Introduction

Cicatrization of chronic venous ulcers of the lower limbs is often problematic, leading to a significant impact on healthcare spending, patient invalidity and sick leave (1). The condition affects between 0.25% and 1.25% of the general population (2-4).

There is still debate concerning how these ulcers form. The hemodynamic theory is based on stasis and venous hypertension (5,6) while an alternative suggests microcirculatory changes involving fibrin cuffs (7,8) and white cell trapping (9,10). Whatever the underlying mechanism, the result is a coagulation and metabolic imbalance that affects the normal cutaneous blood supply. It is in fact chronic local hypoxia that disrupts the equilibrium, triggering a cascade of events which culminates in the formation of an ulcer (8,10).
The efficacy of Iloprost for the treatment of chronic venous ulcers of the lower limbs

Many studies have demonstrated the vasoactive effect of certain drugs on venous ulcers (11-14). Iloprost is a stable synthetic analogue of Prostaglandin I2 (PGI2 or prostacyclin), that has numerous pharmacological properties. These include reduction of platelet adhesion and aggregation, reduction of blood viscosity, a profibrinolytic effect, inhibition of chemotaxis and monocyte and neutrophil adhesion, reduction of vascular permeability in inflammatory conditions, reduction of ICAM1, reduction of metalloproteinase expression, neoangiogenesis and modulation of cytokine production (15-18).

In this retrospective study, we report our experience concerning the efficacy of Iloprost combined with local treatment and elastic compression in the treatment of venous ulcers in the lower limbs.

Patients and methods

A total of 52 patients with chronic venous ulcers of the lower limbs of between 5 and 25 cm in diameter were selected over a two-year period from January 2007 to January 2009. Patients had previously been diagnosed as suffering from chronic venous insufficiency by clinical examination and by echo-color-Duplex. We excluded all patients with chronic obliterative arterial disease of the lower limbs, arterial, neuropathic or diabetic ulcers, blood diseases, vasculitis or neutropathy. Participants were treated as outpatients. Before enrolment, they underwent color-Duplex ultrasound of the lower limbs (19) to determine the cause of their ulcer (variceous or post-thrombotic) and exclude arterial stenosis. Any valvular incompetence of partial or total occlusion of the superficial and deep venous systems and the perforating veins was also evaluated.

Patients were divided into two groups. Group I comprised 29 patients, 19 women and 10 men, with an average age of 52.5 ± 2.9 years. This group received Iloprost infusion therapy for six hours per day for three consecutive weeks. A peristaltic pump was used to administer Iloprost, starting with a dose of 0.5 ng/kg/min on the first day of treatment and ramping up by 0.5 ng/kg/min at 30 minute intervals to 2 ng/kg/min. Thereafter, this full dose of 2 ng/kg/min was administered immediately for the remaining days. Group II comprised 23 patients, 16 women and 7 men, average age 54.5 ± 3.4 years, who received infusion treatment with a saline solution for six hours per day over three consecutive weeks. In both groups the ulcers were also treated locally with a saline solution, antiseptic disinfectant, debridement and surgical toilet. A compression bandage was also used in all cases, with the degree of compression depending on whether the superficial or deep venous system was affected.

All patients were monitored every 15 days over six months. During these follow-ups the state of the ulcers was assessed and its diameter determined using AutoCad 2006 software, calculating the percentage reduction in ulcer size.

Statistical analysis was conducted using the t-test for the follow-up phase and Fisher’s exact test to compare the numbers of healed ulcers in the two groups. P < 0.05 was considered statistically significant.

Results

No serious local effects arose in patients of either group, except for one case of headaches and one of hypotension in Group I. The two groups had similar demographics, medical history, risk factors, venous alterations detected by ultrasound and ulcer size (Table 1). There was a progressive reduction in ulcer size in both groups until cicatrization was complete. This was achieved in all 29 patients (100%) in Group I and 19 (82.60%) in Group II by the end of the 180 day follow-up (P < 0.05). Ulcers healed more rapidly in Group I patients: 65.51% by 60 days, 86.20% by 90 days and 100% by 120 days; the corresponding figures for Group II were 30.43%, 60.86% and 82.60%. The difference between the two groups was statistically significant, with the Iloprost group surpassing the placebo (P < 0.001 long-rank test).

