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PROSTAGLANDIN E_1 TREATMENT OF LEG ULCERS CAUSED BY VENOUS OR ARTERIAL INCOMPETENCE

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Abstract. An open and a double-blind study were undertaken on patients with leg ulcers caused mainly by venous (VI) or arterial incompetence (AI). They were treated with intravenous infusions or injections of prostaglandin E_1 (PGE_1). Eight of 10 patients in the open study experienced relief of pain and a complete or almost complete healing of their ulcers. In the double-blind study (20 patients) 4 out of 5 patients with a history of leg ulcers due to VI for more than 5 years responded to the PGE_1 treatment, compared with one of 5 treated with saline. In the saline group 3 more patients with VI of shorter duration improved. In 3 of 5 patients of PGE_1 with ulcers due to AI the original ulcer area was reduced by 78–65 % after 70 days, while in the 2 remaining cases healing occurred later on. No effect was noted in the 2 patients with ulcers due to AI who received saline infusions. The results indicate the beneficial effect of PGE_1 on pain and healing in leg ulcers caused by peripheral vascular disease.

Key words: Leg ulcers; Arterial, venous incompetence; Prostaglandin E_1 treatment

In humans the most obvious effects of intravenously injected prostaglandin E_1 (PGE_1) are the inhibitory action on platelet aggregation and the dilation of blood vessels, both leading to an increased peripheral blood flow (2, 3). Other effects of PGE_1 are the stabilization of lysosomal membranes (7), an anti-inflammatory action by antagonizing bradykinin (2) and stimulation of epidermal growth (1). These observed effects of PGE_1 could theoretically be beneficial to a patient with ischaemic disease such as ulceration of the lower limb.

In open clinical trials with PGE_1 in patients suffering from advanced peripheral arterial disease, striking relief of resting pain and healing of their ulcers has been observed (4). It has also been shown that the effect of PGE_1 was the same, irrespective of the route of administration, e.g. intra-arterial or intravenous infusion or intravenous injections (4). To further evaluate treatment with PGE_1 in patients with ulcers of the inferior extremities, two series were undertaken—one an open and one a double-blind study, including patients with venous or arterial incompetence.

MATERIAL AND METHODS

Patients

Open study. Ten patients, 3 females and 7 males with the ages ranging from 49 to 85 years were included (Table I). All patients had peripheral arterial disease and were treated with intravenous infusion or injections of PGE_1 at the Department of Dermatology, Karolinska sjukhuset, during the years 1977 to 1979.

Double-blind study. Twenty out-clinic patients with mainly venous or arterial incompetence were selected. Patients with diabetes, cardiac decompensation, rheumatoid arthritis, and arteriosclerotic gangrene and ulcers which were not clearly caused by mainly arterial or venous incompetence were excluded.

The diagnosis was based on the following examination protocol to establish the vascular incompetence as being mainly venous or arterial. Venous incompetence was diagnosed when the patient reported a history of deep venous thrombosis, showed swelling of the legs, signs of perforator insufficiency and ulcer localization on the lower leg overlying perforator veins. The history, symptoms and signs of arterial incompetence should be negligible. Arterial incompetence was diagnosed when the patient gave a history of dysbasia or intermittent claudication, and had pain when resting in the horizontal position. This pain should be revealed by lowering the foot. The patient should have no palpable peripheral pulses. Digital plethysmography and oscillometry should reveal arterial occlusions. The patients should have negligible signs and symptoms of venous incompetence.

The patients were randomized into two age-matched groups with 10 patients in each (Table II). One group was treated with PGE_1 infusions and the other with saline infusion. In the placebo group 8 patients had ulcers due to venous incompetence (VI) and 2 due to arterial incompetence (AI). The distribution in the PGE_1 group was 5 VI and 5 AI.

Treatment protocol

All patients had a standard topical treatment of the ulcers with either: Gentian violet 0.5 % (G) or Debrisan® (D)

Table I. *Clinical data of patients included in the open study and effect of PGE_1 treatment*

AI = arterial incompetence; VI = venous incompetence. Resting pain: +++ very intense; ++ intense; + moderate. Ulcer area: +++ multiple ulcers or one >2 cm^2; ++ 1–2 cm^2; + <1 cm^2. Effects on resting pain: +++ complete abolition; ++ almost complete abolition; + moderate relief
Effects on ulcer healing: +++ complete healing; ++ almost complete healing; + partial healing; 0 no healing

