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ORIGINAL ARTICLE

Efficacy of Alprostadil as an Adjuvant Therapy with Indirect Angiosomal Revascularization in Patients with Critical Limb Ischemia after Failure of Direct Revascularization

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ABSTRACT

Background:

This study assesses the effectiveness of alprostadil (Prostaglandin E1) as an adjunct therapy alongside indirect angiosomal revascularization for patients with critical limb ischemia (CLI) after failed direct revascularization. CLI, particularly in cases of infrainguinal peripheral arterial disease, poses significant treatment challenges, necessitating innovative approaches to enhance outcomes.

Methods:

Between November 2018 and November 2020, 120 patients with CLI resulting from infrainguinal arterial disease were enrolled following unsuccessful direct revascularization. The cohort included 72 males and 48 females with a mean age of 63.41±12.52 years. Patients were monitored for 2 to 2.5 years based on diabetes status. Post-endovascular intervention, alprostadil was administered intravenously at 40 µg in 100 mL saline over 2 hours every 12 hours for six days. Outcomes, including the Ankle-Brachial Index (ABI) and vessel patency, were evaluated pre- and post-treatment.

Results:

The baseline mean ABI of 0.45±0.175 improved to 0.65±0.216, with a mean increase of 0.2±0.041 (P = 0.08, significant). Primary vessel patients were 93.3% at 1 month, and 92.9% at 3 and 6 months. The distribution of patent leg vessels improved, with the no-runoff-vessels group decreasing from 16.7% to 6.67% and the two-runoff-vessels group increasing from 16.7% to 33.3%.

Conclusion:

Alprostadil effectively improved vascular patency and clinical outcomes in patients with CLI and tissue loss, supporting its use as a safe adjuvant therapy.

Keywords: brachial-ankle index (ABI), critical lower limb ischemia, alprostadil, Indirect Angiosomal Revascularization

INTRODUCTION

Peripheral arterial disease (PAD) is increasingly prevalent, affecting as much as 20% of the global elderly population [1]. Critical limb ischemia (CLI), the most severe manifestation of PAD, is characterized by chronic ischemic rest pain, non-healing ulcers on the legs or feet, or gangrene. CLI is clinically defined based on symptoms such as persistent rest pain lasting

more than two weeks (Rutherford categories 4, Fontaine stage III) or the presence of non-healing wounds or gangrene (Rutherford categories 5 and 6, Fontaine stage IV) [2]. Revascularization, achieved through either surgical bypass or percutaneous transluminal angioplasty (PTA), is essential for limb preservation, improving survival, and enhancing the quality of life for individuals with CLI [3]. Without appropriate intervention, nearly 40% of CLI patients may undergo major limb amputation within a year of diagnosis [4]. As such, surgical and endovascular procedures remain the cornerstone treatments to reduce the risk of amputation [5].

The concept of angiosomes, introduced in 1987, describes regions of tissue—including skin, subcutaneous tissue, fascia, muscle, and bone—supplied by a particular artery and its corresponding vein [6]. The foot is divided into six angiosomes: three supplied by the posterior tibial artery, two by the peroneal artery, and one by the anterior tibial artery [7]. In CLI patients with localized tissue loss, tibial artery revascularization can be classified as "direct revascularization" (DR) when the target artery supplies the affected angiosome, or "indirect revascularization" (IR) when it does not [8]. For patients where direct revascularization is not feasible, IR through a different infragenicular artery remains a viable option. In such scenarios, intravenous prostanoids are proposed as an adjunct therapy to promote neovascularization and collateral vessel formation [9,10]. Intravenous prostanoids, such as the prostaglandin PGE1 analogue alprostadil and the prostacyclin PGI2 analogue iloprost, have been assessed in several small-scale, randomized, placebo-controlled studies [11,12]. Trials involving single (60 μg) or twice-daily (40 μg) doses of PGE1 suggest benefits in accelerating ulcer healing, alleviating ischemic pain, and lowering the risk of amputations [13,14]. Early research, including seven randomized, placebo- or reference-controlled trials, supports the clinical efficacy of alprostadil (PGE1) in patients with advanced PAD (stages III/IV) [14,15]. However, these studies were conducted under regulatory standards of the time, and there is a lack of contemporary research meeting current guidelines. Additionally, no studies have specifically evaluated alprostadil's efficacy in cases of indirect revascularization. A recent Cochrane review has highlighted the need for more extensive, high-quality trials to confirm the role of prostanoids in CLI management [14,16].

