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Evaluation of Prostaglandin E1 Analogues to Promote Wound Healing After Infrapopliteal Angioplasty in Patients with Critical Limb Ischemia

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Abstract

Introduction: Revascularization is the cornerstone of critical limb ischemia (CLI) treatment for lower limb preservation. Prostaglandins E1 (PGE1) analogues has a vasodilator effect. Its pharmacological effect has been documented in pre-clinical and clinical studies. This study aims to evaluate PGE1 analogue to promote wound healing in patients affected by ischemic foot ulcers after infrapopliteal angioplasty.

Patients and methods: This is prospective cohort study conducted on 40 patients with critical limb ischemia after failed infrapopliteal angioplasty. Wound assessment was done according to WIFI classification. After debridement of ischemic wound, PGE1 analogues infusion administered twice daily. Additionally, we have injected PGE1 analogues daily dose in skin ulcer area. Main study end-points were ABI increase, wound healing and Limb salvage.

Results: Wound healing is the main outcome in this study. Patients showed significant improvement of wound healing and decrease the risk of major amputation. 17 of 40 patients (42.5 %) showed healed wound after 6 months. 7 of 40 patients (17.5 %) showed good granulation of the ischemic ulcer. (*P*-value 0.001). Morbidity occurred in 11 (27.5 %) patients underwent major amputation due sever infection during the study (three below knee amputations and eight above knee amputations). Mortality occurred in five (12.5 %) patients.

Conclusion: PGE1 analogue administration showed accepted clinical outcomes in terms of technical success, high rate of limb salvage and amputation-free survival.

Keywords: Amputation, Prostaglandin E1, Wound healing

1. Introduction

Clinically, critical limb ischemia (CLI) is defined as ischemic rest pain, tissue loss, or gangrene in the presence of peripheral artery disease (PAD) and hypo-perfusion of the lower extremity. Revascularization is the cornerstone of CLI treatment for lower limb preservation.¹ Prostaglandins E1 (PGE1) analogues have a vasodilator effect. Its pharmacological effects have been documented in preclinical and clinical studies.²

2. Aim

To evaluate the role of PGE1 analogue to promote wound healing in patients affected by ischemic foot ulcers after infrapopliteal angioplasty.

3. Patients and methods

This is prospective cohort study conducted on 40 patients with peripheral arterial occlusive disease (affecting infrapopliteal arteries associated with ulcer) in Al-Azhar University Hospitals.

Study included Patients with CLI with computed tomography angiography (CTA) evidence of significant tibial artery occlusive with infra-popliteal angioplasty with residual stenosis more than 30 %. Patients with generally adequate state of cardiac, respiratory and renal conditions that allow the procedure.

Cases with inevitable amputation, acute on top of chronic ischemia, creatinine greater than 1.4 mg/dl, Poor general condition, residual stenosis less than 30 %, rest pain all were excluded.

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After taking of written consent from all 20 patients. They were subjected to the following. Clinical data for every patient was recorded in a printed vascular Sheet:

General and Local examination and Arterial survey was documented. Wound assessment according to Wound, Ischemia, and foot Infection (WIFI) classification was done. Patients with Trans-Atlantic Inter-Society Consensus (TASC) A, B and C were included in this study.

After debridement of ischemic wound, PGE1 analogues infusion administered after dilution as an IV infusion over 6 h daily through an infusion pump for 14 days. Infusion rate of 0.5 ng/kg/min for 30 min this was increased every 30 min of 0.5 ng/kg/min up to 2.0 ng/kg/min. In case of complications as headache, nausea or hypotension the infusion rate was reduced until improvement of symptoms. In case of severe side effects, the infusion was stopped.

We have injected PGE1 analogues daily dose of 20 ng/cm² of skin ulcer area by multiple injections at a distance of 1 cm far from the ulcer edge for 14 days. TcPO₂ was evaluated every day before injection.

Main study end-point were ABI increase, wound healing and Limb salvage. Follow-up was conducted in Al-Hussein vascular surgery outpatient clinic at 1, 3, 6, and 12 months.

