a number of reasons (such as too much pain, no blister formation or only small blisters after the maximum suction period), it was not possible to induce blisters with sufficient fluid volume for both measurements on both hands for all patients. Paired samples of nitrate and nitrite concentrations were obtained for 17 patients. Sufficient remaining volume was available from 11 paired blister fluid samples to assay ET-1. In all patients at the baseline, there was no significant difference between CRPS and contralateral NO (CRPS:  $53.4 \pm 17.7$  pg/mL, contralateral:  $56.6 \pm 18.2$  pg/mL) or ET-1 concentrations (CRPS:  $2.6 \pm 1.8$  nmol/mL, contralateral:  $2.6 \pm 3.1$  nmol/mL). Table 3 provides the NO and ET-1 concentrations in the treatment groups. For both groups, however, there was a significant increase in the NO concentration over the course of the intervention, but no significant effect of ISDN on the concentration of NO or ET-1. The ULAM outcome measures and the DASH in Table 4 show no significant effect of ISDN on activity level.

Table 1  
Patient Characteristics

	ISDN	Placebo	P-value
<i>n</i>	12	12	
Age, years	$46.3 \pm 8.6$	$43.5 \pm 12.1$	0.52 <sup>a</sup>
Gender (female/male)	10/2	10/2	
Duration of CRPS, months	$51.5 \pm 37.5$	$45.5 \pm 29.6$	0.76 <sup>b</sup>
Smoking (yes/ex-smoker/no)	4/1/7	4/2/6	0.82 <sup>c</sup>
Dominant side affected (yes/no)	5/7	4/8	0.41 <sup>d</sup>
Temperature of CRPS hand	$29.1 \pm 2.7$	$30.8 \pm 2.6$	0.13 <sup>a</sup>
Temperature of contralateral hand	$30.5 \pm 2.4$	$32.3 \pm 1.6$	0.04 <sup>a,e</sup>
Difference in temperature	$1.42 \pm 1.6$	$1.56 \pm 1.6$	0.83 <sup>a</sup>

Values are the mean  $\pm$  standard deviation unless otherwise indicated.

<sup>a</sup>Independent-sample *t*-test.

<sup>b</sup>Mann-Whitney *U* test.

<sup>c</sup> $\chi^2$  test.

<sup>d</sup>Fisher's exact test.

<sup>e</sup> $P < 0.05$ .

Table 2  
Temperature Difference and Pain Measurements

	ISDN		Placebo		$P_t$	$P_{gt}$
	Start	End	Start	End		
Temperature difference (°C)	1.51 ± 1.95	0.62 ± 1.25	1.60 ± 1.49	1.23 ± 1.99	0.11	0.44
VAS	45.2 ± 15.7	41.8 ± 22.4	51.7 ± 18.9	43.4 ± 20.7	0.04 <sup>a</sup>	0.38

Values are the mean ± standard deviation.

$P_t$  =  $P$ value time;  $P_{gt}$  =  $P$ value of group × time interaction

<sup>a</sup> $P < 0.05$

Some patients in both groups reported strange tickling and itching sensations in the affected hand, an increase of pain during the first few weeks, or a burning sensation. A few patients in the ISDN group complained about headache, which disappeared after the first week. There were no severe adverse events.

### Discussion

This double-blind, placebo-controlled, randomized study did not show a significant improvement of blood flow in patients with cold chronic CRPS. This may be because of an incorrect hypothesis, ineffective medication or compliance of the patients, or it may also be because of the small study, which lacks power to show a real difference, although in view of the results, the latter seems unlikely.

Although we tried to recruit a homogeneous population, not all patients reacted similarly to the treatment. Most patients responded well to ISDN with a warmer CRPS hand, and fewer periods of deep cold pain, but two patients experienced no improvement at all, with the CRPS side remaining up to 8°C colder. Lack of compliance might account for these treatment failures, but it seems more likely that other central or peripheral factors contribute to the disturbed vasodynamics in cold chronic CRPS

Type 1 that are not influenced by NO substitution, for example, sympathetic dysregulation.

In our previous study,<sup>25</sup> we demonstrated an inverse relationship between NO<sub>x</sub> and ET-1 in patients with the intermediate cold-type CRPS Type 1, but in the chronic cold population of our present study, we found no significant differences in NO or ET-1 at baseline. This may indicate a change in the relationship between these mediators in intermediate compared with chronic cold CRPS Type 1, thus explaining why the substitution of NO did not have any beneficial effect on pain.

Although the NO and the ET-1 concentrations were lower than those in our previous study,<sup>51</sup> the ET-1 concentration was still higher than the concentrations previously reported by others.<sup>51,52</sup> Apparently, some of these chronic cold patients still have active inflammatory components.

