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A Retrospective Study on Beneficial Effects of Alprostin in Patients with Critical Limb Ischemia and Peripheral Arterial Disease

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ABSTRACT

Objective: Medical management of non re-constructible and failed reconstruction in patients with Peripheral Arterial Disease (PAD) has limited options. The objective was to study the safety and efficacy of Alprostin in the management of the patients presenting with Stages III and IV PAD. We hypothesized that administration of Alprostin will lead to an increase in the TcPO2 and ABI values. It may also aid in decreasing limb pain, promote ulcer healing and increase claudication distance.

Methods: It was a retrospective study comprising of 60 patients who had presented to Vascular Surgery with clinical features of PAD. According to the Fontaine's staging criteria, only those patients who had presented with stage III and IV were included in the study. Patients with critical limb ischemia and non- re-constructible or failed vascular reconstruction disease, who had not improved with conservative management, and patients presenting with stages III and IV PAD were given injection Alprostin. A total of 6 cycles (3 cycles per day) of Alprostin was given; dose being 166.66 mcg over 5 hours per day. A qualitative assessment was performed, assessing change in rest pain, claudication distance, ulcer healing, and development of complications. In addition, a quantitative assessment was performed by measuring the TcPO2 and ABI before and after the administration of Alprostin.

Results: The study comprised of 60 patients, out of whom 55 were males and 5 were females with a mean age of 48.98. The patients were then classified according to the Fontaine Staging, where 50 patients presented with Stage III and 10 patients presented with Stage IV PAD. After the administration of Alprostin, 100% patients reported of decrease in pain in lower limb, 70% reported of ulcer healing, 55% reported of increase in claudication distance, and complications were only seen in 5% of the patients (Table 1).

TcPO2 values showed a significant rise after the administration of Alprostin, with *P* value being 0.001. Lastly, ABI values also showed a significant improvement after the administration of Alprostin, with *P* value being 0.001. (Table 2)

Conclusion: Peripheral arterial disease (PAD) is a common circulatory condition in which the narrowed arteries in the limbs, reduce blood flow to the extremities; most common being lower limbs. There are several lifestyle modifications that can be made in order to control PAD. Alprostin is a prostaglandin E1 analogue, which acts a vasodilator and inhibits platelet aggregation. It helps to reduce vascular cell adhesion molecule levels in circulation, reduces vascular inflammation, promotes ulcer healing, increases claudication distance, and reduces rate of amputation of the affected limb. Hence, it can be concluded that Alprostin has shown to be a safe and effective drug in patients with non- re-constructible peripheral arterial disease.

KEYWORDS: Peripheral arterial disease; Alprostadil; Leg ulcer; Ischemia.

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INTRODUCTION

Peripheral arterial disease (PAD) is an obstructive arterial disease of the lower extremities that reduces arterial flow during exercise or, in advance stages, at rest. It comprises of atherosclerosis of the abdominal aorta, iliac, and lower extremity arteries, is under diagnosed, undertreated and poorly understood by the medical community. Patients with PAD may experience numerous problems such as claudication, ischemic rest pain, ischemic ulcerations, repeated hospitalizations, revascularizations and limb loss. [1] In the United States, more than 8 million people age 40 and older have been reported to have PAD. [2] It is a severe illness with life-threatening complications. Critical limb ischemia is the most advanced stage of PAD and it is characterized by the presence of rest pain or ulceration or gangrene on the leg and/or toes. There are numerous treatment options available for patients in early stages of PAD, with the primary treatment goals being to decrease cardiovascular morbidity and mortality, and to improve limb related symptoms and the quality of life. In advance stages of PAD (i.e. CLI), revascularization is the priority treatment option. However, there are numerous patients in whom management of non re-constructible and failed reconstruction has limited options. In these patients not amendable to revascularization, prostaglandin E1 (PGE1) are recommended to accelerate ulcer healing, reduce pain and avoid amputation. Several older studies, among them seven randomized, placebo or reference controlled clinical studies, have shown clinical efficacy of Alprostin (prostaglandin E1) in patients with PAD stage III/IV. [3-9] Therefore, the objective was to study the safety and

efficacy of Alprostin (PGE1) in the management of the patients presenting with Stages III and IV PAD. We hypothesized that administration of Alprostin will lead to an increase in the TcPO2 and ABI values. It may also aid in decreasing limb pain, promote ulcer healing and increase claudication distance.