METHODS

A prospective, interventional, and descriptive study was conducted on 120 patients (120 limbs) diagnosed with critical limb ischemia (CLI) due to peripheral arterial disease affecting infrainguinal vessels. The study was carried out at the Vascular and Endovascular Surgery Departments of Al-Azhar University Hospitals, Assiut, and Assiut University Hospitals, Egypt, between November 2018 and November 2020.

Inclusion and Exclusion Criteria

This study enrolled adult patients with critical limb ischemia (CLI) characterized by non-healing ischemic foot ulcers or gangrene, corresponding to Rutherford categories 5 and 6 and Fontaine stage IV. Eligibility required patients to have undergone indirect revascularization following unsuccessful attempts at direct revascularization. Participants were also required to provide written informed consent, adhere to the study protocol, and comply with scheduled follow-up evaluations.

Exclusion criteria encompassed individuals at imminent risk of unavoidable limb amputation, those with prior major

amputations on the affected limb, or those with emergent infected lesions such as gas-forming infections. Patients were also excluded if they had hypersensitivity or contraindications to anticoagulants, antiplatelet therapies, contrast agents, or alprostadil. Additional exclusions included acute ischemia, vascular conditions of inflammatory or immunological origin, neuropathic or venous ulcers, and any prostanoid treatment within three months prior to study enrollment..

Diagnostic Procedures

Patients underwent comprehensive examinations of the affected extremities for signs of chronic vascular disease, including ulcers, skin changes, and hair loss. The severity of ischemia was assessed using the ankle-brachial index (ABI) and toe pressure in cases of elevated ankle pressure. Wound and lesion evaluations employed the WIfI classification system to determine limb salvage potential. Laboratory assessments included a complete blood count, coagulation profile, and renal function tests.

Preoperative imaging included duplex ultrasonography with high-resolution color duplex systems to map arterial occlusions and measure velocity spectra. Multi-slice computed tomography angiography was used as an adjunct in cases of suspected inflow disease not confirmed by duplex ultrasonography.

Study Methods

All patients received preoperative antiplatelet therapy with aspirin (75–100 mg/day) and a 300 mg loading dose of clopidogrel administered 6–24 hours before the procedure. Dual antiplatelet therapy was maintained for three months following the intervention, after which aspirin (75–100 mg/day) was continued indefinitely. A nephron-protection protocol was employed for patients not on dialysis, consisting of intravenous saline infusion at 1.5 mL/kg/hr for 12 hours prior to the procedure and 4–6 hours afterward. Additionally, a bolus of 3–5 mL/kg saline was administered immediately before the intervention. For patients with an ejection fraction below 40%, intravenous furosemide (20 mg) was given at both the start and the conclusion of hydration.*Interventional Procedures*

All interventions were performed in a C-arm-equipped room with a Philips Pulsera C-arm system, radiolucent surgical tables, and monitoring equipment for vital signs and ECG. Guidewires (Radifocus® M Stiff and Standard, Terumo; V-18™ Control Wire™, Boston Scientific) and balloon catheters (Admiral Xtreme PTA, Medtronic; Sterling™, Boston Scientific) ensured precision during percutaneous endovascular interventions.

Percutaneous transluminal balloon angioplasty (PTA) was conducted under local anesthesia with hemodynamic monitoring. An antegrade puncture of the ipsilateral or crossover common femoral artery facilitated the insertion of a 6-F sheath. Digital subtraction angiography (DSA) confirmed the ischemic site and target arteries. Following systemic heparinization (80 IU/kg), vessel navigation used the roadmap technique with guidewires and catheters. Direct revascularization (DR) targeted the artery supplying the wound. If DR was unsuccessful, indirect revascularization (IR) was performed to enhance collateral circulation.

