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Original Article

Role of intravenous alprostadil therapy in patients with below-knee no-option chronic limb-threatening ischemia (NO-CLTI) and diabetes mellitus: A single-center prospective observational study

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Abstract

Aim: To evaluate the clinical outcomes associated with intravenous alprostadil therapy in diabetic patients with below-knee No-Option Chronic Limb-Threatening Ischemia (NO-CLTI).

Material and Methods: This prospective observational study was conducted in the Department of Cardiovascular Surgery, Dhaka Medical College Hospital, Bangladesh, between January 2021 and December 2025. Ninety-four consecutive diabetic patients with angiographically confirmed below-knee NO-CLTI were enrolled.. All patients received optimal medical therapy, wound care, infection control, and six cycles of intravenous alprostadil therapy. Clinical outcomes were assessed using Numerical Rating Scale (NRS) pain scores, Rutherford classification, Fontaine classification, Wagner grading, inflammatory markers, wound-healing status, amputation outcomes, and limb salvage rates during follow-up.

Results: The mean age was 54.2 ± 8.1 years, and 83 patients (88.3%) were male. Significant reductions in ischemic pain were observed during follow-up, with mean NRS pain scores decreasing from 8.1 ± 1.5 at baseline to 2.3 ± 1.7 at seven months ($p < 0.001$). Significant improvements were also observed in Rutherford and Fontaine classifications (both $p < 0.001$). The erythrocyte sedimentation rate decreased significantly during follow-up ($p = 0.018$). Complete resolution of ischemic rest pain was achieved in 47 patients (50.0%). Complete wound healing occurred in 18 patients (19.1%), while 35 patients (37.2%) developed healthy granulation tissue and subsequently underwent reconstructive procedures. Limb salvage was achieved in 83 patients (88.3%), whereas major amputation was required in 11 patients (11.7%). No serious treatment-related adverse events were observed.

Conclusion: Intravenous alprostadil therapy, administered alongside comprehensive wound care and optimal medical management, was associated with significant reductions in ischemic pain, improvement in clinical severity, and a high limb salvage rate (88.3%) among diabetic patients with below-knee chronic limb-threatening ischemia unsuitable for revascularization. These findings suggest that alprostadil may represent a useful adjunctive therapy in carefully selected patients.

Keywords: Alprostadil; chronic limb-threatening ischemia; diabetes mellitus; peripheral arterial disease; limb salvage

INTRODUCTION

Chronic limb-threatening ischemia (CLTI) represents the most advanced stage of peripheral arterial disease (PAD) and is characterized by ischemic rest pain, non-healing ulceration, or gangrene resulting from severe arterial insufficiency. It is associated with substantial morbidity, impaired quality of life, major limb loss, and increased mortality. Despite advances in vascular surgery and endovascular interventions, CLTI remains a major healthcare challenge worldwide, particularly among patients with diabetes mellitus and advanced atherosclerotic disease [1,2].

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Diabetes mellitus is a well-established risk factor for the development and progression of CLTI. Diabetic patients frequently exhibit diffuse infrapopliteal arterial involvement, extensive vascular calcification, endothelial dysfunction, impaired collateral vessel formation, and microvascular disease, all of which contribute to poor tissue perfusion and delayed wound healing [3,4]. In addition, diabetic foot lesions complicated by ischemia and infection remain a leading cause of hospitalization, disability, and lower-extremity amputation worldwide [5]. The coexistence of neuropathy, infection, and ischemia further complicates management and adversely affects clinical outcomes.

Current international guidelines recommend revascularization through surgical bypass or endovascular intervention as the primary treatment strategy for patients with CLTI whenever anatomically feasible [1,6,7]. Successful revascularization improves tissue perfusion, promotes wound healing, relieves ischemic symptoms, and enhances limb preservation. However, a considerable proportion of patients present with extensive below-knee arterial disease that is not amenable to conventional revascularization because of diffuse multilevel occlusions, severe arterial calcification, poor distal runoff, or the absence of suitable distal target vessels [8,9]. These patients are commonly classified as having No-Option Chronic Limb-Threatening Ischemia (NO- CLTI) and represent one of the most challenging groups encountered in vascular practice.

