

The efficacy of Iloprost for the treatment of chronic venous ulcers of the lower limbs

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SUMMARY: The efficacy of Iloprost for the treatment of chronic venous ulcers of the lower limbs.

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Background. *The purpose of this study was to assess the effect of Iloprost in the treatment of venous ulcers.*

Patients and methods. *We recruited 52 patients with uncomplicated venous ulcers of the lower limbs. They were divided into two groups: the first (29 patients) was given Iloprost in saline solution for three weeks, while the second (23 patients) received saline solution only. The size and number of ulcers were determined at the start of the treatment and then every 15 days for six months.*

Results. *Ulcer size diminished faster in the patients treated with Iloprost, with 100% healed within 120 days. In the placebo group, 82.60% had healed by the end of the 180-day observation period. This difference was statistically significant. Ulcer cicatrization was also faster in the treatment group (65.51% after 60 days, 86.20% after 90 days and 100% after 120 days), whereas in the placebo group, the ulcers had still not healed in 17.40% of patients by the study end.*

Conclusions. *Iloprost can significantly reduce healing time for venous leg ulcers without any specific complications.*

RIASSUNTO: Efficacia dell'Iloprost nel trattamento delle ulcere venose croniche degli arti inferiori.

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Obiettivo. *Lo scopo di questo studio è stato quello di valutare l'effetto dell'Iloprost sui pazienti con ulcere venose croniche agli arti inferiori.*

Metodi. *Abbiamo selezionato 52 pazienti con ulcera venosa cronica degli arti inferiori. Sono stati formati due gruppi di studio: il primo, di 29 pazienti, è stato sottoposto a trattamento con Iloprost in soluzione fisiologica per 3 settimane; il secondo, di 23 pazienti, è stato trattato solo con soluzione fisiologica. La misura ed il numero delle lesioni ulcerative sono stati valutati all'inizio del trattamento ed ogni 15 giorni per 6 mesi.*

Risultati. *La riduzione della dimensione delle lesioni ulcerose è avvenuta più rapidamente nei pazienti trattati con Iloprost; infatti in questi il 100% delle ulcere si è cicatrizzato in 120 giorni contro solo l'82,60% a 180 giorni del gruppo placebo. Questi risultati mostrano una significatività statistica a favore del gruppo Iloprost rispetto al gruppo placebo. Nel primo gruppo si è avuta una cicatrizzazione delle ulcere in un breve periodo, per il 65,51% dopo 60 giorni, per l'86,20% dopo 90 giorni e nel 100% dopo 120 giorni. Nel gruppo placebo, alla fine del follow-up, nel 17,40% dei pazienti non si è avuta la guarigione della lesione ulcerativa.*

Conclusioni. *L'Iloprost riduce il tempo di guarigione delle lesioni ulcerative venose croniche senza particolari complicanze per i pazienti.*

KEY WORDS: Venous ulcer - Iloprost - Chronic venous insufficiency.
Ulcera venosa - Iloprost - Insufficienza venosa cronica.

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 micro-circulatory 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).

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-Doppler. We excluded all patients with chronic obliterative arterial disease of the lower limbs, arterial, neuropathic or diabetic ulcers, blood diseases, vasculitis or neuropathy. Participants were treated as outpatients. Before enrolment, they underwent color-Duplex ultrasound of the lower limbs (19) to determine the cause of their ulcer (varicose or post-thrombotic) and exclude arterial stenosis. Any valvular incontinence or 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, the full dose of 2 ng/kg/min was administered immediately treatment began. 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

TABLE 1 - PATIENT CHARACTERISTICS.

	Group I, n Iloprost	Group II, n Placebo
<i>Color-Duplex</i>		
Partial or total thrombosis	14	9
Valvular incontinence of superficial veins	21	21
Valvular incontinence of deep veins	20	19
Valvular incontinence of perforating veins	19	15
Saphenofemoral reflux and saphenopopliteal reflux	22	18
<i>Ulcer characteristics</i>		
Average time since onset (months)	5	5
Average ulcer area (cm ²)	14	12

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 2 - ULCER HEALING TIME

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

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, fibronolytic 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.

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