e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(11); 972-977

Original Research Article

Prostaglandins Therapy in Critical Limb Ischemia: Prospective Study

Narayan Sanap[1], Bhaskar Musande[2], Amit Lathoriya[3], Suraj R. Jadhavar[4], T Phani Satyachand[5], Sarika N. Sanap[6], Isha N Kedia[7]

[1]Associate Professor, MGM Medical College and Hospital, Aurangabad, Maharashtra, India
[2]Professor, MGM Medical College and Hospital, Aurangabad, Maharashtra, India
[3,5,7]Junior Resident, MGM Medical College and Hospital, Aurangabad, Maharashtra, India
[4]Senior Resident, MGM Medical College and Hospital, Aurangabad, Maharashtra, India
[5]Department of General Surgery, MGM Medical College and Hospital, Aurangabad, Maharashtra, India
[6]Dental Surgeon, Dr Sanap Health Care, Garkheda, Chatrapati Sambhajinagar, Maharashtra, India

Received: 25-08-2024 / Revised: 23-09-2024 / Accepted: 26-10-2024
Corresponding Author: Dr. Narayan Sanap
Conflict of interest: Nil

Abstract:

Introduction: Critical limb ischemia (CLI) is considered the most severe pattern of peripheral vascular disease. It is presents with chronic ischemic rest pain, ulceration or gangrene attributed to peripheral vascular diseases. Prostanoids are prostaglandin analogues which are potent vasodilators and inhibitors of platelet aggregation. In this study, this property has been utilized in treatment of limb ischemia. The aim of this study is to assess the role of prostaglandin in decreasing the amount of pain due to limb ischemia.

Materials and Methods: A prospective single arm study with 30 patients underwent prostaglandin therapy for 9 to 12 weeks. 1ml of alprostadil (prostaglandin E1) is diluted in 4ml Normal saline to make it 5ml. 1 ml from the 5 ml is diluted in 500 ml ns and given as infusion for 8 hours for 5 days. 3 such cycles repeated. Pain is assessed using visual analog score before and after infusion. Patients present with claudicating pain with proven peripheral vascular diseases even on Doppler are taken into account.

Results: The mean age of the study subjects was 58.13±13.29 years. Majority of 24(80.0%) patients were male and 6(20.0%) were female. The mean VAS score was 8.13 with a standard deviation of 1.04. After the infusion, the mean score significantly decreased to 2.8 with a standard deviation of 1.54. The p-value of <0.0001 indicates that this reduction in pain scores was statistically significant, demonstrating a considerable decrease in pain following the infusion.

Conclusion: The study demonstrates that IV infusion of PGE1 is effective in significantly reducing pain associated with limb ischemia. The findings suggest that PGE1 not only alleviates pain but also has potential implications for reducing amputation rates and promoting ulcer healing.

Keywords: Prostaglandin, limb ischemia, Prostanoids.

Introduction

Limb ischemia, a condition characterized by inadequate blood supply to the extremities, poses a significant clinical challenge due to its debilitating effects on patients' quality of life and the potential for limb loss if left untreated. Among the distressing symptoms associated with limb ischemia, pain stands out as a primary concern, often severely impacting patients' mobility, independence, and psychological well-being.

“Critical limb ischemia (CLI) is the term used to delineate the condition in which vascular diseases has resulted in pain in the foot even at the rest or in a breakdown of the skin [1, 2]. Prostanoids, such as prostaglandin (PG) analogues, exhibit potent vasodilatory and platelet aggregation inhibiting properties, rendering them valuable in managing limb ischemia when direct arterial interventions like surgery or angioplasty are impractical. Iloprost, like other prostanoids, exerts a range of pharmacological effects that can positively impact the course of CLI. These effects comprise the inhibition of “platelet activation, adhesion, and aggregation”, which helps to stop thrombus development and improve blood flow.