Postoperative Management

Postoperatively, patients received alprostadil infusions for six days, followed by wound debridement, minor amputations as necessary, and daily dressing changes. Dual antiplatelet therapy was maintained for three months before transitioning to lifelong aspirin therapy.

Outcomes

Patients were evaluated at six months post-procedure for endpoints including complete wound healing (with or without secondary

interventions such as debridement or skin grafting), limb salvage, and absence of major amputations. Mortality, reintervention rates, and complete healing of ischemic ulcers were also analyzed.

Statistical Analysis

Patient demographics, comorbidities, ischemia severity, lesion characteristics, and ABI values were recorded. Outcomes such as ABI, wound healing, limb salvage, amputation, mortality, and reintervention rates were summarized as mean ± SD or frequencies. Statistical analysis included t-tests for parametric data, Mann-Whitney U tests for non-parametric data, and chi-square tests for categorical variables, with significance set at $P < 0.05$. Multivariate regression identified risk factors for primary patency loss and major adverse limb events (MALE). Kaplan-Meier survival curves depicted primary patency rates.

Ethical Considerations

The study received ethical approval from the research ethics committees of Al-Azhar University and Assiut University in August 2018 and September 2018, respectively.

RESULTS

Study Population and Demographic Characteristics

Between November 2018 and November 2020, 120 patients with infrainguinal peripheral arterial disease and critical limb ischemia (CLI) underwent unsuccessful attempts at direct revascularization at our centers. The median follow-up duration was 2 years for diabetic patients and 2.5 years for non-diabetic patients. Table 1 summarizes the demographic, clinical, and risk factor profiles of the study population. All participants presented with non-healing ischemic foot ulcers or gangrene (Rutherford categories 5 and 6, Fontaine stage IV).

Among the study cohort, 72 patients (60%) exhibited dry gangrene, 44 (36.7%) presented with wet gangrene, and 4 (3.3%) had clean ulcers. Wound classification before intervention was performed using the WIfI system [17, 18], as shown in Table 2.

In terms of lesion characteristics, angioplasty of both the anterior tibial artery (ATA) and posterior tibial artery (PTA) was required in 80 (66.7%) cases to achieve direct revascularization. In 41 cases (34.3%), revascularization targeted both the ATA and peroneal artery, while 28 lesions (23.3%) were treated by PTA angioplasty alone, and 8 lesions (6.7%) required ATA angioplasty only.

The ATA was found to be affected (occlusion or stenosis >30%) in 108 limbs (90%), as was the PTA. The peroneal artery was the least affected. Additionally, 56 cases (46.7%) exhibited segmental involvement of the superficial femoral artery (SFA) along with tibial vessel disease. Successful angioplasty was achieved in 32 limbs (26.7%) for the ATA, 40 limbs (33.3%) for the PTA, and 24 limbs (20%) for the peroneal artery. Failure to achieve angioplasty of any tibial vessel occurred in 24 cases (20%). The SFA was successfully treated via angioplasty in all 14 cases where it was involved.

Follow-up Outcomes

The median follow-up period was 27 months (range 0–30 months). Limb salvage was achieved in 114 patients (96.7%), with 4 patients (3.3%) undergoing below-knee amputation (BKA). Primary patency, as evidenced by preservation of the popliteal pulse during follow-up, was observed in 93.3% of cases at 1 month and 92.9% at both 3 and 6 months.

The mean baseline ankle-brachial index (ABI) was 0.45 ± 0.175, which improved to 0.65 ± 0.216 by the end of the study, reflecting a mean difference of 0.2 ± 0.041 ($P = 0.08$). Wound healing outcomes included complete healing in 32 patients (30.8%), while 72 patients (69.2%) were

referred for plastic surgical coverage (Figure 1).

Vascular assessments revealed significant improvements in runoff vessels. The proportion of no-runoff vessels decreased from 16.7% to 6.67%, while one-runoff vessels reduced from 66.7% to 60%, and two-runoff vessels increased from 16.7% to 33.3%.