For all patients, the mean VAS score was significantly lower after treatment, but there was no significant effect of ISDN. However, most patients reported rapid changes from the moment they began applying the ointment. These changes might have been the result of touching and massaging the hand and rubbing in the ointment, as well as to changes in activity elicited by the exercise program. Most patients in the ISDN group indicated that a previous feeling of deep cold pain disappeared steadily.

Table 3  
Concentrations of NO<sub>x</sub> and ET-1 in Blister Fluid of Affected and Contralateral Hands

	CRPS		Contralateral		$P_t$	$P_{gt}$
	Start	End	Start	End		
NO, pg/mL					0.04 <sup>a</sup>	0.52
ISDN	54.9 ± 20.6	101.7 ± 92.2	61.3 ± 20.9	110.2 ± 101.5		
Placebo	51.9 ± 15.3	79.9 ± 48.6	52.8 ± 15.5	65.2 ± 43.5		
ET-1, nmol/mL					0.32	0.64
ISDN	1.8 ± 1.0	2.1 ± 0.9	2.0 ± 0.8	2.2 ± 0.7		
Placebo	3.2 ± 2.0	3.1 ± 3.1	3.0 ± 4.2	3.4 ± 3.1		

Values are the mean ± standard deviation.

$P_t$  =  $P$ value time;  $P_{gt}$  =  $P$ value of group × time interaction.

<sup>a</sup> $P < 0.05$ .

Table 4  
Activity Limitations

	ISDN		Placebo		$P_t$	$P_{gt}$
	Start	End	Start	End		
ULAM <sup>a</sup>						
Intensity, ms <sup>-2</sup>	0.091 ± 0.038	0.099 ± 0.044	0.076 ± 0.028	0.083 ± 0.026	0.07	0.85
Duration, %	66.3 ± 13.4	69.0 ± 13.9	59.6 ± 12.5	60.5 ± 11.9	0.39	0.68
% Bimanual	60.4 ± 11.6	62.4 ± 12.8	54.9 ± 12.1	52.3 ± 10.4	0.88	0.25
% Bimanual/contra	78.7 ± 12.5	81.5 ± 12.4	76.0 ± 7.2	79.1 ± 10.3	0.05	0.93
DASH <sup>b</sup>	54.0 ± 13.2	51.4 ± 20.2	53.5 ± 16.1	50.0 ± 19.4	0.56	0.78

$P_t$  = P-value time;  $P_{gt}$  = P-value of group × time interaction.

<sup>a</sup>In the ULAM, outcome measure duration is expressed as the percentage of time during which the activity exceeded a motility threshold; % bimanual is the percentage of time that activities were performed with both hands and % bimanual/contra is % bimanual divided by the percentage of time that activities were performed with the contralateral hand. A higher value indicates better performance.

<sup>b</sup>In the DASH questionnaire, a lower value indicates better performance.

The results for the ULAM outcome measures intensity and duration of upper limb activity during sitting were comparable to previous findings.<sup>44</sup> In both treatment groups, upper limb activity was clearly reduced compared with healthy subjects.<sup>42</sup> However, there were no significant changes in the upper limb activity, although both treatment groups showed small improvements.

Our patients reported a higher degree of disability on the DASH than a previous study of chronic CRPS;<sup>43</sup> this difference may be attributed to our specific recruitment of patients with cold chronic CRPS Type 1. There was no significant effect of ISDN on the DASH score. The improvements in self-reported limitations of activity are consistent with the small improvements in performed upper limb activity measured using the ULAM. Such changes, although not significant, indicate that a physiotherapy program directed at improving functioning may be effective for patients with cold chronic CRPS Type 1, even for patients who have had the disease for more than four years. Because pain-related fear of movement also plays a role in CRPS,<sup>53</sup> these small improvements may also have been caused by a reduction in fear avoidance.

In conclusion, in the present setup, ISDN failed to produce a significant improvement in temperature asymmetry in chronic cold CRPS Type 1 patients. A 10-week treatment with this NO donor did not result in the expected reduction in pain and increase in activity compared with placebo. Future studies investigating the effectivity of ISDN ointment in chronic cold CRPS should focus on patients with endothelial dysfunction and a disturbed

NO<sub>x</sub>/ET-1 ratio. Therefore, patients with distinct sympathetic vascular dysregulation should be excluded, which calls for dynamic videothermographic measurements,<sup>31</sup> and the studies should also include methods to evaluate the endothelial function, for example, flow-mediated vasodilation.

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