Additionally, Iloprost induces vasodilation, protecting vascular endothelial cells and enhancing their function. It also provides cytoprotection to the endothelium, which is crucial in mitigating ischemic damage. Furthermore, Iloprost inhibits leucocyte activation, reducing inflammation and tissue injury. These combined actions make Iloprost a valuable therapeutic option for altering the otherwise progressive and severe course of CLI, offering potential benefits in improving limb

preservation and overall patient outcomes [3]. Intravenous (IV) infusion of PGs presents a promising therapeutic approach for managing pain associated with limb ischemia. PGs, particularly PGE1, play a crucial role in directly targeting vascular tone and inflammation. By inducing vasodilation, PGE1 improves blood flow to ischemic tissues, which can significantly alleviate pain caused by reduced blood supply. This enhanced blood flow not only reduces ischemic pain but also helps preserve limb viability by improving tissue perfusion and preventing further ischemic damage. Overall, IV PGs offer a rapid, effective, and finely adjustable therapy that can complement other interventions and improve outcomes for individuals with CLI [4].

Assessing the efficacy of intravenous PG infusion in managing pain associated with limb ischemia is crucial due to the limited treatment options available and the significant impact of pain on patients' quality of life. PGs have vasodilatory properties that could potentially alleviate pain by improving blood flow to ischemic tissues. However, the specific role of PG infusion in pain relief needs to be rigorously evaluated through clinical studies to fill the existing evidence gap and optimize patient care in this challenging condition.

Hence, this study aimed to systematically examine and evaluate the efficiency of IV infusion of PG in the management of pain associated with limb ischemia. "The purpose of the study was to present the results after short-term (9 weeks to 12 weeks) IV infusion therapy of PGE1- alprostadil via peripheral line in patients with severe pain and ischemic tissue changes."

Materials and Methods

This prospective longitudinal study was conducted in the Department of General Surgery "MGM Medical College and Hospital, Aurangabad" from October 2022 to September 2024 after institutional ethical committee approval. A total of 30 patients satisfying the below inclusion and exclusion criteria were involved in the study.

Study Design: prospective longitudinal study

Study site: The current study is a single-centre, Department of General Surgery, MGM Medical College and Hospital, Aurangabad"

Inclusion Criteria: All patients with proven peripheral vascular disease on Doppler presenting with limb ischemia are taken into account.

Patients who were willing to participate in study.

Exclusion Criteria: Patients with hypersensitivity, brochial asthma and pregnancy are excluded from the study.

Ethical Consideration: Ethical clearance letter was obtained from college ethical committee.

Methodology: A written informed consent was obtained from all the patients before their enrolment in the research study. Rutherford, Fontaine's and Wong bakers face pain grading system were used to grade the symptoms of patient. After the PG E1 therapy, the patients were followed up for short term for assessing benefits of improvement in pain due to limb ischemia.

All patients properly work up with haematological investigations which included haemoglobin, complete blood count, aPTT, blood sugar levels, lipid profile, liver function test and renal function test, Cardiac profile such as ECG and 2D echo. For arterial status arterial Doppler study was also included.

We used one ampule of 500 microgram of 1 ml for one cycle for average 50kg adult patient. Take one ml solution in syringe and dilute it to 5ml with distilled water. So, each ml contained 100 micrograms of PGE1 to be added in 500 ml of normal saline and infused slowly for 8 hours in a day for five days. Same cycle was repeated after 3 weeks. Three such cycles were infused to each patient."

Statistical Analysis: Data was entered in Microsoft Excel and analyzed using SPSS version 20.0th Mean and SD was calculated for quantitative variables and proportions was calculated for categorical variables. Paired t-test will be applied to check significance difference between before and after infusion. P- Value of <0.05 was considered statistically significant.

Observation and Results:

In present study a total 30 patients of proven peripheral vascular disease on Doppler presenting with limb ischemia are taken into account.

Table 1: Distribution of age

Age (years)	Frequency (n)	Percentage (%)
≤40	2	6.67
41-50	8	26.67
51-60	8	26.67
61-70	5	16.67
71-80	6	20.00
>80	1	3.33
Total	30	100

The mean age of the study subjects was 58.13±13.29 years. Out of the total 30 patients, the majority were between the ages of 41 and 60 years, with each of these age category encompassing 8 individuals, representing 26.67% of the total sample for each group. Patients aged 61 to 70 years accounted for 16.67% of the sample, while those aged 71 to 80 years made up 20.00%. The groups of individuals aged 40 years or younger and those older than 80 years were the least represented, comprising 6.67% and 3.33% of the sample, respectively.

