*Original Article*

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

J. George Groeneweg, PT, Frank J.P.M. Huygen, MD, PhD, Sjoerd P. Niehof, PhD, Feikje Wesseldijk, MD, Johannes B.J. Bussmann, PT, PhD, Fabienne C. Schasfoort, PT, PhD, Dirk L. Stronks, PhD, and Freek J. Zijlstra, PhD
*Pain Treatment Centre (J.G.G., F.J.P.M.H., S.P.N., F.W., D.L.S.), Department of Rehabilitation Medicine (J.B.J.B., F.C.S.), and Department of Anesthesiology (F.J.Z.), Erasmus Medical Center, Rotterdam, The Netherlands*

***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. 

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

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*Address correspondence to:* J. George Groeneweg, PT, Department of Anesthesiology, Pain Treatment Centre, Erasmus Medical Center, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands. E-mail: j.groeneweg@erasmusmc.nl

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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.[1,2] Diagnosis is based mainly on consensus-derived clinical criteria.[3,4] 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.[5,6] Activity limitations are common.[7] The symptoms may be related to exaggerated local inflammatory response mediated by cytokines,[8–11] neurogenic inflammation mediated by neuropeptides,[10,12–14] or both.[5] 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.[15–17]

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

The microcirculation is regulated by neural and endothelial factors.[23] 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.[24] 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.[24]

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.[25] 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,[26] 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® 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.[3] 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.