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ORIGINAL ARTICLE

Effectiveness of prostaglandin E1 in patients with mixed arterial and venous ulcers of the lower limbs

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Key words
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Abstract

Mixed arterial and venous ulcers of the lower limbs are present in around 15–30% of patients with chronic venous ulcers (CVUs) and are considered difficult-to-heal wounds. The aim of this study was to evaluate the results of the treatment of mixed arterial and venous ulcers of the lower limbs with prostaglandin E1 (PGE1) infusion. This study was carried out in 48 consecutive patients. Patients who showed intolerability to PGE1, and patients with peripheral neuropathy, blood or systemic diseases, malignancy and acute wound infections or necrotic tissue on the wound bed were excluded. The patients were separated at random into two main groups: group I (25 patients) received standard treatment and PGE1 infusion. Group II (23 patients) received only standard treatment. Pre-treatment data indicated the area of ulceration. The number of healed ulcers and the variation in the area of ulceration were considered as endpoints. The endpoints were noticed after 120 days from the beginning of treatment. Healing occurred in 80% of limbs of group I and in 52·2% of limbs of group II patients. The average reduction in area was 92% versus 60% in patients of group I and II, respectively. During the whole treatment period, the incidence of adverse events was 8% in group I: there was one case of headache and one case of headache and hypotension combined. No side effects were recorded in patients of group II. In conclusion, PGE1 infusion is a determinant in the reduction of the healing time of mixed ulcers of the lower limbs.

Introduction

Chronic venous ulcers (CVUs) represent a disability, with a prevalence of 0·25–1·25% (1–13) in the general population. The aetiology is multifactorial (5): venous hypertension and stasis play an important role in the genesis of venous ulcers, but microcirculatory alterations (14–17) and inflammation are also involved. Several studies have shown that matrix metalloproteinases (MMPs) are the main biological effectors of the inflammatory process, which characterises the pathophysiology of vascular (18–30) and non-vascular disease (31). Contemporary signs of peripheral arterial disease with a reduced ankle-brachial pressure index (ABPI <0·8) are present in around 15–30% of patients with CVU (5,32–35). Mixed ulcers are characterised by edema, eczema, hyperkeratotic skin, maceration, inadequate presence of granulation tissue, rolled wound edges, and delayed healing (5) (Figure 1).

Key Messages

- mixed venous and arterial ulcers account for approximately 15–30% of all venous leg ulcerations
- mixed ulcers are characterised by an inadequate presence of granulation tissue and delayed healing, and represent an important challenge for physicians
- Prostaglandin E1 (PGE1) seems to have multiple effects in wound healing processes
- in this study, PGE1 infusion in patients with mixed ulcers of the lower limbs was shown to be effective in reducing the healing time

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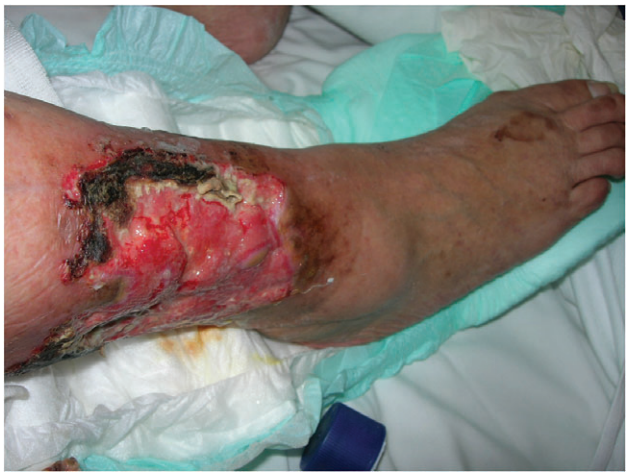

Figure 1 Example of mixed and arterial ulcer.