Case no.	Diagnosis	Sex	Age yrs	Resting pain	Ulcer area	No. of treatments	Follow up time, months	Effect	
								Resting pain	Ulcer healing
0–1	AI	M	72	+++	+++	2	4	+++	++
0–2	AI	F	85	+	+++	5	12	+	+
0–3	AI	M	77	+++	++	2	9	+++	++
0–4	AI + VI	M	70	+++	+++	2	4	+++	+++
0–5	AI	F	79	++	+++	2	13	+++	+++
0–6	AI	M	77	+	+++	2	2	+	0
0–7	AI	M	56	+++	+++	1	3	++	++
0–8	AI	M	63	+++	++	4	1	++	++
0–9	Mb Bürger	F	49	+++	+++	6	28	+++	+++
0–10	AI + VI	M	72	+++	+++	13	3	+++	+++

(Pharmacia, Uppsala, Sweden) combined with elastic Dauer K bandage® (L) (Lohmann GmbH Company KG, D-545 Neuwied 12, Germany) in those patients with venous incompetence, or Zincaband® (Z) (Seton Products Ltd., Oldham, Lancashire, UK) combined with Elastoplast® (E) (Beiersdorf AG, Hamburg, Germany) applied as a fixed double bandage changed weekly in the same group of patients. This treatment was not altered during the period of the study.

Correction of low zinc or iron levels in the serum was made prior to entering the study.

In the open study 7 patients received intermittent injections of 20 μg/10 ml PGE_1 given slowly during a period of 5–10 min every second hour seven times a day for 3 days, the total dose of PGE_1 being 0.42 mg. The other 3 patients received infusions of PGE_1 (see below). This was repeated once a month (Table I). *In the double-blind study* the patients were treated twice with continuous infusions over a 3-day period with an interval of one month. All patients received 3-litre saline infusions over 72 h, to which was added 0.36 mg PGE_1 or saline as the placebo. Thus, the dosage of PGE_1 was 5 μg/h. The treatment was given intravenously on the ward by personnel not involved in the evaluation of the results.

At each control the ulcers were drawn on a transparent sheet placed on top of the ulcer. The area was photographed and calculated planimetrically.

Control of the patients was made on the day before the first treatment and at intervals during the observation period of about 10 weeks and in some cases somewhat longer.

RESULTS

Open study (Table I)

Eight of the 10 patients had intense or very intense resting pain prior to the treatment, forcing the patients to hang the afflicted leg outside and below the bed every night. They also had a high consumption of potent analgetics and sedatives. Six of these patients received a complete abolition of pain. Two others became almost free of resting pains and were able to reduce their consumption of analgetics. Two patients with moderate resting pains prior to treatment experienced only minor improvements.

The ulcers in cases 0–4, 0–5, 0–9 and 0–10 healed completely. In cases 0–9 and 0–10 the PGE_1 treatment was given as a last resort, since amputation of the extremity involved was suggested by a consulting orthopedic surgeon. Almost complete healing occurred in 4 subjects and 3 of these (0–1, 0–7, and 0–8) are doing well. The observation period is only 1–4 months in these cases (Table I). Case 0–9 has been reported on recently (6). In case 0–2 a moderate influence of the healing of the ulcer was observed and in case 0–6 no effect at all was noted during and 2 months after the period of treatment with PGE_1.

Double-blind study

Venous incompetence was diagnosed in 13 cases, which are detailed in Table II and Fig. 1*a* and 1*b*. After the 10-week period, in 4 of the 5 cases with PGE_1 treatment, the ulcers diminished compared with 4 out of seven patients in the saline group. When the patients with a history of ulcers longer than 5–10 years in these groups were selected, 4 of 5 patients in the PGE_1 group responded with healing, compared with one of of 5 patients in the placebo group.

Table 11. *Clinical data of patients included in the double-blind study and the effect of PGE_1 and NaCl infusions on the ulcer area*

AI = arterial incompetence, VI = venous incompetence, G = gentian violet 0.5%, D = Debrisan®, Z = Zincaband®, L = Dauer K bandage®, E = Elastoplast®

