Vasodilative Effect of Isosorbide Dinitrate Ointment in Complex Regional Pain Syndrome Type 1

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Background: In complex regional pain syndrome type 1 (CRPS1) vascular changes occur from the initial, inflammatory event onto the trophic signs during chronicity of the disease, resulting in blood flow disturbances and marked temperature changes. Pharmacotherapeutic treatment is generally inadequate.

Aim: To determine whether local application of the nitric oxide donor isosorbide dinitrate (ISDN) could cause vasodilation and thereby improve tissue blood distribution in the affected extremity.

Methods: In a pilot study, 5 female patients with CRPS1 in one hand were treated with ISDN ointment 4 times daily during 10 weeks. As a primary objective videothermography was used to monitor changes in blood distribution in both the involved and contralateral extremities.

Results: Patients treated with ISDN showed an increase of 4°C to 6°C in mean skin temperature of the cold CRPS1 hands, reaching values similar to that of the contralateral extremities within 2 to 4 weeks time, suggesting normalization of blood distribution. This was confirmed by an improvement in skin color. In 3 patients the Visual Analog Scale pain declined, whereas in the other 2 patients the Visual Analog Scale pain was unchanged over time.

Conclusions: In this pilot study, topical application of ISDN seems to be beneficial to improve symptoms for patients with cold type CRPS1, but further study is needed.

Key Words: complex regional pain syndrome, cold dystrophy, endothelin-1, nitric oxide, videothermography, isosorbide dinitrate

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Complex regional pain syndrome (CRPS) is a painful disorder that usually occurs after an often minor precipitating event or trauma such as a fracture, sprain, or after surgery. The main characteristics are continuous pain, marked changes in tissue blood flow and skin surface temperature, edema and sweating, movement disorders and trophic changes of the skin, and the severity of the symptoms is disproportionate to the initial event.[1,2] The diagnosis of CRPS is entirely based upon consensus-derived clinical criteria.[3–5] In the Netherlands, the incidence of complex regional pain syndrome type 1 (CRPS1) is approximately 2.6% for different fractures, which results in approximately 5100 new patients yearly, of whom a substantial portion will not recover.[6,7] The female to male ratio is approximately 3:1, with a median age of 52.7 years at onset.[8] The hand is affected twice as often as the foot.

Available treatments are limited and insufficient to induce recovery.[6] Analgesics and local anesthetics are used to suppress continuous pain. The long-term prognosis for recovery is poor. Owing to pain and severe trophic disturbances, chronic CRPS1 can even lead to amputation of the dystrophic extremity.

The pathophysiology of CRPS1 has not been unravelled, but growing evidence indicates the involvement of exaggerated inflammatory processes. Both central and peripheral mechanisms have been proposed to play a prominent role.[6] Central sensitization leading to exacerbations of pain is thought to be the result of neuroimmune activation of cells in the peripheral nervous system.[9] During the neurogenic inflammation neuropeptides,[10] cytokines, and other mediators are released.[11] This leads to a so-called warm dystrophy with signs of inflammation such as redness, increased skin temperature, loss of function, and pain.[5,6,12]

During the chronic, disabling stage of the disease signs of extravasation and edema change into atrophy; regional blood flow declines and increased skin temperature changes into diminished temperature.[13,14] These findings point to impaired microcirculation that affects nutritive blood flow in superficial and deep tissues.[15,16] The microcirculation is regulated by neural and endothelial factors and the contribution of the latter could be crucial. Recently, we have shown that in patients with an intermediate type of CRPS the endothelin-1 (ET-1) levels in skin blister fluid were increased in affected extremities, whereas the nitric oxide (NO) levels, measured as

$NO_2 + NO_3$ (NO_x), were decreased.[17–19] As a consequence the ET-1 related vasoconstriction will be overexpressed in comparison with the diminished vasodilative activity of NO.

This pilot study investigates the effects of topical application of the NO donor isosorbide dinitrate (ISDN) on the tissue blood distribution. This vasodilator might be effective in the renormalization of the disturbed balance between ET-1 and NO_x and the diminished microcirculation, thereby reducing tissue acidosis and the resulting pain.

MATERIALS AND METHODS

Patients

Five female patients with mean age 49.6 ± 7.1 years were selected to be treated in an open label study with ISDN. The mean duration of the disease was 39.8 ± 23.9 months, and all patients were diagnosed as stable cold CRPS1.

