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Original Research Article

A study on prostaglandin E1 therapy in critical limb ischaemia patients to evaluate the improvement in vascularity

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ABSTRACT

Background: Diffuse peripheral arterial disease or peripheral occlusive vascular disease (POVD) involving the lower limb is a debilitating illness with high incidence of morbidity and mortality. The objective of this study was to assess the improvement of ulcer healing and improvement of the level of amputation in patients with diffuse peripheral arterial disease after administration of prostaglandin E1.
Methods: From June 2013 to November 2014, a total of 45 patients having critical limb ischaemia (Fontaine's grade III and IV) not suitable for angioplasty and stenting or bypass procedures received different courses of Prostaglandin E1 (PGE1). 20 patients (44.44%) received 6 full courses of PGE1, 3 patients (6.66%) received 5 courses, 5 patients (11.11%) received 4 courses, 4 patients (8.8%) received 3 courses, 4 patients (8.8%) received 2 courses and 9 patients (20%) received one course. PGE1 was administered through intravenous infusion (Alprastodil 100mcg) over 10 hours a day for 5 days in one month (1course). They were followed up for 3 years till June 2017.The improvement in level of amputation, ulcer healing and complications were assessed.
Results: 14 patients (31.1%) did not require amputation of limbs/ toes, 24 patients (53.3%) have the same amputated status while 7 patients (15.6%) required higher amputation. This study justifies the role of PGE1 therapy in improving the peripheral arterial pulsations and thereby augmenting ulcer healing and improving the level of amputation.
Conclusions: After diagnosing a patient with advanced CLI where angioplasty and stenting or bypass procedures are not possible, aggressive treatment for the non-healing ulcer, amputation of gangrenous limbs or toes and starting the PGE1 therapy early not only arrest the progression of POVD but even reverses it to some extent.

Keywords: Critical limb ischemia, Level of amputation, Prostaglandin E1, Ulcer healing

INTRODUCTION

Diffuse peripheral arterial disease or peripheral occlusive vascular disease (POVD) involving the lower limb is a debilitating illness with high incidence of morbidity and mortality. Early diagnosis and starting of intervention early is a key to successful outcome.[1,2]

The goals in treating CLI are to relieve claudication pain and rest pain, to heal ulcer, to prevent amputation of limbs, to improve quality of life and to prolong survival.[1,2]

Increase of blood flow in the ischemic leg is believed to represent the main action of PGE1 in the therapy of POVD. Though PGE1 is used for treatment of advanced Critical Limb ischaemia (CLI) by Indian doctors, studies have so far not been published about the effects of PGE1 on the improvements in peripheral pulsations, ulcer healing, or amputation levels after administration of PGE1 amongst Indian population. This research is done

to study the effects of PGE1 in Indian patients with diffuse peripheral arterial disease.

The objective of this study was to study the improvement of ulcer healing and improvement of the level of amputation, if necessary, in patients with peripheral occlusive vascular disease after administration of prostaglandin E1.

METHODS

The research was conducted after receiving approval from Institutional Research Committee and Institutional Ethical Committee. A written informed consent was obtained from all the subjects before their enrolment in the research study. This prospective study was conducted in the Department of General Surgery Government Medical College Kottayam over a period of 4years, between June 2013 and June 2017 with 45 CLI patients. Diagnosis of disease was made on the basis of clinical examination and Doppler study. Parameters taken into account were ulcer (infected or debrided), amputated status and peripheral pulsations of the extremities. Fontaine's grading system was used to grade the symptoms of patient. After the PGE1 therapy the patients were followed up for 3years till June 2017 for assessing long term benefits in improving ulcer healing, improvement in peripheral pulsations and level of amputation. The improvement in peripheral pulsations was assessed by clinical examination and Doppler study.

Inclusion criteria

All cases of POVD not suitable for angioplasty and stenting or by-pass procedures who presented during the study period and who have not received prostaglandin E1 treatment.

Exclusion criteria

Patient not willing to undergo treatment with prostaglandin E1 and those not willing to give consent.

Injection prostaglandin E1 was administered as continuous slow intravenous infusion once a day for 5 days in a month (1 course) up to 6 months, for those with end stage POVD where no alternative medical management was available. 1 ampoule contains 500 micrograms of PGE1. It was diluted with 9 ml of normal saline in a 10-ml syringe. 2 ml (equivalent to 100 micrograms) was put in 500 ml of normal saline and was given as continuous intravenous infusion with micro drip set at 50 micro drops/ minute to be completed in 10 hours because rapid infusion can induce myocardial ischaemia due to coronary steal effect produced by peripheral vasodilatation. The result was analyzed using Microsoft excel, Chi square test and T-test.

RESULTS

The research work which was done on 45 patients included 30 (66.7%) males and 15 (33.3%) females. The most common age group affected was 60-70 years and majority of patients have no peripheral pulsations on admission. 14 patients (31.1%) in this study presented with non-healing ulcers which required a thorough debridement before administration of PGE1.

Of the 45 patients, twenty patients (44.4%) completed 6 full courses, three patients completed 5 courses (6.7%), 5 patients (11.1%) completed 4 courses, four patients (8.9%) completed 3 courses, four patients (8.9%) completed 2 courses and nine patients took only one course. 3 patients dropped out of this study after taking the first course. The main reason given by the patients for non-completion of the course was due to relief of pain or wound healing.