MATERIALS AND METHODS

A. Study Design

A retrospective study was conducted in the Vascular Surgery department of Shree Krishna Hospital from March 21, 2017- August 31, 2017. A total of 60 patients who had presented to the Vascular Surgery department with clinical features of PAD were studied. A thorough clinical history and physical examination was performed to determine the Fontaine stage of each patient . Transcutaneous oxymetry (normal= >55mmHG) and Ankle Brachial Index (normal= 1.0- 1.3) was measured before and after the administration of Alprostin for each patient.

Inclusion Criteria

1. Patients with critical limb ischemia and non- re-constructible or failed vascular reconstruction disease
2. Patients non- responsive to conservative management
3. Patients presenting with Fontaine stage III and IV

Exclusion Criteria

Patients presenting with having a recent history of myocardial infarction and/or chronic heart failure.

Patients with critical limb ischemia and non- re-constructible or failed vascular reconstruction disease, who had not improved with conservative management, and patients presenting with Fontaine stages III and IV PAD were given injection Alprostin. . A total of 6 cycles (3 cycles per day) of Alprostin was given; dose being 166.66 mcg over 5 hours per day. A qualitative assessment was performed, assessing change in rest pain, claudication distance, ulcer healing, and development of complications. In addition, a quantitative assessment was performed by measuring the TcPO2 and ABI before and after the administration of Alprostin.

B. Ethics

A verbal consent was taken from each patient to use his/ her details for the study. The personal information of all the patients was kept confidential and in no manner manipulated. No harm was done to the patients. The patients' details were solely used for this study only and no other research studies.

RESULTS

The study comprised of 60 patients who had presented with clinical features of PAD. There were a total of 55 males and 5 females with a mean age of 48.98. The patients were then classified according to the Fontaine staging, where

50 patients presented with Stage III PAD and 10 patients presented with Stage IV PAD . After the administration of of Alprostin, 100% patients reported of decrease in pain in lower limb, 70% reported of ulcer healing, 55% reported of increase in claudication distance, and complications were only seen in 5% of the patients (Table 3).

TcPO2 values showed a significant rise after the administration of Alprostin, with *P* value being 0.001. Lastly, ABI values also showed a significant improvement after the administration of Alprostin, with *P* value being 0.001 (Table 4).

DISCUSSION

This study was designed to examine the safety and efficacy of administering Alprostin (PGE1 analogue) patients presenting with critical limb ischemia and non- re-constructible or failed vascular reconstruction disease, who had not improved with conservative management, and patients presenting with Fontaine stages III and IV PAD. Prostaglandin E1 analogues have an anti-ischemic and vasodilator effect on patients with peripheral arterial disease. In addition to the known effects on blood flow, viscosity, fibrinolysis and platelet aggregation, it also inhibits monocyte and neutrophil function, suggesting that PGE1 will also have anti-inflammatory effects. Moreover, they also inhibit expression of adhesion molecules (E-selectin, ICAM-1, and VCAM-1), release of inflammatory cytokines (TNF-alpha, MCP-1), matrix components and generation and release of growth factors (CYR61, CTGF). These actions may also contribute to the long-term effects of PGE1, particularly in more advanced stages of PAD. [10] In our study it can be noted that after the administration of Alprostin, 100% patients reported of decrease in pain in lower limb, 70% reported of ulcer healing, 55% reported of increase in claudication distance.

