Prostacyclin Reduces Symptoms and Sympathetic Dysfunction in Erythromelalgia in a Double-blind Randomized Pilot Study

Article in Acta Dermato Venereologica · February 2003
DOI: 10.1080/00015550310015031 · Source: PubMed

CITATIONS 15
READS 285

3 authors:

- Ole Magne Kalgaard
  Frogner Helseenter
  8 PUBLICATIONS 179 CITATIONS
  SEE PROFILE

- Cato Mørk
  Norwegian University of Science and Technology
  55 PUBLICATIONS 1,623 CITATIONS
  SEE PROFILE

- Knut Kvernebo
  Oslo University Hospital
  108 PUBLICATIONS 2,207 CITATIONS
  SEE PROFILE

Some of the authors of this publication are also working on these related projects:

Project Microvascular hemodynamics View project
Sympathetic dysfunction and skin microvascular arteriovenous shunting with insufficient nutritive perfusion and tissue hypoxia have been reported in patients with erythromelalgia. The objective of this study was to determine whether iloprost, a synthetic prostacyclin analogue – primarily a vasodilator and inhibitor of platelet activation – improves symptoms and sympathetic function in patients with erythromelalgia. Erythromelalgia is a rare condition, but we managed to collect 12 primary cases for a double-blind, randomized, parallel-group pilot trial evaluating the effect of iloprost \((n=8)\) and placebo \((n=4)\). The treatment effect was determined by the need for cooling of affected skin and by vasoconstrictor tests following Valsalva’s manoeuvre and contralateral cooling. The results show a significant reduction in symptoms \((p<0.05)\) and sympathetic dysfunction \((p<0.05)\) in the iloprost group. Further studies with oral prostacyclins or analogues are suggested. Key words: clinical trial; erythromelalgia; iloprost.

(Accepted June 12, 2003.)

Acta Derm Venereol 2003; 83: 442–444.

Cato Mørk, Rikshospitalet University Hospital, Department of Dermatology, NO-0027 Oslo, Norway. E-mail: cato.mork@rikshospitalet.no

Erythromelalgia (EM) is a rare disorder of skin circulation in the hands and/or feet. It is characterized by burning pain that is aggravated by warming and relieved by cooling, erythema and increased temperature of affected skin \((1, 2)\). The condition can be primary or secondary to another disease \((3)\).

The pathogenesis of EM is debated. Our group has previously hypothesized that EM is not a specific disease entity, but a symptom complex caused by one common pathophysiological mechanism: skin microvascular arteriovenous shunting with insufficient nutritive perfusion and a corresponding tissue hypoxia \((4–6)\). Autonomic dysfunction \((7–9)\) and endothelial injury \((10)\) have also been reported, but it is not known whether these mechanisms are primary or secondary to the vascular dysfunction.

Reviews of current therapeutic approaches have been published recently \((11–13)\), but the results have generally been disappointing; no treatment apart from cooling is consistently effective, and the level of evidence behind each therapeutic approach is weak. Effects of parenteral prostaglandin E1, prostacyclins or prostacyclin analogues have been reported \((4, 14)\). The theoretical rationale for these drugs is a dilatatory effect on cutaneous circulation, cytoprotective and thromboocyte aggregation inhibitory effect \((15–17)\). Our group has repeatedly argued that a maldistribution of skin microcirculation, with increased thermoregulatory shunt flow and an inadequate nutritional perfusion, is a pathomechanism in EM \((4–6)\).

Our prestudy hypothesis was that the vasodilatory and thromboocyte aggregation inhibition effect of prostacyclin may improve nutritive perfusion. So far, no properly designed trial of drug treatment of EM has been published. Using both clinical and physiological endpoints, in this pilot study we report the results of a double-blinded, placebo-controlled, randomized trial of iloprost treatment in 12 patients with EM.

MATERIALS AND METHODS

Patients

From our database of patients with EM, 14 patients were recruited \((18)\) and screened for laboratory abnormalities and current EM symptoms. Fertile females were instructed to practice medically approved contraception during the study. Exclusion criteria included confounding concurrent diseases or drugs, active gastrointestinal ulcerations, history of intracranial bleeding, pregnancy (positive gravitest) and deficient haemostatic function. Twelve patients [female/male = 8/4, 52 \((17–74)\) years (median with range), duration of EM 9.9 \((3.6–23.4)\) years] were eligible for the study, with a definite diagnosis of primary EM localized to the feet. Informed written consent was obtained as well as approval from the local ethics committee and the Norwegian Medicines Control Board.