Case no.	Age (y.)	Sex	Duration of illness (y.)	Type of incompetence	Local treatment	Original area (mm^2)	Remaining area after 70 days (%)
PGE_1 infusion							
1	83	F	10	VI	G+L	247	53
2	34	F	10	VI	D+L	490	43
3	82	F	10	VI	Z+E	1 660	69
4	25	M	5–10	VI	G+L	3 456	79
5	62	F	10	VI	G+L	3 580	115
6	60	F	1	AI	G	252	22
7	82	M	2	AI	G	602	35
8	87	M	1	AI	G	1 806	25
9	79	F	10	AI	G	3 095	120
10	79	M	10	AI	D	5 680	262
NaCl infusion							
11	50	M	3	VI	G+L	264	0
12	82	M	10	VI	G+L	336	113
13	81	F	4	VI	Z+L	382	24
14	82	M	10	VI	Z+E	406	103
15	73	M	10	VI	G+L	418	28
16	71	M	4	VI	G+L	620	61
17	57	F	10	VI	G+L	1 021	100
18	54	F	10	VI	G+L	4 298	100
19	67	M	5	AI	D	219	105
20	68	M	10	AI	G	3 876	98

Arterial incompetence was diagnosed in only 7 cases (Table II and Fig. 1*c* and 1*d*). Due to the randomization process, 5 cases were treated with PGE_1. In cases 6, 7 and 8 a good clinical result with decreasing ulcer areas were seen. Cases 9 and 10 had a more complicated cause due to intercurrent erysipelas as can be seen from the following summarized case reports.

Case 9

Woman, 79 years. Recurrent leg ulcers since 1962. Lateral and medial ulcers of the leg and foot since 1976. Plethysmography and oscillometry showed arterial obliterations in both popliteal arteries. Immediately after the first infusion of PGE_1 in September 1979 erysipelas complicated the course and her ulcers grew considerably during the interval between the two infusions. In the lateral wound a tendon became apparent. Slow improvement after the second PGE_1 infusion. In January 1979 the ulcers were covered with granulation tissue suitable for skin transplantation, which was performed in February 1979. Ten months after the first PGE_1 infusion the patient had only small residues of the ulcers.

Case 10

Man, 79 years. Since 1969 intermittent claudication and recurrent ulcers of the leg and foot. Heavy smoker since the age of 19. In January 1979 erysipelas in the leg. During and after the infection two increasing necrotic ulcers. In March 1979 digital plethysmography and oscillometry indicated almost total arterial obliterations in the left leg. The first infusion was given in March 1979 and the second one a month later. After the first infusion, almost free from pain. However, the ulcers continued to grow (Fig. 1) until one week after the second infusion. Since then the patient's condition gradually improved. When the code had been broken after the first 10 weeks it was decided to continue the treatment and the patient had another three PGE_1 infusions. In September 1979 the ulcers were superficial and covered by fresh granulation tissue. The patient has practically no pain and can walk freely. In October 1979 the remaining ulcerated areas received a skin transplant.

All patients with arterial incompetence treated with PGE_1 obtained considerable relief from pain and it was possible for them to keep their legs horizontal in bed during sleep. Consumption of analgetics decreased and they could start to do walking exercises again.

Six patients, 3 with venous and 3 with arterial incompetence, treated with PGE_1, had an original total ulcer area less than 2 000 mm^2 prior to the treatment. In these cases the ulcer area was re-