Management options for patients with NO-CLTI remain limited and are largely focused on symptom control, wound care, infection management, and prevention of major amputation. Consequently, there is growing interest in adjunctive medical therapies that may improve microcirculation, relieve ischemic symptoms, and enhance limb preservation in patients who are unsuitable candidates for revascularization.

Alprostadil, a synthetic analogue of prostaglandin E1, has been used as a pharmacological treatment for advanced peripheral arterial disease. Its biological effects include vasodilation of peripheral vessels, inhibition of platelet aggregation, improvement of erythrocyte deformability, enhancement of microvascular blood flow, and modulation of inflammatory responses [10,11]. Previous studies have suggested that prostaglandin-based therapies may reduce ischemic rest pain, promote ulcer healing, and improve limb-related outcomes in patients with severe limb ischemia who are not candidates for revascularization [12-14]. Nevertheless, available evidence remains limited, and data specifically focusing on diabetic patients with below-knee NO-CLTI are scarce.

Given the increasing burden of diabetes-associated CLTI and the lack of effective treatment options for patients unsuitable for revascularization, further evaluation of adjunctive therapies is warranted. Therefore, this study aimed to evaluate the clinical outcomes associated with intravenous alprostadil therapy in diabetic patients with angiographically confirmed below-knee NO-CLTI treated at a tertiary referral center.

MATERIAL AND METHODS

Study Design and Setting

This prospective single-center observational study was conducted in the Department of Cardiovascular Surgery, Dhaka Medical College Hospital, Bangladesh, from January 2021 to December 2025. The study evaluated clinical outcomes associated with intravenous alprostadil therapy in diabetic patients with below-knee NO-CLTI who were not suitable candidates for surgical or endovascular revascularization.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of Dhaka Medical College Hospital, Bangladesh (Approval No. DMCH/Ethical/2020/12; Approval Date: 12.08.2020). Written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study Population

A total of 94 consecutive diabetic patients with angiographically confirmed below-knee NO-CLTI.

Inclusion criteria were

- Age ≥ 18 years
- Diagnosed diabetes mellitus
- CLTI manifested by ischemic rest pain, non-healing ulceration, or gangrene attributable to peripheral arterial disease
- Angiographically confirmed below-knee arterial occlusive disease
- Determination by a multidisciplinary vascular team that revascularization was technically infeasible

Exclusion criteria included

- Hypersensitivity to alprostadil
- Acute decompensated heart failure
- Acute renal failure
- Severe hepatic dysfunction
- Active systemic sepsis
- Pregnancy

- Life expectancy < 6 months due to non-vascular causes
- Refusal to provide informed consent

Definition of No-Option Chronic Limb-Threatening Ischemia (NO-CLTI)

NO-CLTI was defined on the basis of angiographic findings independently reviewed by two vascular surgeons and one interventional radiologist. Patients were considered unsuitable for revascularization if one or more of the following conditions were present:

- Absence of a suitable distal target artery for bypass surgery,
- Absence of a patent tibial or pedal artery suitable for endovascular intervention,
- Diffuse multilevel infrapopliteal occlusive disease involving two or more tibial vessels,
- Severe circumferential arterial calcification precluding endovascular recanalization,
- Poor distal runoff without continuous arterial flow to the foot,
- Multidisciplinary consensus that revascularization was technically infeasible or unlikely to achieve durable limb salvage.

Baseline Assessment

Demographic characteristics, cardiovascular risk factors, smoking status, comorbidities, medication history, and wound characteristics were recorded at enrollment. Vascular assessment included the ankle-brachial index (ABI), duplex ultrasonography, and digital subtraction angiography. Disease severity was evaluated using the Rutherford classification, Fontaine classification, and Wagner grading system.