Risk differences for limb amputation before and after intervention, based on WIfI classification, are depicted in Figure 2. These findings underscore the effectiveness of revascularization in reducing amputation risk and improving wound healing outcomes.

Table 1: - patient demographics and risk factors

variable	N(%)
Age, mean ± SD	63.41±12.52
Male	72 (60%)
Female	48 (40%)
Smoker	68 (56%)
Diabetes	100 (83.3%)
Hypertension	36 (30%)
Hyperlipidemia	88 (73.3%)
Coronary artery disease	20 (16.7%)
History of stroke	8 (6.7%)
WIfI risk stratification	
Low (clinical stage 2)	0 (0%)
moderate (clinical stage 3)	48 (40%)
High (clinical stage 4)	72 (60%)
Affected limb	
Right limb	56 (46.7%)
Left limb	64 (53.3%)
Level of lesion	
SFA+ IP	56 (46.7%)
IP	64 (53.3%)
Nature of lesion	
Dry gangrene	72 (60%)
Wet gangrene	44 (36.7%)
Clean ulcer	4 (3.3%)

WIFI, Wound, Ischemia and foot Infection; SFA, superficial femoral artery; IP, infrapopliteal

Table 2: - Follow-up ABI Data presented as frequency and percentage. Mean ± SD

FOLLOW UP	Number of patients	**ABI** measures					
		≤0.39	0.4:0.59	0.6:0.79	0.9:1.1	False high	Mean ± SD
1-month	**N= 120**	28 (23.3%)	16(13.3%)	48(40%)	20 (16.7%)	8 (6.7%)	0.6 ± 0.231
3-months	**N= 112**	24 (21.4%)	12 (10.7%)	48 (42.9%)	20 (17.9%)	8 (7.1%)	0.62 ± 0.228
6-months	**N= 104**	16 (15.4%)	12 (11.5%)	48 (46.2%)	20 (19.2%)	8(7.7%)	0.65 ± 0.216

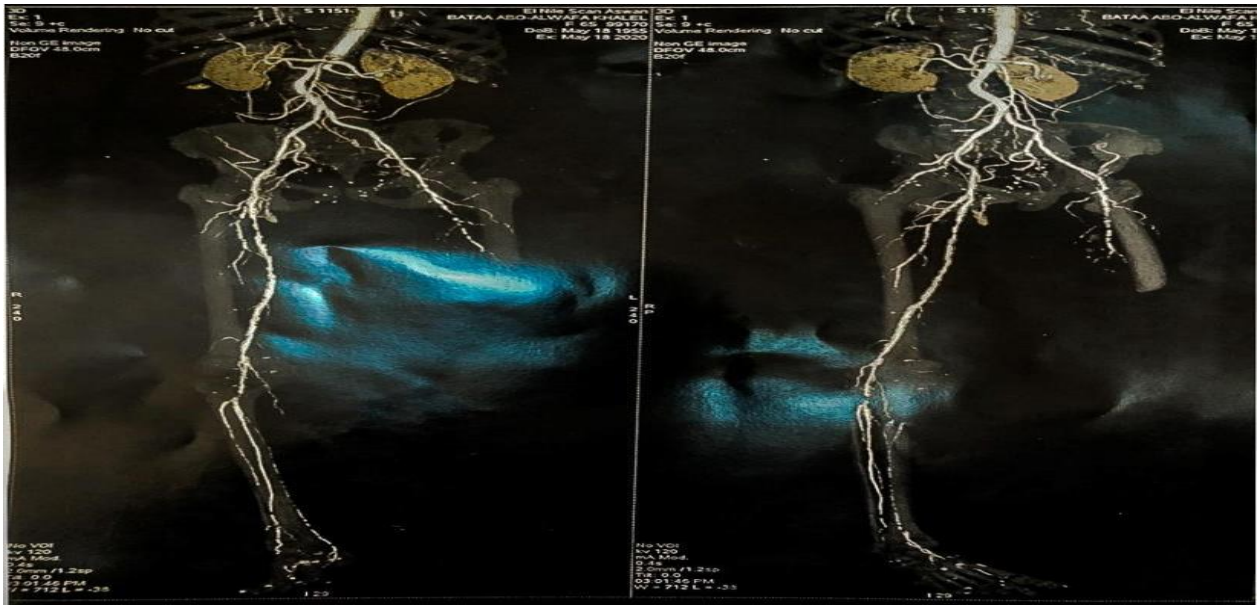

Figure 1A: -Preoperative CTA of a case It is demonstrating right LL multiple SFA stenoses and occluded popliteal artery with totally occluded PTA and ATA and stenosed peroneal artery.