Table 2: Distribution of sex

Sex	Frequency (n)	Percentage (%)
Female	6	20
Male	24	80
Total	30	100

In present study, majority of 24(80.0%) patients were male and 6(20.0%) were female.

Table 3: Distribution of comorbidities

Comorbidities	Frequency (n)	Percentage (%)
Diabetes	11	36.67
Hypertension	4	13.33
Diabetes and hypertension	5	16.67
Diabetes and IHD	1	3.33
IHD	2	6.67
AVR	1	3.33
Nil	6	20.0
Total	30	100

Diabetes was the most common comorbidity, affecting 11(36.67%) patients of the total sample. Hypertension was reported in 4(13.33%) patients, representing. Additionally, 5(16.67%) patients had both diabetes and hypertension. 1(3.33%) patient had both diabetes and ischemic heart disease (IHD), while 2(6.67%) patients had only IHD. Aortic valve replacement (AVR) was noted in 1 (3.33%) patients. Lastly, 6 (20%) patients had no comorbidities.

Table 4: Distribution of personal history

Personal history	Frequency (n)	Percentage (%)
Smoking	21	70
Smoking and alcoholism	1	3.33
Nil	8	26.67
Total	30	100

Smoking was reported by 21(70%) patients, making up of the total sample. 1(3.33%) patients reported both smoking and alcoholism. The remaining 8 (26.67%) patients, or had no history of smoking or alcoholism.

Table 5: Distribution of ulcer

Ulcer	Frequency (n)	Percentage (%)
Present	13	43.33
Absent	17	56.67
Total	30	100

Out of the total, 13 (43.33%) patients had ulcers, while 17 (56.67%) patients did not have any ulcers.

Table 6: Comparison of VAS score before and after infusion

Assessment intervals	VAS score		P-value
	Mean	SD	
Before infusion	8.13	1.04	<0.0001
After infusion	2.8	1.54	

Before the infusion, the mean VAS score was 8.13 with a standard deviation of 1.04. After the infusion, the mean score significantly decreased to 2.8 with a standard deviation of 1.54. The p-value of <0.0001 indicates

that this reduction in pain scores was statistically significant, demonstrating a considerable decrease in pain following the infusion.

Table 7: Distribution of VAS score before and after infusion

VAS score	Before infusion		After infusion	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
0	0	0	3	10
2	0	0	14	46.67
4	0	0	11	36.67
6	3	10	2	6.67
8	22	73.33	0	0
10	5	16.67	0	0
Total	30	100	30	100

Prior to the infusion, the majority of patients reported high pain levels, with 22(73.33%) scoring 8 and 5(16.67%) patients scoring the maximum of 10. Only 3(10%) patients had a score of 6, and there were no reports of scores 0, 2, or 4. After the infusion, a marked decrease in pain scores was observed: 14(46.67%) patients had a score of 2, and 11(36.67%) patients reported a score of 4. Additionally, 3(10%) patients reported a score of 0, while only 2(6.67%) patients had a score of 6. There were no reports of scores 8 or 10 post-infusion.

Discussion

The study aimed to assess the efficacy of intravenous (IV) infusion of PGE1 in alleviating pain due to limb ischemia, its role in reducing the level of amputation, and its effectiveness in promoting the healing of limb ischemia. The results obtained provide significant insights into the therapeutic potential of PGE1 in the context of limb ischemia. In this study a total of n=30 patients with limb ischemia were recruited. The demographic distribution of patients indicates that limb ischemia predominantly affects older adults, with the mean age of patients being 58.13±13.29 years. The majority of patients fell within the age range of 41-60 years, suggesting that middle-aged and elderly populations are more susceptible to this condition. The gender distribution was skewed, with 80% male and 20% female patients. These findings are comparable with the study conducted by Patel J et al.[5] and Samuel V et al.[6]