All the collected data were coded on the computer and the statistical analysis was done using SPSS program (Statistical Package for Social Science). χ^2 test was used to find the difference. *P* value less than 0.05 was considered significant, *P* value greater than 0.05 insignificant.

4. Results

Totally 40 patients were studied. Range (41–84). 23 (57.5 %) males and 17 (42.5 %) females. The main symptoms are shown in (Figs. 1 and 2).

Preprocedural results of CTA are summarized in the following (Table 1):

Assessment of wound pre PGE1 analogue injection along study period: The (Table 2) shows progression in increasing of Ankle Brachial Pressure Index (ABPI) in patients 6 months after PGE1 treatment.

TcPO₂ increase in the microcirculation of the skin around the wound with improvement of vascularity. These data suggest that the complete restoring of the microcirculation needs some weeks after PGE1 treatment are shown in (Fig. 3).

After medical treatment, surgical debridement, pus evacuation with anti-ischemic measures in combination with PGE1 analogue and strong antibiotics. The infection is eradicated gradually represent 50 % of all patients one month after procedure, 25 % after 3 months and 12.5 % at 6 months that are shown in (Table 3).

Wound healing is the main outcome in this study. Patients showed significant improvement of wound

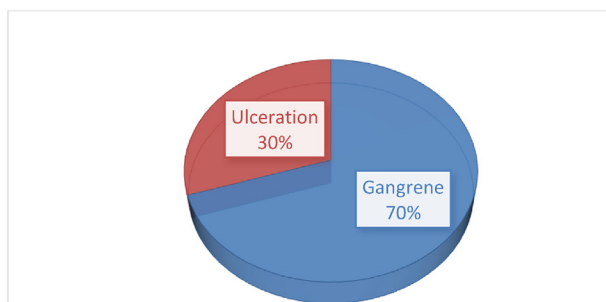


Fig. 1. The associated diseases and risk factors are shown in chart.

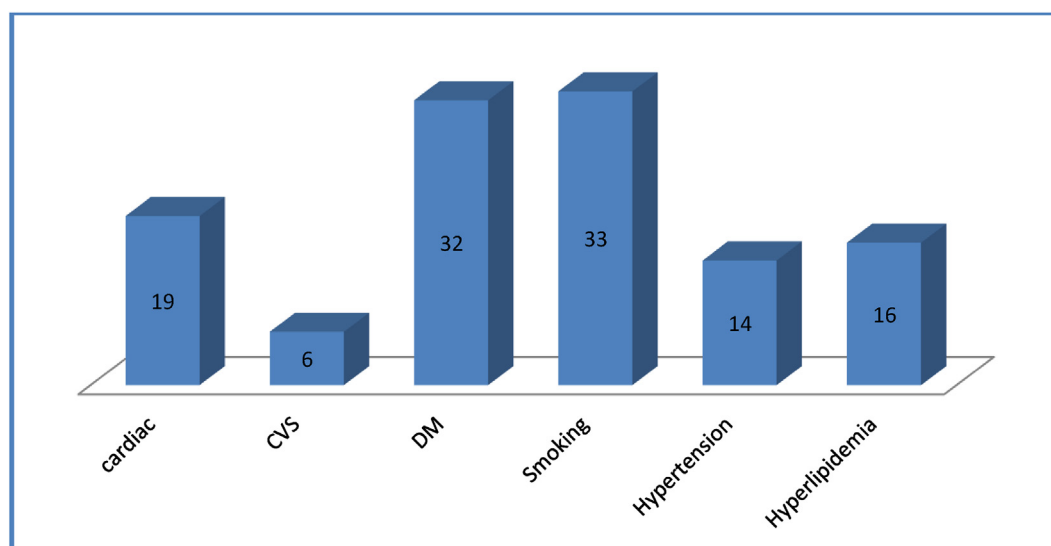


Fig. 2. The associated diseases and risk factors in the studied patients.

Table 1. Preprocedure results of computed tomography angiography.

	n (%)
Combined tibial and other vessels	13 (32.5 %)
Isolated tibial disease	27 (67.5 %)
Three vessel disease	34 (85 %)
Two vessel disease	6 (15 %)
Post occlusion vessel runoff	15 (37.5 %)
Visualized arch	9 (17.5 %)

Table 2. Assessment of wound according to ABPI through 6 months.