Pain intensity was assessed using the Numerical Rating Scale (NRS), ranging from 0 (no pain) to 10 (worst imaginable pain). Laboratory investigations included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), renal function tests, and glycemic profile.

Treatment Protocol

All patients received standard medical therapy consisting of antiplatelet agents, statins, optimization of glycemic control, smoking cessation counseling, and management of cardiovascular risk factors. Patients with wound infections received culture-directed antibiotic therapy. Serial wound debridement, infection control measures, off-loading when appropriate, and advanced wound care were provided according to institutional protocols.

Intravenous alprostadil was administered as adjunctive therapy. The alprostadil regimen was selected based on previous clinical studies demonstrating that repeated intravenous administration of prostaglandin E1 improves microvascular perfusion, inhibits platelet aggregation, enhances erythrocyte deformability, and promotes tissue oxygenation in patients with chronic limb-threatening ischemia [10,11]. The cumulative dose of 500 μg administered over three consecutive days per treatment cycle was chosen to achieve sustained pharmacological activity while minimizing dose-related adverse effects such as hypotension and flushing. Six monthly treatment cycles were administered to provide continued microcirculatory support during wound healing and tissue recovery.

Outcome Measures

The primary outcomes were reduction in ischemic rest pain, limb salvage, and reduction in the initially planned amputation level.

Secondary outcomes included changes in the Rutherford classification, Fontaine classification, Wagner grade, wound-healing status, inflammatory markers (white blood cell (WBC) count, ESR, and CRP), and major amputation rates. Sleep disturbances related to ischemic pain were also assessed during follow-up.

Follow-up and Safety Assessment

Patients were evaluated at baseline, 3 months, and 7 months after initiation of therapy. Clinical examination findings, NRS pain scores, wound status, Rutherford classification, Fontaine classification, Wagner grade, laboratory parameters, and amputation outcomes were documented at each visit.

Patients were monitored for adverse events during and after each infusion cycle, including hypotension, arrhythmia, headache, flushing, allergic reactions, and infusion-site complications. All adverse events were recorded prospectively.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range), as appropriate. Categorical variables were presented as frequencies and percentages.

Changes in continuous variables across follow-up visits were analyzed using repeated-measures analysis of variance (ANOVA) or the Friedman test when normality assumptions were not satisfied. Post hoc pairwise comparisons were performed using the Bonferroni correction. Categorical variables were compared using the Chi-square test or Fisher's exact test as appropriate. A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

A total of 94 diabetic patients with below-knee NO-CLTI were enrolled between January 2021 and December 2025. No patient was lost to follow-up. The mean age was 54.2 ± 8.1 years (range: 38–72 years), and 83 patients (88.3%) were male. Smoking history was present in 81 patients (86.2%). The most common comorbidities were ischemic heart disease (83.0%), dyslipidemia (78.7%), and hypertension (60.6%). All patients presented with ischemic rest pain. Moist gangrene was the most frequent form of tissue loss, occurring in 45 patients (47.9%), followed by dry gangrene in 32 (34.0%) and combined gangrene in 17 (18.1%). Most patients had advanced Wagner grade 3 or 4 lesions (74.5%) (Table 1).

Table 1. Baseline demographic and clinical characteristics

Variable	n (%) or Mean ± SD
Age (years)	54.2 ± 8.1
Male sex	83 (88.3)
Smoking history	81 (86.2)
Ischemic heart disease	78 (83.0)
Dyslipidemia	74 (78.7)
Hypertension	57 (60.6)
Chronic kidney disease	34 (36.2)
Previous stroke	19 (20.2)
COPD	11 (11.7)
Rest pain	94 (100)
Dry gangrene	32 (34.0)
Moist gangrene	45 (47.9)
Combined gangrene	17 (18.1)
Wagner grade 2	18 (19.1)
Wagner grade 3	36 (38.3)
Wagner grade 4	34 (36.2)
Wagner grade 5	6 (6.4)