The presence of comorbidities such as diabetes and hypertension was notable among the patients, with 36.67% having diabetes and 13.33% having hypertension. The combined occurrence of diabetes and hypertension was found in 16.67% of the patients. Additionally, IHD and AVR were present in smaller proportions. These findings are consistent with existing literature, which identifies diabetes and hypertension as significant risk factors for peripheral artery disease and subsequent limb ischemia [7,8]. Personal habits such as smoking were prevalent among the patients, with 70% reporting a history of smoking. This is a critical observation as smoking is a well-established risk factor for vascular diseases, including limb ischemia. The high prevalence of smoking among the patients underscores the need for targeted smoking cessation programs as part of comprehensive management strategies for limb ischemia. The study's primary objective was to evaluate the efficacy of PGE1 in reducing pain associated with limb ischemia, measured using the Visual Analog Scale (VAS). We used a dosage of 500 micrograms (1 ampule) per cycle for an average adult patient weighing 50 kg. One millilitre of the PGE1 solution was diluted with 5 milliliters of distilled water, resulting in a solution where each millilitre contained 100 micrograms of PGE1. This diluted solution was then added to 500 milliliters of normal saline and infused slowly over 8 hours each day for five days. Same cycle was repeated after 3 weeks. Three such cycles were infused to each patient The significant reduction in VAS scores from a mean of 8.13 pre-infusion to 2.8 post-infusion ($p < 0.0001$) demonstrates the potent analgesic effect of PGE1. This marked decrease in pain scores is clinically significant and highlights the potential of PGE1 as an effective pain management strategy for patients with limb ischemia.

The distribution of VAS scores before and after infusion further supports the efficacy of PGE1. Prior to the infusion, a majority of patients reported high pain levels, with scores predominantly in the range of 8-10. Post-infusion, there was a significant shift towards lower pain scores, with 46.67% of patients reporting a score of 2 and 36.67% reporting a score of 4. Additionally, 10% of patients reported a complete absence of pain (score of 0) post-infusion. This distribution indicates a substantial improvement in pain levels and overall quality of life for the patients. Additionally, the study noted that 43.33% of patients had ulcers, indicating a significant level of advanced limb ischemia within the study population. Post-infusion, a marked improvement in wound healing was observed among these patients, reinforcing the

potential of PGE1 to positively impact both pain and ulcer healing. These findings are consistent with previous research. Creutzig et al. reported a superior response to PGE1 treatment compared to placebo, with a higher percentage of patients experiencing ulcer healing or pain reduction (47.8% for PGE1 vs. 25.2% for placebo, p = 0.0294) [9]. Kurien JS et al. observed reductions in pain scale scores and Fontaine's grades, with 31.1% of patients avoiding limb or toe amputation [10]. Patel J et al. found that administration of Alprostin (a PGE1 analogue) led to reduced lower limb pain, and ulcer healing in 70% of patients, and improved claudication distance in 55% of cases [5].

Furthermore, Elbnawany MM et al. highlighted the favourable clinical outcomes associated with PGE1 analogues, including high rates of limb salvage and amputation-free survival [11]. Mandadapu S et al. suggest that "PGE infusion in CLI has significant relief due to profuse vascularity in healing ulcers and prevention of amputation of gangrenous limbs or toes [12]. Amrita G. concluded that intravenous infusion of PGE1 alprostadil on 5 days a cycle basis in selective patients with severe rest pain and ischemia seems very effective, without any serious complications [13]. Gujar AA et al. showed intravenous infusion of PGE1 alprostadil on 5 days a cycle basis, in selected patients with severe rest pain and ischemia seems to be very effective, without any serious complications [14]."

The present study demonstrates that IV infusion of PGE1 is effective in significantly reducing pain associated with limb ischemia. The findings suggest that PGE1 not only alleviates pain but also has potential implications for reducing amputation rates and promoting ulcer healing. These results support the further exploration of PGE1 as a therapeutic option for patients with limb ischemia, particularly those with concomitant risk factors such as diabetes and hypertension.