ABPI	Preoperation	Post	1 month	3 months	6 months	P-Value
0.6–0.79	5	6	10	16	19	<0.001
0.4–0.59	22	21	19	13	7	<0.001
≤0.39	13	9	4	2	1	<0.001

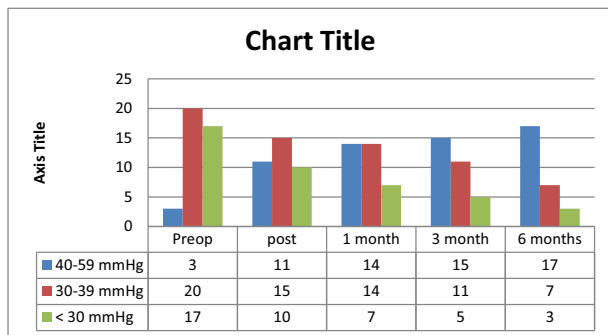


Fig. 3. Assessment of wound according to TcPO2 within 6 months.

Table 3. Assessment of wound according to wound infection (grades of WIFI Classification) within 6 months.

Infection	Preoperation	Post	1 month	3 month	6 months	P-value
Grade 0	9	9	15	21	24	<0.001
Grade 1	15	14	10	6	4	<0.001
Grade 2	11	10	7	3	1	<0.001
Grade 3	5	3	3	1	0	0.38

healing and decrease the risk of major amputation. 17 of 40 patients (42.5 %) showed healed wound after 6 months. 7 of 40 patients (17.5 %) showed good granulation of the ischemic ulcer (P -value 0.001).

Morbidity occurred in 11 (27.5 %): eight patients underwent major amputation due sever infection during the study (three below knee amputations and five above knee amputations). Three (7.5 %) patients underwent major amputation after the end of study. Mortality occurred in five (12.5 %) patients (2 septic shock, 2 myocardial infarction, and 1 cerebral infarction).

5. Discussion

In about one third of CLI patients revascularization procedures are impossible, carry a poor chance

of success, or have previously failed.³ In these patients not amenable to revascularization, prostanoids are recommended to accelerate ulcer healing, reduce pain, and avoid amputation.⁴

Therapy with prostanoids has also been investigated and showed some favorable results in limb salvage, but the evidence was not conclusive.⁵

The present study demonstrates the result of intravenous infusion and local infiltration of PGE1 analogue in ischemic foot ulcer in accelerating wound healing, limb salvage improvement and decrease risk of major amputation after poor results of infrapopliteal angioplasty.

We targeted patients with dry gangrene and unhealed ulcers and exclude patients have rest pain as the study directed on wound healing as Valentina Izzo et al. study.⁶

The present study depended on WIFI classification for wound assessment. This classification included ischemia, infection and wound extension. This was comparable with Valentina Izzo et al. which depended on University of Texas staging.⁶ Elgzyri and colleagues depended on Wagner's grading during follow up of wound healing.⁷ Lawall and colleagues depended on Fontaine classification.⁸

Number of patients with ABPI less than 0.6 were 12.5 % pre procedure which increased to 47.5 % after 6 months (P -value 0.001). T. Elgzyri et al. reported 46 % of patients have ABPI greater than 0.6 by the end of the study.⁷ It was found that PGE1 did not directly improve ABPI in the short term. Gradual development of collateral flow along time may interpret this observation.

Telles and colleagues reported No improvement of ABPI at the end of the study.⁹ Lawall and colleagues reported mean systolic pressure at the ankle pre procedure 39.4 ± 24.1 mmHg and 42.7 ± 28.2 by the end of treatment ($P > 0.05$).⁸

Other studies not include measuring of ABPI in their studies Negus et al.,¹⁰ Böhme et al.,¹¹ Altstaedt et al.,¹² Belch et al.¹³

In the present study TcPO2 showed improvement during follow-up. TcPO2 less than 30 mmHg represent 42.5 % and greater than 30 mmHg represent 57.5 % of the patients pre procedure. There was significant improvement in TCPO2 immediately post PGE1 treatment represented 25 % and 65 %, respectively. Then 7.5 % and 60 %, respectively at the end of study. That indicates the TcPO4 increasing in the microcirculation of the skin around the wound with improvement of vascularity.