Treatment and evaluation procedures

A double-blind parallel group trial was designed. The eligible patients were allocated to either iloprost \((n=8)\) or placebo \((n=4)\) infusions according to a weighted randomization schedule (Table I). A study nurse administered and monitored the treatment. Iloprost was diluted to a concentration of 0.2 \(\mu\)g/ml in saline identical in appearance to placebo \((0.9\%\) NaCl). The study medication was given in a peripheral vein for 6 h on 3 consecutive days while patients were hospitalized. The dosage was from 10 to 40 ml/h: On the first day of...
**RESULTS**

The cooling score was significantly reduced in the iloprost group after treatment ($P<0.05$) as compared to baseline values (Table II). The reductions in flux after Valsalva’s manoeuvre and contralateral cooling were significantly higher ($P<0.05$) one month after treatment with iloprost compared to the baseline values (Table II). No differences were demonstrated for the clinical and demographic data (Table I), nor for the primary and secondary endpoints (Table II) between the iloprost and placebo groups.

Mild adverse events were only reported among patients in the iloprost group: erythema ($n=5$) or warm sensation ($n=2$) at the injection site, headache ($n=5$), nausea ($n=1$) and hypotension ($n=1$). The symptoms were dose-related and resolved rapidly on reduction of the infusion rate. Maximum dosage was tolerated for three patients in the iloprost group at the third day of intervention. No clinically significant changes in blood tests were demonstrated.

**DISCUSSION**

This pilot study indicates that treatment with iloprost significantly reduces the need for cooling of the affected skin, and the sympathetic dysfunction, previously demonstrated in patients with EM, improves significantly.

EM is a rare condition. A limitation of this study was the low number of patients included. Previously, only case reports or small series with treatment of EM have been published. We managed to collect 12 patients — too small a number of patients to perform prestudy estimates of sample size based on power considerations. A weighted randomization was applied to get more patients in the iloprost group to make statistical analyses possible.

Relief by cooling of affected skin is the focus of test was used to analyse post-treatment as compared to pretreatment endpoints. Chi square and Mann-Whitney tests were used to compare discrete data. Significance levels are reported two-tailed and considered to be significant with $P \leq 0.05$ using SPSS 10.0 software (SPSS Inc., Chicago, Ill., USA).
attention for patients with EM and their daily activities are often limited because of the need for cooling. Cooling score has previously been applied as an indicator of EM severity (18). Significant improvement in cooling score was observed in the iloprost group. Variability in EM symptoms is well known. Using mean values of daily recordings for one week reduced the effect of daily variations in symptoms. Two of the four placebo-treated patients also experienced a reduced need for cooling.

The physiological outcome measures were chosen based on the previous demonstration of attenuated vasoconstrictor responses involving central sympathetic reflexes in patients with EM (9). Also these physiological endpoints imply a positive treatment effect of iloprost with reversal of sympathetic dysfunction.

Deranged prostaglandin metabolism in relation to skin vasculature has been described in patients with EM (19). According to the microvascular shunt hypothesis of pathogenesis, vasoconstrictor treatment is contraindicated, while vasodilators such as sodium nitroprusside, prostaglandins and prostacyclins may enhance nutritional blood flow, improve tissue oxygenation and induce symptom relief (20). The dosage of iloprost was based on a previous study protocol, and before this study we had treated four patients with EM with beneficial effect using the same regimen (21). No dose–response study has been performed for the treatment of EM. The reported adverse events related to iloprost treatment may have confounded the blinding in this study.

The results of this study indicate that iloprost has a treatment effect on EM. Prostacyclin analogues are now commercially available as tablets, and we believe that the results of this pilot study give a rational basis for planning a properly designed placebo-controlled study of the effect of these analogues on a larger EM patient material.

ACKNOWLEDGEMENT
We thank Schering AG for study medication delivery.

REFERENCES