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

The patients received 1 g ointment containing 1% (10 mg) ISDN 4 times daily (at 8 AM, 12 NOON, 4 PM, and 8 PM) during 10 weeks. The medication was supplied by the local pharmacy department.

Thermographic Measurements

Registration of skin surface temperature by means of computer-assisted videothermography is an objective parameter to study the long-term effects of pharmacotherapeutics.[20,21] Changes in skin temperature of the extremities are caused either by local inflammation of the tissue or by changes in blood flow in vessels located just underneath the skin. Besides inflammation, vasodilation and enhanced blood distribution also cause a visible increase in skin temperature. In contrast, a decrease in local skin temperature, as normally observed in chronic CRPS1, is directly related to diminished tissue blood distribution.[22]

Under normal conditions the degree of thermal asymmetry between opposite sides of the body is very small. Using computerized thermography in healthy persons, the skin temperature difference between both sides of the body is less than 1% or $< 0.25^{\circ}C$.[21,23,24] Therefore, in the present study a difference in matched regions of $> 1^{\circ}C$ was considered to be a significant disease-related effect.

The skin temperature of both hands was registered with a computer-assisted infrared thermographic camera (ThermaCAM SC2000, Flir Systems, Berchem, Belgium) following a standard protocol.[19,20] Thermographic images of the CRPS1 hand and the contralateral hand were compared and the mean temperature (in °C) and the differences in temperature (maximal − minimal temperature) of the hand and the fingertips were determined as described before.[20,21]

Measurements of Pain and Muscle Force

The patients used a weekly diary to record daily pain [Visual Analog Scale (VAS), recorded in 0 to 100 mm], comedication, and the occurrence of any adverse events. This pain score was recorded 3 times daily, at 8 AM, 12 AM, and 8 PM.

Pain intensity was assessed with the McGill Pain Questionnaire-Dutch Language Version (MPQ-DLV), measured by counting the total number of words selected.[25,26]

The force of the elbow extensor and flexor muscles was measured using a MicroFet 2 dynamometer (Hoggan Health Industries Inc, West Jordan, UT). The elbows were positioned on a table with 45 degrees of flexion and the dynamometer was first placed on the dorsal and then on the ventral side of the distal forearm, just proximal of the processes styloideus ulnae. The patient was asked to resist the movement of the examiner with maximal force, according to the "break" method.[27,28] The value of 3 measurements was noted.

The maximal isometric grip force of the hands was measured with a Jamar dynamometer (Sammons Preston Rolyan, Bolingbrook, IL), with the adjustable handle in the second position. The dynamometer was held freely, the forearms rested on a table with both elbows flexed at 90 degrees without touching the trunk. The wrist was held between 0 and 30 degrees dorsiflexion and between 0 and 15-degree ulnar deviations. The patients were asked to exert maximal force to the dynamometer. The value of 3 trials was noted and the results are expressed as means ± SD.[29–32]

RESULTS

A marked and continual increase in skin surface temperature of the CRPS1 affected hand of more than 4°C was observed in all patients within 2 weeks, reflecting improved tissue blood distribution. Although ISDN was applied locally, systemic effects were observed within 1 week, reflected by a simultaneous increase of temperature in the contralateral side. Thermographic images were taken before and after 2 weeks of treatment and the calculated mean temperatures and derived data are given in Table 1.

Three patients reported headache during the first 2 weeks. Figure 1 shows that the VAS of 3 patients improved, whereas 2 patients did not report any change in VAS pain. At the end of the 10-week treatment period the mean difference in VAS pain score had decreased from 41 ± 10 to 34 ± 15 mm, and the MPQ was slightly improved from 15 ± 3.4 to 14 ± 6.3 selected words.