Brass and colleagues reported that PGE1 analogue failed to improve TcPO2 by the end of the study¹⁴ in contrast with Tondi and colleagues who showed a statistically significant improvement in TcPO2.¹⁵

In the present study infection act as a significant problem in ischemic wounds as it may lead to extend of minor amputation. Major amputation or death due to sepsis and septic shock.

The risk of amputation correlates directly with increasing infection severity. Especially in patients with diabetes, infection is often the major event that prompts hospitalization and leads to amputation.¹⁶

In the present study infection represented 77.5 % of patients ranging from mild local infection to severe local infection with systemic toxic manifestations.

Treatment of infection included antibiotics, surgical debridement and pus evacuation. Then anti-ischemic measures in combination with PGE1 analogue was administered. The infected limbs decreased from 77.5 % to 50 %, 25 %, 12.5 % at 1, 3, and 6 months, respectively after procedure.

In Lawall and colleagues infection represent 45 % of the patients in the study. No other studies included infection of the wound in their results.⁸

Wound healing is the main outcome in this study. Patients showed significant improvement of wound healing and decrease the risk of major amputation. 17 of 40 patients (42.5 %) showed healed wound after 6 months. Seven of 40 patients (17.5 %) showed good granulation of the ischemic ulcer. (*P*-value 0.001).

In the study by Lawall and colleagues, the rate of complete healing was 18.4 %. But authors reported nonsignificant change in 'area decrease of ulcers' in comparison with placebo.⁸ Also, Hammer and Miao studies showed no significant differences between treatment and control groups in wound healing at 6 months.^{17,18}

Elgzyri and colleagues reported a primary healing rate of 38 % in surviving patients.⁷ Belch and colleagues reported that percentage of patients without any amputations was 43 % in patients receiving PGE1 analogue at 6 months.¹³

Dormandy and Rutherford compared between placebo, low dose and high dose PGE1 groups regarding wound healing. The difference between the three groups was significant (*P* < 0.05) 18 % of patients in the placebo group compared with 23 % in the low dose PGE1 group and 26 % in the higher dose PGE1.¹⁹

In the present study major amputations represented 11 (27.5 %) patients. 8 of 11 patients had above knee amputation. Other 3 patients had below knee amputation. Elgzyri et al. reported the major amputation occur in 17 % from all patients.⁷ In Lawall and colleagues the rates of major amputation was 12.6 %.⁸ Nagus et al., reported 5/14 participants (35 %) amputation rate.¹⁰

Our study agrees with the results reported by Dormandy and Rutherford,¹⁹ Altstaedt et al.,¹²

Table 4. Assessment of wound according to wound healing within 6 months.

Healing	Pre	Post	1 month	3 months	6 months	<i>P</i> -value
Healed	0	0	2	11	17	<0.001
Granulated	11	11	16	12	7	<0.001
Ischemic	22	18	13	6	2	<0.001
Gangrenous	7	7	4	2	1	<0.001

Norgren et al.²⁰ studies in decreasing major amputation rate.

In the present study, five (12.5 %) deaths occurred, this was still lower than the 33 % seen in other studies Elgzyri et al.⁷ In Lawall and colleagues study the mortality rate represented 4.8 %. Cardiovascular events were the causes of death.⁸ Dormandy reported that Within a six-month period, 20 % of patients died.¹⁹

It is difficult, however, to attribute these peri-study deaths directly to the procedure rather than overall illness severity.²¹ In our study, mortality occurred in two patients due to septic shock as a complication of severe infection, two (5 %) patients; due to myocardial infarction and the other one (2.5 %) due to cerebral infarction.

5.1. Conclusion

PGE1 analogue administration showed accepted clinical outcomes in terms of technical success, high rate of limb salvage and amputation-free survival. Conservative treatment options as PGE1 analogue for this patient population are still limited with minor impact on prognosis, quality of life and amputation rate (Table 4).

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

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Conflicts of interest

The authors declared that there were NO conflicts of Interest.

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