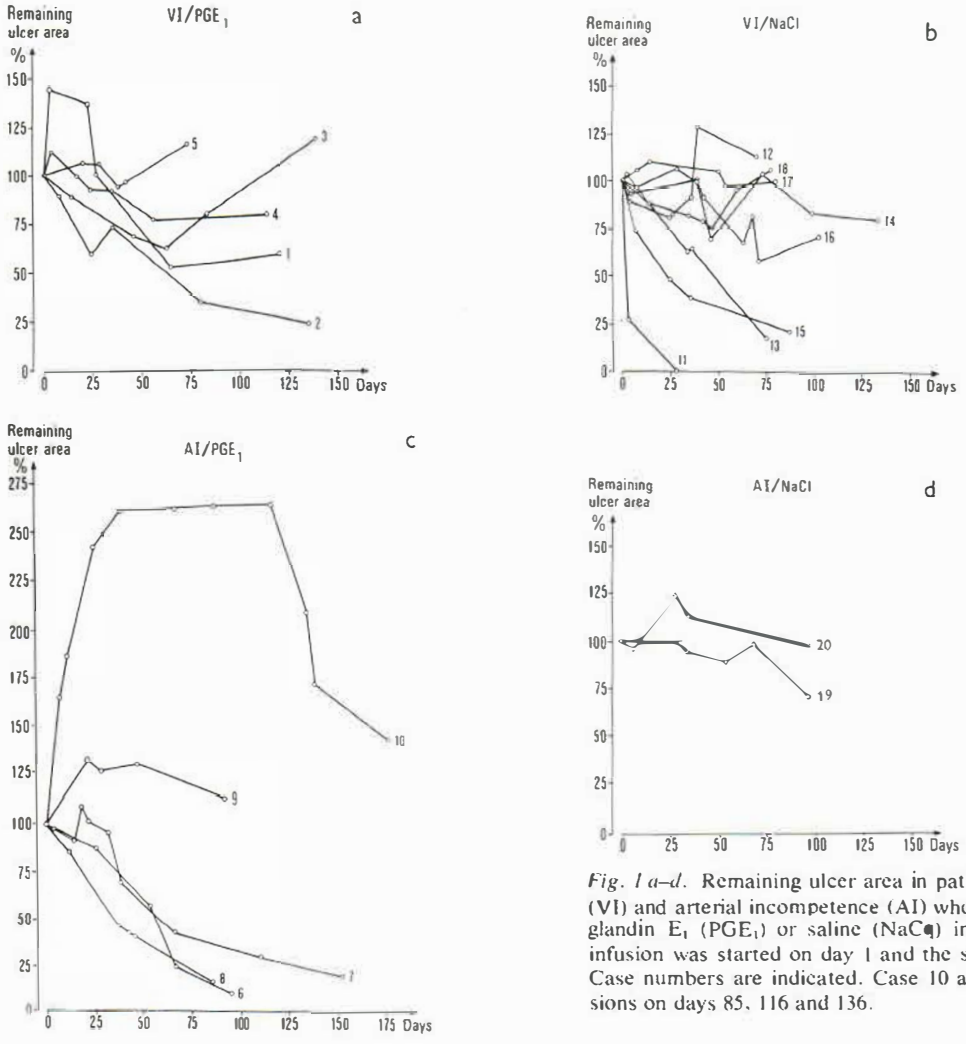

Fig. 1 a–d. Remaining ulcer area in patients with venous (VI) and arterial incompetence (AI) who received prostaglandin E_1 (PGE_1) or saline (NaCl) infusion. The first infusion was started on day 1 and the second on day 28. Case numbers are indicated. Case 10 also received infusions on days 85, 116 and 136.

duced by 78–31% after the 10-week period. In the remaining cases with larger ulcer areas, no reduction of the ulcer area was evident after 70 days. It may be pointed out, however, that in the 2 cases of arterial incompetence, reduction was observed eventually, as outlined in the case presentations. In the material, no differences were seen in response to the topical treatment. We were also unable to demonstrate any relationship between the effect of any treatment given, and age, sex, or ulcer localization.

Complication during treatment

The rate of complications was low. During infusions of the prostaglandin E_1 almost all cases showed slight irritation along the vein being infused and the area around the infusion needle. The irritation and redness were mostly localized to a few cm proximal to the site of the infusion. In those patients who were given intermittent injections, similar signs were present but disappeared mostly within 15 to 30 min after the end of the injection. In one case thrombophlebitis was observed in this area. The PGE_1 infusions were stopped in one patient because of chest pains and signs of congestive heart failure. The reason for this complication was probably an increase of plasma volume due to the infusion. This complication was avoided by intermittent injection of PGE_1 as performed in some of the open cases. Intermittent injections were preferred by those patients who have tried both ways.