TcPO2 is a non-invasive method reflecting local arterial skin blood flow and oxygenation and can be used as a means of determining severity and clinical progression of PAD. [11] In our study TcPO2 was found to be lower in patients with a mean of 27.68 with standard deviation of ±11.57, before the administration of Alprostin. Following the administration of Alprostin, it was noted that there was an increase in the TcPO2 values with a mean of 46.78 with standard deviation of ±13.72. Therefore, it can be concluded that the improvement in TcPO2 values are statistically significant ($P \leq 0.001$) after the administration of Alprostin.

The ABI is the ratio of the ankle systolic pressure to the arm systolic pressure; an ABI of less than 0.90 indicates that the patient has PAD. A low ABI has been shown to be an independent predictor of increased mortality. [12] Patients with an ABI of less than 0.90 are twice as likely to have a history of MI, angina, and heart failure than patients with an ABI of 1.0 to 1.5. [12] In our study it was found that the ankle brachial index was lower before the administration of Alprostin with a mean of 0.65 ± 0.24. It was noted that after the administration of Alprostin, there was an increase in ABI with a mean of 0.98 ± 0.34. Hence, it can be concluded that there was a statistically

significant increase ($P \leq 0.001$) in blood flow in the lower extremities of the patients following the administration of Alprostin.

Although, the above results show a significant benefit in the use of Alprostin in patients with Fontaine Stage III and IV PAD, it must be noted that the study presents some limitations. Firstly, since it is a retrospective study, the long-term management of PAD, increase or decrease in the probability of amputation, and the quality of life cannot be accurately assessed. In addition, in order to analyze the data correctly, past history of the patients must also be considered. Some co-morbidities such as diabetes, hypertension and cardiovascular conditions are in direct co-relation with the development of PAD. Lastly, if the study were to be repeated, it would be essential to include a larger study population. This is because a small sample size may not necessarily represent the population correctly. Therefore, it is important to have a bigger sample size, which would be an accurate representation of the population.

CONCLUSION

Peripheral arterial disease (PAD) is a common circulatory condition in which the narrowed arteries in the limbs, reduce blood flow to the extremities; most common being lower limbs. There are several lifestyle modifications that can be made in order to control PAD. Alprostin is a prostaglandin E1 analogue, which acts a vasodilator and inhibits platelet aggregation. It helps to reduce vascular cell adhesion molecule levels in circulation, reduces vascular inflammation, promotes ulcer healing, increases claudication distance, and reduces rate of amputation of the affected limb. Hence, it can be concluded that Alprostin has shown to be a safe and effective drug in patients with non- re-constructible peripheral arterial disease.

Table 1: Fontaine Staging

Stages	Symptoms
I	Asymptomatic, incomplete blood vessel obstruction
II	Mild claudication pain in limb
IIA	Claudication at a distance of >200m
IIB	Claudication at a distance of <200m
III	Ischemic rest pain
IV	Ulceration/ Necrosis/ Gangrene

Table 2: Patient Demographics

Patient profile	Number
Gender	
Male	55
Female	5
Age distribution (years)	
20- 30	5
31-40	11
41-50	22
51-60	8
61-70	8
>70	6
Extremity involvement (lower limb)	
Right side	34
Left side	23
Both sides	3
Fontaine Staging	
Stage III	50
Stage IV	10

Table 3: Qualitative parameters assessing the effect of Alprostin

QUALITATIVE PARAMETERS	FREQUENCY	PERCENTAGE
1. Decrease in pain in the lower limbs	60	100%
2. Ulcer healing	42	70%
3. Increase Claudication distance	55	92%
4. Development of complications	3	5%

Table 4: Quantitative Parameters Assessing the Effect of Alprostin

QUANTITATIVE PARAMETERS	MEAN ± SD	*P* VALUE
Pre- TcPO2	27.68 ± 11.57	0.001
Post- TcPO2	46.78 ± 13.72	
Pre- ABI	0.65 ± 0.24	0.001
Post- ABI	0.98 ± 0.34	

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