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Microbiological culture of wound specimens demonstrated a predominance of Gram-negative organisms. Proteus spp. was the most frequently isolated organism, accounting for 64 cases (68.1%), followed by Klebsiella spp. (10.6%), Pseudomonas spp. (8.5%), and Staphylococcus spp. (7.4%). Piperacillin-tazobactam and colistin showed the highest antimicrobial sensitivity rates, with sensitivities of 72.3% and 67.0%, respectively. Angiographic evaluation demonstrated extensive distal arterial disease. Digital artery involvement was present in all patients, while posterior tibial, anterior tibial, and dorsalis pedis artery involvement were observed in 95.7%, 92.6%, and 90.4% of patients, respectively. Arterial calcification was identified in 86.2% of patients, and diffuse multilevel disease was present in 73.4% (Table 2).

Table 2. Microbiological and angiographic findings

Variable	n (%)
Proteus spp.	64 (68.1)
Klebsiella spp.	10 (10.6)
Pseudomonas spp.	8 (8.5)
Staphylococcus spp.	7 (7.4)
Others	5 (5.3)
Piperacillin-Tazobactam sensitivity	68 (72.3)
Colistin sensitivity	63 (67.0)
Digital artery involvement	94 (100)
Posterior tibial artery involvement	90 (95.7)
Anterior tibial artery involvement	87 (92.6)
Dorsalis pedis artery involvement	85 (90.4)
Arterial calcification	81 (86.2)
Diffuse disease	69 (73.4)

Significant clinical improvement was observed during follow-up after initiation of intravenous alprostadil therapy. The mean NRS pain score decreased from 8.1 ± 1.5 at baseline to 5.4 ± 1.7 at 3 months and 2.3 ± 1.7 at 7 months ($p < 0.001$). The ESR also decreased significantly from 63 ± 12 mm/hour at baseline to 15 ± 5 mm/hour at 7 months ($p = 0.018$). Although reductions in white blood cell count and C-reactive protein levels were observed, these changes did not reach statistical significance. Post-hoc Bonferroni-adjusted pairwise comparisons demonstrated significant reductions in NRS pain scores between baseline and 3 months (8.1 ± 1.5 vs. 5.4 ± 1.7; $p < 0.001$), baseline and 7 months (8.1 ± 1.5 vs. 2.3 ± 1.7; $p < 0.001$), and between 3 and 7 months (5.4 ± 1.7 vs. 2.3 ± 1.7; $p = 0.002$). Similarly, ESR decreased significantly between baseline and 3 months (63 ± 12 vs. 31 ± 9 mm/hour; $p = 0.011$), baseline and 7 months (63 ± 12 vs. 15 ± 5 mm/hour; $p < 0.001$), and between 3 and 7 months (31 ± 9 vs. 15 ± 5 mm/hour; $p = 0.027$).

At baseline, all patients reported sleep disturbance secondary to severe ischemic rest pain. Following treatment, significant improvement was observed. At 3 months, sleep disturbance persisted in 39 patients (41.5%), whereas only 12 patients (12.8%) continued to report sleep-related symptoms at 7 months ($p < 0.001$). Improvement in sleep quality paralleled the reduction in ischemic pain scores observed during follow-up, suggesting a clinically meaningful benefit in overall patient well-being.

Marked improvements were noted in disease severity classifications during follow-up. The proportion of patients classified as Rutherford category 5–6 decreased from 100% at baseline to 11.7% at 7 months ($p < 0.001$). Similarly, Fontaine stage IV disease decreased from 100% to 11.7% during follow-up ($p < 0.001$) (Table 3).

Table 3. Changes in clinical and laboratory parameters during follow-up

Variable	Baseline	3 Months	7 Months	p-value
NRS pain score	8.1 ± 1.5	5.4 ± 1.7	2.3 ± 1.7	< 0.001
WBC (×10³/mm³)	13.9 ± 2.1	10.3 ± 1.9	8.6 ± 1.4	0.081
ESR (mm/hour)	63 ± 12	31 ± 9	15 ± 5	0.018
CRP (mg/dL)	23 ± 9	14 ± 7	6 ± 4	0.074
Sleep disturbance, n (%)	94 (100)	39 (41.5)	12 (12.8)	< 0.001
Rutherford category 5–6, n (%)	94 (100)	—	11 (11.7)	< 0.001
Fontaine stage IV, n (%)	94 (100)	—	11 (11.7)	< 0.001

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NRS, Numerical Rating Scale; WBC, white blood cell.