Previous studies on the anti-ischemic effects of some drugs (36), in particular in CVU, are reported in the literature (5,37–41). Prostaglandin E1 (PGE1) is a constituent of membrane phospholipids and it acts mainly on membrane receptors on the intercellular adenyl-cyclase, producing an increase in cyclic adenosine monophosphate, which is responsible for numerous actions, such as reduction of the adhesiveness and platelet aggregation; inhibition of the proliferation of smooth muscle cells of the media; reduction of hematic viscosity; profibrinolytic effects; inhibition of chemiotaxis and activation of white cells; restoration of the equilibrium between the microvascular flow-regulating system and the microvascular defence system, with a reduction of endothelial permeability; inhibition of the vasoconstrictive activity of thromboxane A2, serotonin, leukotrienes, and endothelin; and stimulation of the formation and growth of collateral circulation (42).

In this retrospective study, we report our experience of the efficacy of PGE1 in the treatment of mixed arterial and venous ulcers of the lower limbs.

Materials and methods

We performed an open-label, parallel-group study, which was conducted between January 2010 and December 2013 in two clinical departments (Catanzaro and Messina) and with prior approval from the Investigational Review Board of CIFL at University Magna Graecia of Catanzaro, in accordance with the Declaration of Helsinki. Before the beginning of the study, all participants had provided written informed consent. At the time of admission, the medical history of all the patients was recorded and clinical examination, laboratory tests, and arterial and venous duplex ultrasonography were performed, as previously described (18–21,43,44).

Patients

Patients of both gender and older than 20 years, with a clinical and instrumental diagnosis of mixed ulcer were eligible for this study. In accordance with our previous study (5), presence of venous reflux flow, ABPI >0·5 and <0·8, ulcer duration >6 weeks, ulcer size 2·5–10 cm^2, and >50% granulation tissue on the wound bed were detected.

Patients were excluded if they had diabetes mellitus; rheumatoid arthritis; malignancy; blood disorders; systemic disease; no current episode of ulceration; wound infection; ABPI <0·5 (patients with severe arterial disease at presentation were considered for arterial imaging with a view to revascularisation) or >0·8; systolic ankle pressure<60 mmHg; presence of necrotic tissue on the wound bed; medications that might impair wound healing; pain at rest; sensory loss (neuropathy); cardiac insufficiency; and medial calcinosis. Non-compliant patients and patients who showed intolerability to PGE1 were also excluded.

The ulcers were observed at each visit and a scan of each trophic lesion was registered. As previously described (45), the size of the ulcers was calculated from contour sheets at a central location by computerised planimetry using digital scanning and analysis software.

Healing evaluation

In agreement with previous studies (5,6,12), for each patient, healing was calculated by means of computerised planimetry at the beginning of the treatment and then at 30 (T1), 60 (T2), 90 (T3) and 120 days (T4). The result was divided by the number of weeks that the patient had been observed to obtain the total area healed per week.

For wound healing evaluation, rapid-healing ulcers should have a healing speed rate of ≥1 cm^2/week and slow-healing ulcers should have a healing speed rate of <1 cm^2/week.

Results

A total of 48 patients presenting with CVU of the lower limbs, an ulcer area between 5·4 and 9·76 cm^2, and contemporary signs of arterial impairment were enrolled. Patients were between 34 and 86 years of age; 28 were females and 20 males. All patients were similar with regard to comorbidities, risk factors, demographic characteristics, and venous and arterial disease (Table 1). Patients were randomised into two main groups: group I (25 patients) received surgery if required and PGE1 infusion [(Prostavasin, Schwarz Pharma) 60 mg PGE1 dissolved in 250 ml normal saline solution and administered by constant infusion over a period of 3 hours, twice daily, for 21 days]; group II (23 patients) received the same treatment, but without PGE1 infusion. All patients received daily wound care, consisting of ulcer cleaning with saline solution and topical antiseptics, and periodical surgical toilet and debridement. All patients were subjected to the most appropriate surgical treatment (defined as standard treatment), also taking into consideration the patient's wishes. The type of surgery, when it was accepted, was chosen according to the anatomical level of vein incompetence: superficial venous surgery [Cure Conservatrice et Haemodinamique de l'Insuffisance Veineuse en Ambulatorie (CHIVA) procedure was used for the correction of superficial venous reflux] and/or subfascial endoscopic perforating surgery after computed hemodynamic mapping, as previously described (5,44). All patients received a multicomponent, multilayer, compression bandage with pressure of 20–30 mmHg.