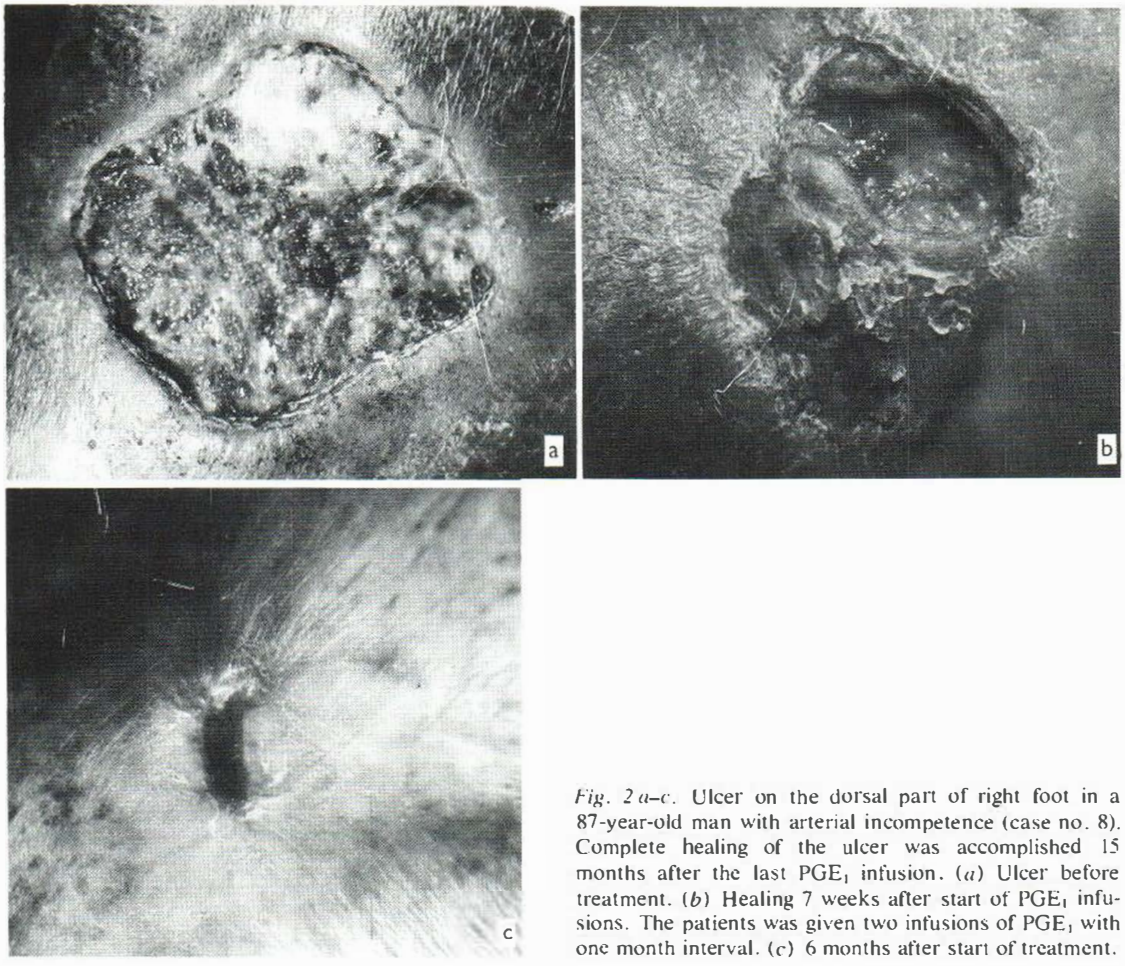

Fig. 2 a–c. Ulcer on the dorsal part of right foot in a 87-year-old man with arterial incompetence (case no. 8). Complete healing of the ulcer was accomplished 15 months after the last PGE_1 infusion. (*a*) Ulcer before treatment. (*b*) Healing 7 weeks after start of PGE_1 infusions. The patients was given two infusions of PGE_1 with one month interval. (*c*) 6 months after start of treatment.

DISCUSSION

The number of cases in the present study is too small to allow of firm conclusions as regards the healing effects of PGE_1 in venous incompetence, compared with saline. It should be noted, however, that patients with a long history of ulcers due to venous incompetence did react to the PGE_1 treatment. This was not the case for the corresponding subjects in the saline-treated group. This must imply that PGE_1 treatment offers an additive healing effect in persistent ulceration due to venous incompetence.

The observed relation between PGE_1 treatment and the original ulcer area might be thought to suggest that this treatment has a healing effect only on small ulcers but not in the larger ones. However, even the large ulcers are affected by PGE_1, though after a longer period, as was shown in the follow-up of our cases with arterial incompetence. This is in agreement with stereophotogrammetric measurements of leg ulcers showing that large ulcers initially shrink in volume before the ulcer area becomes affected (5).

Amputation was seriously considered in cases 0–9, 0–10, 8, 9 and 10. The treatment with PGE_1 avoided this imminent alternative. We do not know, however, whether the PGE_1 treatment has a direct effect on the healing of the ulcer or whether it is secondary to the mobilization of the patient due to the relief of pain. In the double-blind study, cases 6, 7, 8 and 10 had severe pain at rest, which was completely abolished by the PGE_1 treatment. In these cases, resulting effective mobilization of the patients was accomplished which might further stimulate the healing.

The small number of subjects included in the

double-blind study was due to the great difficulty we encountered in gathering patients fulfilling all our preconditions for entering the study. Conclusions from our results must therefore be drawn with caution. However, the similarities in the effect of the PGE_1 treatment in leg ulcers due to arterial incompetence observed in the double-blind study, in our open study, and in uncontrolled studies of others (4), indicates that the imminent threat of amputation in these patients is abolished. It is therefore of importance to follow the course of this group of patients and to call for further investigations to evaluate the mechanism of PGE_1 in leg ulcer therapy.

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