Figure 1B: - Wound examination of the Case after 1 month.

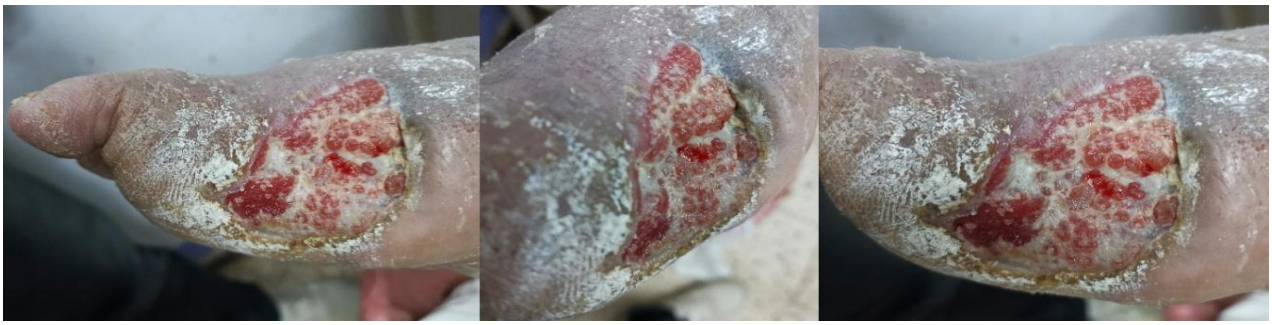

Figure1C: - wound examination of the same case after 3 months

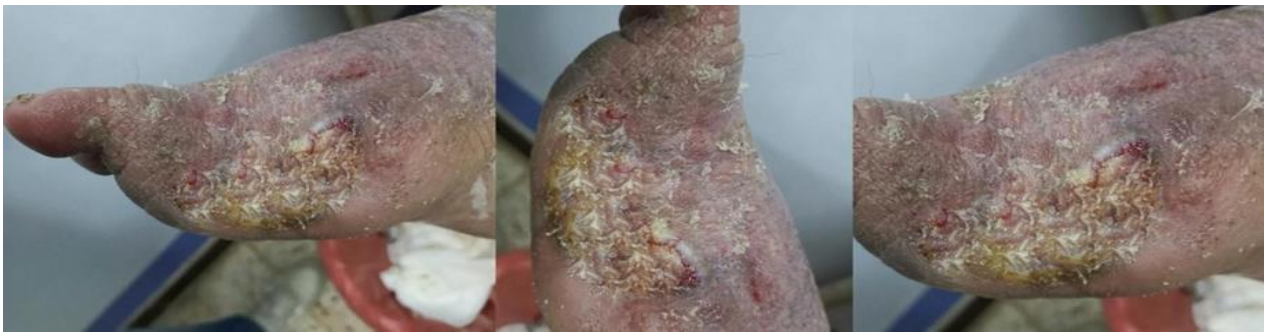

Figure 1D: - wound examination of the same case after 6 months

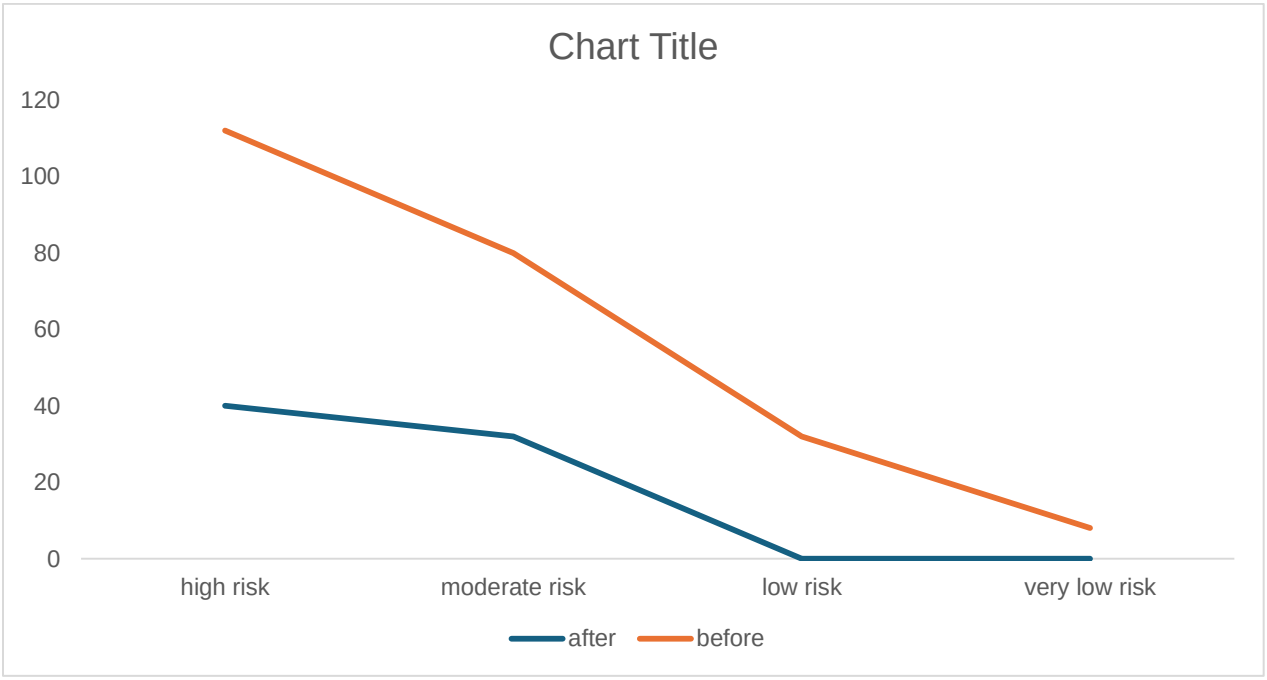

Fig. 2: - Differences between the risk of limb amputation before and after our study according to WIfI classification.

Discussion

This study evaluated the safety and efficacy of intravenous alprostadil (PGE1) infusion combined with indirect angiosomal revascularization in patients with critical limb-threatening ischemia (CLTI) following failed direct revascularization. A total of 120 patients (120 limbs) with peripheral arterial disease underwent successful indirect revascularization followed by alprostadil infusion (40 µg diluted in 100 ml of normal saline over 2 hours, administered every 12 hours for 6 days). The dosing protocol adhered to guidelines established by Creutzig et al. (2004), who recommended similar PGE1 regimens and demonstrated their efficacy and safety in ischemic conditions through meta-analysis [14]. Lawall et al. (2017) also described a similar protocol, with alprostadil administered intravenously at a dose of 40 µg twice daily for 4 weeks [9]. While the current study employed a shorter administration duration of approximately 1 week, no drug-related complications were observed, consistent with Samuel et al. (2019), who also reported no complications associated with PGE1 infusion [19].

The study enrolled 120 participants with a male-to-female distribution of 60:40. The average age of the patients was 63.41 ± 12.52 years, ranging from 40 to 85 years. These findings are comparable to the study by Machado-Alba and Machado-Duque (2018), which reported a mean age of 72.5 ± 10.7 years (range: 47–90 years) [13], and Kreider et al. (2020), which documented a mean age of 73 ± 10 years [20]. Among the risk factors identified in this study, diabetes mellitus was the most common (83.3%), followed by hyperlipidemia (73.3%), hypertension (30%), coronary artery disease (16.7%), and smoking (16.7%). These results are consistent with the observations of Lawall et al. (2017), who reported diabetes prevalence of 43% and tobacco use of 26.3% in the alprostadil group [9].