Table 1 Patients' characteristics and comorbidities

	Group I (%)	Group II (%)
Total number of patients	25 (100)	23 (100)
Mean age	55·3	54·7
Sex		
Male, *n* (%)	13 (52)	11 (47·8)
Female, *n* (%)	12 (48)	12 (52·2)
Comorbidities		
Hypertension, *n* (%)	13 (52)	12 (52·2)
Smoking, *n* (%)	11 (44)	12 (52·2)
Obesity, *n* (%)	18 (72)	16 (69·6)
Chronic obstructive disease, *n* (%)	16 (64)	15 (65·2)
Diabetes mellitus, *n* (%)	20 (80)	18 (78·3)
Dyslipidemia, *n* (%)	23 (92)	20 (86·9)
Venous insufficiency		
Partial or complete deep thrombosis	7 (28)	5 (21·7)
Partial or complete superficial thrombosis	7 (28)	6 (26·1)
Sapheno-femoral incompetence	15 (60)	12 (52·2)
Sapheno-popliteal incompetence	4 (16)	7 (30·4)
Superficial vein valvular incompetence	9 (36)	8 (34·8)
Deep vein valvular incompetence	7 (28)	6 (26·1)
Perforating vein valvular incompetence	5 (20)	4 (17·4)
Arterial insufficiency (ABPI >0·5 and < 0·8)		
Claudication		
Walking distance >200 m, *n* (%)	19 (76)	16 (69·6)
Walking distance <200 m, *n* (%)	6 (24)	7 (30·4)
Ulcer characteristics		
Average months from onset	5	6
Ulcer area in cm^2	12·5	11·3

ABPI, ankle-brachial pressure index.

Table 2 Healing of mixed ulcers

	Group I	Group II
Median ulcer area for each time point	6·08 cm^2 (T1) 4·34 cm^2 (T2) 3·88 cm^2 (T3) 1·62 cm^2 (T4)	7·25 cm^2 (T1) 6·18 cm^2 (T2) 4·95 cm^2 (T3) 3·72 cm^2 (T4)
Mean area of healing per week (cm^2/week)	1·10 (T1) 1·2 (T2) 2·9 (T3) 3·98 (T4)	0·87 (T1) 0·75 (T2) 1·44 (T3) 1·99 (T4)

During the follow-up period, a progressive reduction in ulcer size was observed in both groups: in patients of group I, a faster reduction in lesion size was observed, especially in the first 60 days after the beginning of PGE1 infusion, while in group II, the diameter of ulcers reduced slowly and gradually. Complete ulcer healing occurred in 80% of limbs of group I and in 52·2% of those of group II patients at 120 days (Table 2).

The average area reduction was 92% versus 60% at 120 days in groups I and II, respectively. Clinically, a reduction of edema was observed in 15 patients of group I and 6 patients of group II. Over a period of 6 months, cramps and eczema did not re-occur in 17 patients of group I and 5 patients of group II. Parallel to this, an increase in the Tanscutaneous Oxygen Pressure ($TcPO_2$) in the ulcer area with a mean of 46·4% and 25·4% was observed in patients of groups I and II, respectively.

During the whole treatment period, the incidence of adverse events was 8% in group I, with one case of headache and one case of headache and hypotension combined. No side effects were recorded in patients of group II. The main results are presented in Table 3.