One patient's hand was dystonic without any voluntary movement; this did not change after treatment. The muscle force of the elbow flexors in the remaining 4 patients improved from 63 ± 48 to 103 ± 58 Newton (N),

TABLE 1. Thermographic Data: Mean Temperature in °C ± SD in 5 Patients Before Treatment, After 2-week ISDN and After 10-week of Treatment

Week	CRPS Fingertips*	Contralateral Fingertips	CRPS Hand†	Contralateral Hand
0	28 ± 4.5	30 ± 3.8	29 ± 3.7	32 ± 1.9
2	34 ± 1.3	34 ± 1.1	33 ± 1.5	34 ± 1.1
10	33 ± 2.1	31 ± 4.0	33 ± 1.6	31 ± 3.0

*The mean fingertip temperature was calculated from 5 fingers.
†The mean hand temperature was calculated from the whole hand as shown in Figure 1.

and the extensor muscles from 59 ± 31 to 77 ± 13 N. Although the isometric hand grip force improved in 3 patients, the mean score in all 4 patients decreased from 87 ± 76 N before treatment to 79 ± 75 N after 10 weeks (difference not significant).

DISCUSSION

This is the first study in which the NO donor ISDN has been used to induce vasodilation in CRPS1 patients. Although the role of NO in CRPS has not yet been fully elucidated, an in vitro study has shown an increased production of NO from interferon-γ stimulated peripheral blood monocytes obtained from CRPS patients.[33] As indicated above, our previous studies showed an inverse relationship between *increased* ET-1 and *diminished* NO_x in CRPS compared with contralateral blister samples.[17,19] This inverse relationship has also been observed in vascular homeostasis where endothelium dysfunction plays a prominent role.[34] In male patients with erectile dysfunction, significantly increased venous plasma ET-1 levels and decreased venous NO levels were found.[35]

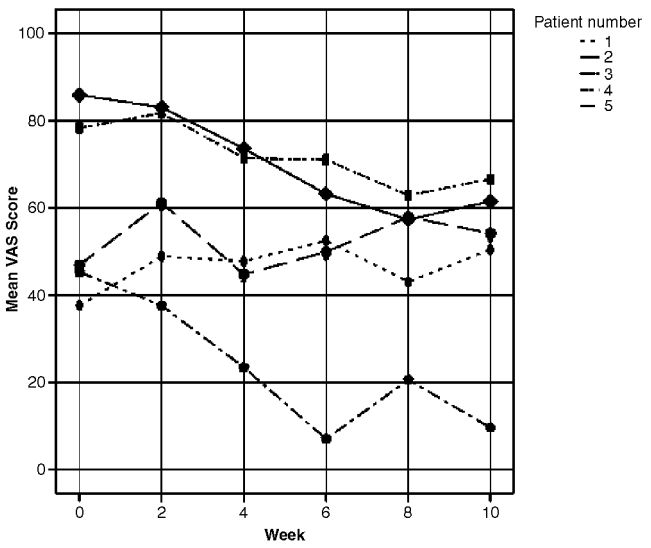

FIGURE 1. VAS ranging from 0 to 100 mm. The 5 patients registered their pain scores daily at 8 AM, 12 AM, and 8 PM in the week preceding each clinical visit. The figure shows the median pain score before and during 10 weeks of ISDN treatment. In 3 patients the VAS score diminished, but in 2 patients the score remained practically unchanged.

In view of the assumed diminished tissue blood flow, the focus should not be on inhibition of the NO synthase but, on the contrary, NO donors should be supplemented.[36]

Transdermal ISDN ointment has been reported to increase the hand vein diameter.[37] The same NO donor has also been successfully used in the treatment of anal fissures,[38] chronic painful diabetic neuropathy,[39,40] and obstructed hand veins.[37]

In the current pilot study, we found that local application of ointment improved tissue blood distribution in CRPS1. The study does, however, have some limitations. Because only 5 patients were included, the changes in temperature can be considered to be no more than an indication for the effect of the medication. There was no control group, nor were patients and investigators blinded. To show the effects of a NO donor on the endothelial dysfunction more information is needed on the changes in NO/ET-1 values.

However, an interesting finding was that the VAS scores improved most in those patients reporting "a cold pain deep within." The combined use of descriptive questionnaires like the Neuropathic Pain Scale,[41] the McGill Pain Questionnaire, and the VAS might reveal more about the nature of these changes. It would also be interesting to investigate whether the changes in muscle force correlate with changes in patient's arm-hand activity level. A larger double-blind randomized controlled trial is needed to address all these questions.

In conclusion, NO seems to function as a controlling mechanism against ET-1–induced vasoconstriction in the chronic, cold stage of CRPS1. Prolonged vasodilation induced by NO donors could result in an improved blood distribution as the first step toward remission of this severely invalidating disease.

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