All patients presented with non-healing ischemic foot ulcers or gangrene (Rutherford 5 and 6, Fontaine IV). Dry gangrene was observed in 60% of cases, wet gangrene in 36.7%, and clean ulcers in 3.3%. Kreider et al. (2020) similarly included patients with CLTI (Rutherford class 4 or higher) without explicitly characterizing lesion types [20]. The WIfI classification system was employed to categorize wounds before and after treatment, a novel methodology not widely reported in similar studies.

The improvement in ankle-brachial index (ABI) observed in this study was consistent with Samuel et al. (2019), who reported an average increase of 0.2 in ABI among patients with infrapopliteal or femoropopliteal involvement [19]. In contrast, Lawall et al. (2017) reported negligible changes in systolic pressure (3.4 ± 14.1 for alprostadil vs. 3.8 ± 12.3 for placebo), likely due to the absence of revascularization or consideration of runoff vessels in their study [9].

The mortality rate in this study was 6.67%, with deaths unrelated to the intervention occurring within the first two months. This rate aligns with Lawall et al. (2017), who reported all-cause mortality rates of 4.8% in the alprostadil group and 3.5% in the placebo group [9]. Limb salvage was achieved in 92.9% of patients, exceeding the rates reported by Biancari and Juvonen (2014) in a meta-analysis of direct (86.2%) and indirect revascularization (77.8%) [10]. The major amputation rate was 7.1%, lower than the rates reported by Creutzig et al. (2004) (13.7%) and Lawall et al. (2017) (12.6%) [9,14]. This improved outcome is likely attributable to the combination of alprostadil with indirect revascularization, whereas other studies utilized only one modality [9,10,13,14].

Wound healing outcomes were notable, with 30.8% achieving complete healing and 69.2% requiring plastic surgical coverage. These results align with Creutzig et al. (2004), who reported better ulcer healing and pain reduction with PGE1 (47.8% vs. 25.2% for placebo, p = 0.0294) [14]. Similarly, Machado-Alba and Machado-Duque (2018) observed 58% of patients demonstrating ulcer improvement [13]. However, Lawall et al. (2017) reported only 18.4% complete healing in their alprostadil group, potentially due to the absence of revascularization and insufficient data on ABI, ischemia severity, or runoff vessels [9].

Limitations

The strength of this study lies in its novel combination of alprostadil therapy with indirect revascularization, in contrast to prior studies that employed only one modality. However, limitations include the relatively small sample size, which may reduce the sensitivity of multivariate analyses, and incomplete technical details for patients with prior interventions. Additionally, the unequal distribution of diabetic patients may have influenced outcomes. Future research should focus on comparing diabetic and non-diabetic cohorts to better elucidate the impact of diabetes on treatment efficacy.

Conclusion

Alprostadil demonstrated efficacy and safety as an adjunct therapy alongside indirect angiosomal revascularization for patients with critical limb-threatening ischemia and tissue loss. The study results suggest its potential to improve vascular patency, facilitate wound healing, and enhance limb salvage rates in this high-risk population. These findings emphasize the importance of combining pharmacological treatments with revascularization techniques to achieve better clinical outcomes in advanced peripheral arterial disease. However, further investigations are needed to validate these findings and assess the long-term benefits of this therapeutic approach.

Declaration of conflicting interests

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Informed consent

Informed consent and consent for publication including the patient’s data and photographs were obtained from the patient

Ethics approval:

The research ethics committee approved the study at Al-Azhar University with code number MSR/AZ.AST. /VAS015/47/215/1/2023.

Contributorship

Mohammed Alsagheer proposed the study idea. Seif and Ashraf Mohammed contributed to protocol development, obtained ethical approval, facilitated patient recruitment, and performed data analysis. Mohammed Alsagheer and Seif prepared the initial draft of the manuscript. All authors reviewed, revised, and approved the final version of the manuscript.

Conflict of Interest: None

Financial Disclosures: None

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Citation

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