Discussion and conclusion

In this randomized study patients with chronic venous ulcers were treated with Iloprost or placebo in combination with elastic compression and topical treatment. The six-month follow-up was sufficient to assess the effects of the treatment (20). Intravenous administration of Iloprost was found to be truly effective in patients with chronic venous ulcers of the lower limbs. The treatment seemed to accelerate cicatrization and heal the ulcers completely: all lesions in the active treatment group healed within 120 days, two months before the end of the six-month follow-up, compared with only 60.86% at 120 days and 82.60% at 180 days for the placebo group. This difference was statistically significant.

Rudofsky (21) demonstrated that 40% of resistant ulcers healed quickly and completely when treated intravenously with PGE1. Another study (22) confirmed the efficacy of infusion therapy using PGE1 on patients with venous ulcers, achieving 100% cicatrization in under 100 days.

The difference between the two groups was already evident in the first 30 days, with significantly better results regarding reduction in ulcer size and cicatrization.

<table>
<thead>
<tr>
<th>Table 1 - PATIENT CHARACTERISTICS.</th>
<th>Group I, n</th>
<th>Group II, n</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Iloprost</td>
<td>Placebo</td>
</tr>
<tr>
<td>Color-Duplex</td>
<td></td>
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<tr>
<td>Partial or total thrombosis</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Valvular incompetence of superficial veins</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Valvular incompetence of deep veins</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Valvular incompetence of perforating veins</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Saphenofemoral reflux</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Saphenopopliteal reflux</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Ulcer characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average time since onset (months)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Average ulcer area (cm²)</td>
<td>14</td>
<td>12</td>
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in the active treatment group. The positive effects achieved with Iloprost are due to its numerous beneficial effects (23,24): inhibition of chemotaxis and monocyte and neutrophil adhesion, stabilization of the endothelial membrane, fibrinolytic effect and reduction on the adhesion of lymphocytes on the endothelium (25,26). It also reduces the expression of adhesion molecules (27-29), regulates capillary permeability (30) and acts locally on the microcirculation (21). However, its long term effects are very difficult to explain. It has low stability, a short half life and is quickly eliminated, making its persistent clinical effect post-treatment counter-intuitive. In fact, while its direct effect on vascular cells lasts just a few hours, its indirect effects on fibrinolysis, responsible for its clinical effect, continue for some time (22).

The cost-benefit ratio is another aspect to be considered. Chronic venous ulcers have a significant impact on both healthcare spending and working days lost. Several studies (31) have suggested that the high costs of managing these patients can only be lowered by shortening the ulcer healing time—especially if this can be reduced to six months or less (32,33,34). This is also beneficial for patients, with less time spent in hospital, a better quality of life and a quicker return to work.

In conclusion, Iloprost therapy in patients with chronic venous ulcers is effective in reducing healing time, lowering costs and improving quality of life.

### Table 2 - Ulcer Healing Time

<table>
<thead>
<tr>
<th>Time</th>
<th>Group I, n</th>
<th>Group II, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iloprost</td>
<td>Placebo</td>
</tr>
<tr>
<td>30 days</td>
<td>11/29 (37.93%)</td>
<td>3/23 (13.04%)</td>
</tr>
<tr>
<td>60 days</td>
<td>19/29 (65.51%)</td>
<td>7/23 (30.43%)</td>
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<tr>
<td>90 days</td>
<td>25/29 (86.20%)</td>
<td>11/23 (47.82%)</td>
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<tr>
<td>120 days</td>
<td>29/29 (100%)</td>
<td>14/23 (60.86%)</td>
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<tr>
<td>150 days</td>
<td></td>
<td>17/23 (73.91%)</td>
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<tr>
<td>180 days</td>
<td></td>
<td>19/23 (82.60%)</td>
</tr>
</tbody>
</table>

### References

17. Weksler BB, Jaffe EA, Brower MS, Cole OE. Human leukocyte cathepsin G and elastase specifically suppress thrombin-induced
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