

Evaluation of Efficacy of Prostaglandin E-1 in Peripheral Arterial Disease Patients with Intermittent Claudication: A Randomized Double Blind Placebo Controlled Study

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Abstract

Peripheral arterial disease is common disabling disease in middle age and elderly population, Intermittent claudication being the most common presenting symptom. The reason for the symptoms is haemodynamically significant lesions of lower limb arterial tree. PGE1 is an active drug used for treatment in patients where surgical revascularization is not possible. In this study, conducted at CTVS DEPTT; SSH Hospital GMC Jammu we included total seventy six patients. In active group 56 patients and 20 patients were kept in placebo group on randomized double blind placebo controlled study. All patients received PGE1 (alprost) or placebo on indoor basis with monitoring of pulse & blood pressure. In our study patients who had received PGE1 showed significant improvement in intermittent claudication pain, increased pain free walking distance, maximum walking distance and improvement as per quality of life questionnaire. Fifty one (91%) out of fifty six patients in active group showed significant improvement as per quality of life questionnaire; whereas no improvement was observed in placebo group patients. Prostaglandin (PGE1) is a wonder drug in patients with intermittent claudication pain affecting their day to day quality of life. It should be used in patients with peripheral vascular disease where surgical revascularization is not possible.

Key Words

Prostaglandin (PGE1), Intermittent Claudication, Peripheral Vascular Disease

Introduction

Peripheral arterial occlusive disease presenting as intermittent claudication is one of the most common cause of pain and disability in middle aged population. This symptom of intermittent claudication is seen in-around 5% of the middle aged group of patients. The reason for causation of this symptom is haemodynamically significant lesions of Aortoiliac/Femoropopliteal/Infrapopliteal arteries. The presenting complaint of intermittent claudication is an indicator of generalised atherosclerosis. Majority of cases having complaints of intermittent claudication are managed conservatively. (1,2) Mainstay of the treatment is to retard progression of the disease and to reduce arterial insufficiency and treat symptomatically. The present study has been conducted with the aim of studying the effect of

Prostaglandin PGE1 on the treatment of intermittent claudication. As documented PGE1 is a potent vasodilator as well as an inhibitor of platelet aggregation, There is growing evidence in literature that platelet aggregation and WBCs are involved in pathogenesis of POAD. Studies with use of PGE1 as treatment for intermittent claudication are being conducted in different centers. As PGE1 is rapidly inactivated in the lungs, it needs to be given thru intraarterial route or a large bolus intravenously. (3,4,5)

Material and Methods

This study was carried out as Double blind placebo controlled study in the Department of CardioThoracic Vascular Surgery, GMC Jammu for patients presenting to our OPD from Jan 2011 to Jan 2014.

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In this study 76 patients were included out of which 56 patients were administered PGE1 and 20 patients were in placebo group. Out of 56 patients 48 were male patients and 8 were female patients. The median age group of patients was 56 years. Patients included in this study were having intermittent claudication pain on walking and patients had mean walking distance ≥ 30 meters to ≤ 300 meters were included in this study. Patients in our study had no ulcer or gangrenous changes on lower limb, patients had presented with only symptom of intermittent claudication. All patients had sign of peripheral vascular disease on colour Doppler study, arteriography or CT angiography. In all patients included in the study, colour Doppler and arteriography (CT angiography) was conducted routinely. All the patients included were those where surgical management was not possible all patients had Infrapopliteal vascular disease alone or with Femoropopliteal or iliofemoropopliteal or iliopopliteal disease. All the patients received PGE1 on indoor admission basis. PGE1 was given as intravenous bolus infusion of 100 microgram per day and total of 500 microgram given over 5 days. Patient was given 3 such cycles over a gap of 4 weeks. Patients enrolled were later accessed on the basis of a quality of life questionnaire for peripheral vascular disease and walking Impairment questionnaire to access improvement in symptoms on followup.

Inclusion Criteria

- 1 Patients with history of claudication pain alone.
- 2 Patients having no ulcer or gangrenous changes.
- 3 Patient with significant peripheral arterial disease on colour Doppler and CT angiogram and not amenable to surgical management
- 4 Patient in this study received only PGE1 and no other vasoactive drug was given during the study period.
- 5 Patients on vasoactive drugs were included in study after stopping them 4 weeks prior.
- 6 Patients with ankle brachial index less than 0.8 and more than point 0.4 were included in study.

Exclusion Criteria

- 1 Patients with ankle brachial index below 0.4 were not included in study.
- 2 Patients with significant coronary disease and dyspnoea were excluded from study.
- 3 Patients with lower limb ulcers are pregangrenous or

gangrenous changes were excluded from study.

4 Patients with significant renal disease (S. Creatinine > 3 mg % were not included in study).

Patients in placebo group were having same age group and similar inclusion and exclusion criteria and they were also accessed on quality of life questionnaire and walking impairment questionnaire.