At the final follow-up, complete resolution of ischemic rest pain was achieved in 47 patients (50.0%). Complete wound healing occurred in 18 patients (19.1%), while 35 patients (37.2%) developed healthy granulation tissue and subsequently underwent reconstructive procedures. Limb salvage was achieved in 83 patients (88.3%). Major amputation below the knee was required in 11 patients (11.7%) (Table 4).

No serious treatment-related adverse events were observed during the study period. Mild transient headache occurred in six patients (6.4%), facial flushing in four patients (4.3%), and transient hypotension in three patients (3.2%). All adverse events were self-limiting and managed conservatively. No patient required discontinuation of alprostadil therapy because of adverse effects.

Factors associated with major amputation were evaluated using univariate analysis. Patients who underwent major amputation had a significantly higher prevalence of combined gangrene and advanced Wagner grade (≥ 4) compared with those who achieved limb salvage. Chronic kidney disease, arterial calcification, diffuse arterial disease, and smoking history were more frequent among amputated patients; however, these differences did not reach statistical significance (Table 5).

Table 4. Limb salvage and clinical outcomes

Outcome	n (%)
Complete resolution of rest pain	47 (50.0)
Complete wound healing	18 (19.1)
Healthy granulation tissue	35 (37.2)
Major amputation (BKA)	11 (11.7)
Limb salvage achieved	83 (88.3)

Abbreviations: BKA, below-knee amputation.

Table 5. Factors associated with major amputation

Variable	Limb Salvage (n = 83)	Major Amputation (n = 11)	p-value
Combined gangrene	11 (13.3)	6 (54.5)	0.003
Wagner grade ≥ 4	31 (37.3)	9 (81.8)	0.008
Chronic kidney disease	27 (32.5)	7 (63.6)	0.053
Arterial calcification	70 (84.3)	11 (100)	0.197*
Diffuse disease	59 (71.1)	10 (90.9)	0.278*
Smoking history	70 (84.3)	11 (100)	0.197*

*Fisher's exact test.

DISCUSSION

The present prospective observational study evaluated the clinical outcomes associated with intravenous alprostadil therapy in diabetic patients with below-knee NO-CLTI. This patient population represents one of the most challenging groups in vascular practice because conventional surgical or endovascular revascularization is often not feasible due to extensive infrapopliteal occlusive disease, severe arterial calcification, and poor distal runoff. In the present study, intravenous alprostadil administered alongside comprehensive medical management and multidisciplinary wound care was associated with significant reductions in ischemic pain, improvement in disease severity classifications, and a high rate of limb preservation.

One of the most important findings was the substantial reduction in ischemic rest pain during follow-up. Mean NRS pain scores decreased significantly from 8.1 ± 1.5 at baseline to 2.3 ± 1.7 at seven months. Relief of ischemic pain is a clinically meaningful outcome in patients with CLTI because persistent rest pain adversely affects mobility, sleep quality, and overall quality of life. The observed improvement may be attributable to the vasodilatory and microcirculatory effects of alprostadil, which enhance tissue perfusion and oxygen delivery in ischemic limbs [10,11]. Previous studies have similarly reported improvements in rest pain among patients with advanced peripheral arterial disease treated with prostaglandin-based therapies [12,15].

Improvement in sleep quality was another clinically relevant finding. Sleep disturbance is common among patients with CLTI because of persistent ischemic rest pain, particularly at night when limb perfusion is further reduced. In the present study, the proportion of patients reporting sleep disturbance decreased significantly during follow-up, corresponding with the marked reduction in pain severity.