Conclusion

The study demonstrates that IV infusion of PGE1 is effective in significantly reducing pain associated with limb ischemia. The findings suggest that PGE1 not only alleviates pain but also has potential implications for reducing amputation rates and promoting ulcer healing.

These results support the further exploration of PGE1 as a therapeutic option for patients with limb ischemia, particularly those with concomitant risk factors such as diabetes and hypertension. Future research should aim to validate these findings in larger, controlled studies to establish definitive clinical guidelines for the use of PGE1 in limb ischemia management.

References

1. Stricker H, Kaiser U, Frei J, Mahler F. Acute and long-term effects of prostaglandin E1 assessed by clinical and microcirculatory parameters in critical limb ischemia: a pilot study. International Journal of Microcirculation. 1996 Nov 25; 16(2):57-63.
2. Novo S, Coppola G, Milio G. Critical limb ischemia: definition and natural history. Current Drug Targets-Cardiovascular & Hematological Disorders. 2004 Sep 1; 4(3):219-25.
3. Varu VN, Hogg ME, Kibbe MR. Critical limb ischemia. Journal of vascular surgery. 2010 Jan 1; 51(1):230-41.
4. Wolfe JH, Wyatt MG. Critical and subcritical ischaemia. European journal of vascular and endovascular surgery. 1997 Jun 1; 13(6):578-82.
5. Patel J, Shah P, Gandhi F. Beneficial effects of alprostin in patients with critical limb ischemia with peripheral arterial disease: A retrospective study. Indian Journal of Vascular and Endovascular Surgery. 2022 Jan 1; 9(1):18-21.
6. Samuel V, Selvaraj D, Kota AA, Stephen E. The Use of Intravenous Prostaglandins in Extremity Ischemia. International Journal of Recent Surgical and Medical Sciences. 2019 Jul; 5(02):53-7.
7. Ying AF, Tang TY, Jin A, Chong TT, Hausenloy DJ, Koh WP. Diabetes and other vascular risk factors in association with the risk of lower extremity amputation in chronic limb-threatening ischemia: a prospective cohort study. Cardiovascular Diabetology. 2022 Jan 8; 21(1):7.
8. Fudim M, Hopley CW, Huang Z, Kavanagh S, Rockhold FW, Baumgartner I, Berger JS, Blomster JI, Fowkes FG, Katona BG, Mahaffey KW. Association of hypertension and arterial blood pressure on limb and cardiovascular outcomes in symptomatic peripheral artery disease: the EUCLID trial. Circulation: Cardiovascular Quality and Outcomes. 2020 Sep; 13(9):e006512.
9. Creutzig, Lehmacher, Elze. Meta-analysis of randomised controlled prostaglandin E1 studies in peripheral arterial occlusive disease stages III and IV. Vasa. 2004 Aug 1; 33(3):137-44.
10. Kurien JS, Ulahannan SE, Varghese SA, et al. Effectiveness of prostaglandin E1 in the pain management of patients with critical limb ischaemia- A prospective observational study. J. Evid. Based Med. Healthc. 2017; 4(67), 4011-4014.
11. Elbnawany MM, Sharaby AE, Daha AS. Evaluation of prostaglandin E1 analogues to promote wound healing after infrapopliteal angioplasty in patients with critical limb ischemia. Al-Azhar International Medical Journal. 2023; 4(7):29.
12. Mandadapu S, Singh TV, Namadar S. Study of

prostaglandins e1 therapy in limb ischemia in Telangana population. Int J Acad Med Pharm. 2024; 6(3):113-5.
13. Amrita G, Dharia A, Gujar AA. Experience of Intravenous infusion of prostaglandin E1 for cessation of rest pain and further ischemic changes in patients with PVD. International Journal of Medical Reviews and Case Reports. 2023 Aug 1; 7(6):43.
14. Gujar AA, Khan N, Gujar A, Dharia A. Intravenous infusion of prostaglandin E1 in ischemic ulcer and rest pain for extremities due to peripheral vascular disease. International Journal of Surgery. 2020; 4(3):64-7.