Quality of Life Questionnaire

- 1 General feeling
- 2 Physical functioning
- 3 Climbing stairs in more than one flight
- 4 Climbing stairs in one flight
- 5 Walking more than one mile
- 6 Walking 0.5 to 1 mile
- 7 Walking 50 yards to 0.5 mile
- 8 Walking indoors

Livelihood Activities

- 1 Vigorous
- 2 Moderate
- 3 Sitting
- 4 Hygiene related questioner
- 5 Health Status
- 6 General Impact of treatment

Results

The patients included in study had peripheral arterial disease of distal vessels (INFRAPOPLITEAL) alone or with iliofemoral or Femoropopliteal or Iliofofemoropopliteal (Table 2). In all these cases surgical management was ruled out or not possible. In all patients included in study had no gangrenous changes in limb and patients with such changes were not included in study. All patients in the study were followed up after completion of PGE1 infusions after period of 1,3 and 6 months. All patients were assessed as per the questionnaire and improvement in pain free walking distance, mean walking distance, all patients under went treatment as per protocol- No significant side effects were noted in any patient because of which drug had to be discontinued. Only 6 patients had nausea and vomiting which was taken care of with antiemetics. In our study patients had significant improvement in pain free claudication distance on followup at 1,3 and 6 months, five patients showed no improvement in symptoms with PGE1 infusions. In our study 51 (91%) patients out of 56 showed significant improvement in pain free walking distance, maximum

Table.1 Showing Demographic Profile

	PGE 1	Placebo
A No. of Patients	56	20
B Male/Female	48/8	16/4
C Median age	56	54
D Diabetic	12	4

Table.3 Showing Comparative Effect Walking Time

	No. of patients before PG1 infusion	Placebo
A Walking more than one mile	0	0
B Walking 0.5 to 1 mile	20	6
C Walking 50 yards to 0.5 mile	21	9
D Walking indoors	15	5

walking distance and improvement as per quality of life questionnaire for peripheral vascular disease .There was progressive improvement in active treatment group and no improvement in placebo group.

In our study out of 56 patients there were 36 patients who were in category of 50 yards to 500 mtrs walking distance. Ten Patients were in sitting category or limited activity and couldnot perform day to day activity without claudication pain. The patients who were in sitting or limited activity 50 to 500 mtrs showed improvement in walking distance and day to day activity on followup and their walking distance improved more than 500 mtrs to 1 km or even more than that. (Table 3& 4).

The judgment was made according to questionnaire and divided into groups as much better, better, satisfactory, unchanged and worsened (Table 5) as per the patient feedback to quality of life questionnaire and livelihood activity

Discussion

Prostaglandin (PGE1) are used in treatment of peripheral vascular disease where patient has advanced vascular disease and surgical management (revascularization)is not possible .These patients are having intermittent claudication pain only. In our study

Table.2 Showing Comparative Profile of PVD

	PGE1	Placebo
A Infrapopliteal	24	8
B Illeofemropopliteal and Infrapopliteal	12	3
C Illeopopliteal and Infrapopliteal	7	5
D Femoropopliteal and Infrapopliteal	13	4

Table.4 Showing Comparative Effect on Activity

	No. of patients before PG1 infusion	No. of Patients after PG1 Infusion
A Vigorous	0	15
B Moderate	20	36
C Sitting or Limited activity	36	5

Table.5 Showing Comparative Effect on Satisfaction

Judgment	Assessment after PGE-1 Infusion	Placebo
A Much Better	15 (26.7%)	Nil
B Better	30 (53.5%)	Nil
C Satisfactory	6 (10.7%)	Nil
D Unchanged	2 (3.5%)	7 (35%)
E Worsened	3 (5.3%)	13 (65%)

Much Better : Much Better Group patients improved markedly in claudication distance
Better : Improved in claudication Distance but limited activity
Satisfactory : Improvement in indoor Day to Day Activity and Personal hygiene
Unchanged : No change

PGE1 (alpostin) drug was given-to all patients in active group as per protocol. A clear dose response was seen in patients of peripheral vascular disease with intermittent claudication pain where assessment was done on the basis of quality of life questionnaire, pain free walking distance and maximum walking distance after completion of our study regime Jn our study we have found encouraging results of prostaglandin (PGE1) in improvement of intermittent claudication pain in 51(91%)patients out of 56 patients. Protaglandins (PGE1) has antiischemic effect on peripheral vascular disease and is thus helpful in not only in intermittent claudication, but also shows benefit in healing of ulcers due to increase in blood flow

Prostaglandin (PGE1) has direct vasodilator action and in addition has effect on platelet aggregation, blood viscosity and fibrinolysis .(10-16). Prostaglandin (PGE1) also has anti inflammatory property such as inhibition of expression of adhesion molecules (E-selection, ICAM1, VCAM-5), release of inflammatory cytokines (TNF alfa, MCP-1), matrix component and release of growth factors. These actions contribute to long term effects of PGE1 in advanced stages of peripheral vascular disease. These actions may also contribute to the long-term effects of PGE1, particularly in more advanced stages of PAD. Gene-expression experiments with chemically stable prostacyclins and PGE1 suggest that several genes in vascular smooth muscle cells and fibroblasts are modified by prostaglandins at the transcriptional level. This includes TNF alpha-induced VCAM expression in vascular smooth muscle cells which appears to be inhibited via the prostaglandin EP2 receptor as well as IL-1-induced expression of the type-1 collagen gene in fibroblasts. Thus, regulation of gene transcription by PGE1 may contribute to tissue protection in critical ischemia of the lower limbs. Prostaglandin PGE1 has proved miraculous in these advanced cases where patients quality of life has suffered a lot. Patients assessed with quality of life questionnaire for peripheral vascular disease in our study have shown significant improvement in lifestyle of patients whereas in placebo group there was no improvement in patients quality of life rather deterioration in some cases. In our study patients showed improvement in intermittent claudication distance significantly after prostaglandin infusion as assessed on quality of life questionnaire and showed improvement in their category from sitting or limited activity to moderate or vigorous activity and those in moderate activity improved to vigorous activity. The observation is in concordance with observations of other studies conducted in various centres by Creutzling A *et al*, Schrok *et al*, Amendt , Petronella *et al*. (7,8,12,13).

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