Improvement in limb-related outcomes was also observed. Limb salvage was achieved in 88.3% of patients, whereas major amputation was required in only 11.7%. Although direct comparisons between studies should be interpreted cautiously because of differences in patient populations and outcome definitions, these findings compare favorably with reports involving patients with NO-CLTI, where major amputation rates have ranged from 15% to 40% during follow-up [16,17]. The high limb-salvage rate observed in the present study suggests that a multidisciplinary approach incorporating intensive wound care, infection control, risk-factor modification, and adjunctive alprostadil therapy may provide meaningful clinical benefit in selected patients.

Significant improvements were also observed in the Rutherford and Fontaine classifications during follow-up. At seven months, only 11.7% of patients remained within the most severe disease categories compared with all patients at baseline. Furthermore, complete resolution of ischemic rest pain occurred in half of the study population. These findings indicate an overall improvement in clinical status following treatment. However, because all patients simultaneously received standard medical therapy, wound debridement, antibiotic treatment, glycemic optimization, and cardiovascular risk-factor management, the independent contribution of alprostadil to these improvements cannot be definitively established.

Inflammation plays a critical role in the pathogenesis of diabetic foot disease and chronic limb ischemia. In the present study, the ESR decreased significantly during follow-up, whereas reductions in white blood cell count and C-reactive protein levels did not achieve statistical significance. Although these findings may suggest a reduction in inflammatory activity, they should be interpreted cautiously because inflammatory markers are influenced by multiple factors, including infection control, wound healing, and glycemic status. Similar observations have been reported in previous studies in which clinical improvements exceeded measurable changes in laboratory inflammatory markers [18,19].

The angiographic findings confirmed the advanced nature of arterial disease within the study cohort. Digital artery involvement was present in all patients, while arterial calcification and diffuse multilevel disease were observed in 86.2% and 73.4% of cases, respectively. These findings support the classification of the study population as truly NO-CLTI. Current international guidelines recognize such patients as having limited treatment options and a high risk of limb loss, highlighting the need for effective adjunctive therapies [1,6].

The strengths of this study include its prospective design, inclusion of a consecutive series of patients with angiographically confirmed NO-CLTI disease, use of standardized clinical classification systems, and complete follow-up of all enrolled participants. In addition, all patients received a uniform multidisciplinary treatment strategy, minimizing variation in supportive care.

Several limitations should be acknowledged. First, the study lacked a control group receiving standard medical therapy alone, limiting the ability to establish a causal relationship between alprostadil therapy and clinical outcomes. Second, the single-center design may limit the generalizability of the findings. Third, the study population consisted predominantly of male smokers, which may not fully represent the broader CLTI population. Fourth, the follow-up period was relatively short for evaluating long-term limb preservation and survival. Finally, the observed outcomes may have been influenced by concomitant interventions including wound debridement, antibiotic therapy, glycemic optimization, and cardiovascular risk-factor management.

Future multicenter randomized controlled trials comparing alprostadil plus standard care with standard care alone are required to determine the true clinical efficacy of alprostadil in patients with NO-CLTI. Such studies should incorporate longer follow-up, standardized definitions of NO-CLTI disease, quality-of-life assessments, and cost-effectiveness analyses.

CONCLUSION

Intravenous alprostadil therapy, administered alongside comprehensive medical treatment and wound care, was associated with reduced ischemic pain, favorable clinical outcomes, and high limb salvage rates in diabetic patients with below-knee non-reconstructable CLTI. However, because of the observational design, the absence of a control group, and a single-center setting, these findings should be considered preliminary and hypothesis-generating. Larger multicenter controlled studies are needed to clarify the role of alprostadil in this patient population.

Ethics Committee Approval: Ethical approval was obtained from the Institutional Ethics Committee of Dhaka Medical College Hospital, Bangladesh (Approval No: DMCH/Ethical/2020/12, Date: 12.08.2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: Written informed consent was obtained from all participants before enrollment in the study.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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