Table 3 Results recorded during follow-up period

	Group I	Group II
Complete healing at 120 days (%)	20 patients (80%)	12 patients (52·2%)
Average reduction in area at 120 days (%)	92%	60%
TcPO2 increase in ulcer area at 120 days (%)	46·4%	25·4%
Adverse events	8%	–

Discussion

Mixed ulcers have the characteristics of CVU in combination with signs of arterial impairment; therefore, diagnosis of mixed ulcers is crucial because CVU is best managed using multilayer graduated compression bandaging (5), while compression alone is not appropriate for mixed ulcers because it may cause deterioration of tissue vitality and limb loss. Recent studies have shown that compression therapy with pressure of 20–30 mmHg can improve arterial perfusion and venous function in patients with ABPI between 0·5 and 0·8 and support ulcer healing (46).

In this study, the effects of intravenous PGE1 infusion on the healing of mixed ulcers of the lower limbs in 48 consecutive patients were evaluated. The results recorded during follow-up period highlight the effectiveness of intravenous PGE1 infusion in the healing of mixed ulcers of the lower limbs, which is in agreement with other studies reported in the literature (42,47–49). In fact, a faster reduction in ulcer size and a faster healing of the lesions was observed in patients of group I: healing occurred in 80% of lower limbs of group I versus 52·2% of those of group II. The average reduction in ulcer area was 92% and 60% in patients of groups I and II, respectively.

No studies about the effects of PGE1 on both venous and arterial ulcers of the lower limbs are reported in the literature, while results of the treatment of venous or arterial ulcers are described in the current literature.

Brodszky *et al.* (50) demonstrated the favourable effect of prostanoids on rest pain relief and ulcer healing in patients affected by critical lower limb ischemia, analysing seven randomised controlled trials including 964 patients. Ruffolo *et al.* (51) analysed data collected from the Cochrane Central Register of Controlled Trials and concluded that further well-conducted, high-quality randomised double-blinded trials should be performed to give definitive data on the long-term effectiveness and safety of different prostanoids in patients with critical lower limb ischemia. Milio *et al.* (42) performed a randomised, placebo-controlled, single-blind study in which 87 patients with venous leg ulcers were treated for 20 days with an infusion of PGE1 or placebo, in conjunction with topical therapy.

The reduction in the size of the mixed ulcers was faster in the patients treated with PGE1: in this group, 100% of the ulcers healed in <100 days, whereas in the placebo group, only 84·2% did so by the end of the 120-day observation period ($P < 0·05$).

Rudofsky (49) demonstrated in a double-blind controlled study a complete healing of 40% of 'resisting' ulcers in patients treated with PGE1 versus 9% in patients on placebo.

Even if the mechanism responsible for the appearance of venous ulcers has not been explained as yet, PGE1 probably plays a role through a range of concomitant actions such as reduction of adhesiveness and platelet aggregation; inhibition of the proliferation of smooth muscle cells of the media; reduction of hematic viscosity; profibrinolytic effect; inhibition of chemiotaxis and activation of white cells; restoration of the equilibrium between the microvascular flow-regulating system and the microvascular defence system, with a reduction of endothelial permeability and inhibition of the vasoconstrictive activity of thromboxane A2, serotonin, leukotrienes, and endothelin, and stimulation of formation and growth of collateral circulation. Furthermore, such effects could also be related to the local improvement in microcirculation, as suggested by Rudofsky (49).

In addition, although PGE1 has a very brief half-life of about 30 s, its clinical efficacy persists well beyond its period of administration: probably, the prolonged efficacy is related to one of its metabolites, PGE-0, that provides a longer half-life. Even if treatment with PGE1 involves a cost, the faster healing of ulcers reduces the duration of hospitalisation and it improves the quality of life of patients who are mostly young individuals.

In conclusion, in patients affected by mixed ulcers of the lower limbs, the intravenous infusion of PGE1 improves healing and microcirculation and it should be proposed for difficult-to-heal and refractory mixed ulcers of the lower limbs.

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