The sum of the total course of PGE1 taken by the patients (6 courses + 5 courses + 4 courses + 3 courses + 2 courses + 1 course) is 172. The sum of the reduction in Fontaine's grade for the patients irrespective of the course completed was 110. The overall reduction in Fontaine's grade was 2.44.

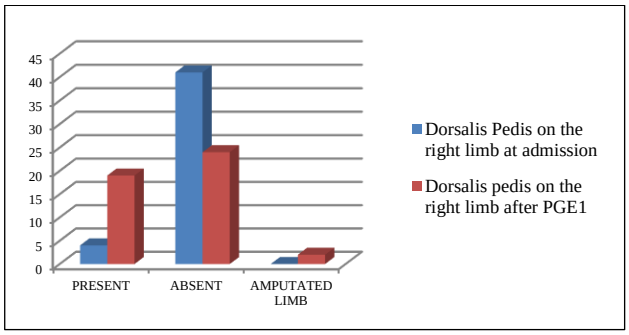

Figure 1: Improvement in pulsation of right Dorsalis pedis artery after PGE1 administration. The third row represents patient who had undergone a higher amputation because of which the pulsation could not be assessed.

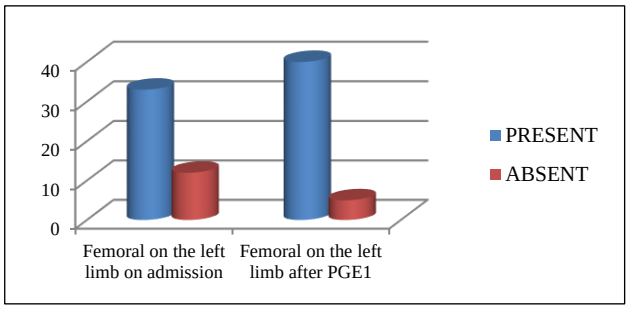

Figure 2: Improvement in pulsation of left femoral artery after PGE1 administration.

PGE1 therapy also improved the pulsations at all the levels. Improvement in peripheral pulsations were

assessed separately for dorsalis pedis, popliteal, and femoral arteries on either side. Representative charts of right Dorsalis pedis and left femoral arteries are given in Figure 1 and 2. After PGE1 administration, only 7 patients (15.5%) needed higher amputation as the wound was infected, not getting better with debridement or ascending gangrene.

Table 1: Paired samples correlations.

		N	Correlation	Sig. (p-value)
Pair 1	Dorsalis pedis on the right limb at admission and Dorsalis pedis on the right limb after PGE1	45	0.341	0.022
Pair 2	Dorsalis pedis on the left limb on admission and Dorsalis pedis on left limb after PGE1	45	0.564	0.000
Pair 3	Popliteal on the right limb at admission and Popliteal on the right limb after PGE1 administration	45	0.547	0.000
Pair 4	Popliteal on the left limb at admission and Popliteal on the left limb after PGE1	45	0.623	0.000
Pair 5	Femoral on the right limb on admission and Femoral on the right limb after PGE1	45	0.584	0.000
Pair 6	Femoral on the left limb at admission and Femoral on the left limb after PGE1	45	0.586	0.000

Table 2: Significant table (p-value).

		t	df	Sig. (p-value)
Pair1	Amputated status-before - Amputation status after prostaglandin E1 administration	4.509	44	0.000
Pair 2	Fontaine's grading-BEFORE - Fontaine's grading-6	37.195	44	0.000

P-value is significant in all the comparisons, vise, Fontaine's grade before and after PGE1 administration, amputated status before and after PGE1 administration and pulsation levels before and after PGE1 administration (Tables 1 and 2).

In the follow up period, 1 death was registered in the patient group receiving 6 full courses. Patient died due to cerebrovascular accident. Death happened 6 months after receiving the full course. 1 death also was registered in patient group receiving 5 courses. Patient died, 3 months after receiving 5 courses, of cerebrovascular accident and 2 patients died after receiving 2 courses. Both were known cases of coronary artery disease. One died 2 weeks after PGE1 administration while the other died one month after PGE1 administration. Both died of myocardial infarction. 3 deaths were registered in patients receiving only one course of PGE1. One patient was a known case of coronary artery disease died after 1 week after discharge, second patient was a known case of pulmonary tuberculosis with COPD died 6 months after PGE1 therapy due to pulmonary tuberculosis and the third patient underwent left AK amputation, had POVD on the right lower limb and the patient expired one month later. All these deaths were registered after the end of PGE1 treatment and none were related to the administration of PGE1.

Thus, this research study and analysis justify the role and use of PGE1 treatment in advanced critical limb ischemia patients for reduction of Fontaine's grade and improvement of ulcer healing and amputated status.

DISCUSSION

Critical Limb Ischemia (CLI) was defined for the first time in 1982 by P. R. F. Bell as a manifestation of peripheral artery disease which describes patient with typical chronic ischemic rest pain or ischemic skin ulcers or gangrene.[3] This term of CLI should only be used in patients with chronic ischemic disease, defined as presence of recurring rest pain that persists for more than two weeks, requiring regular analgesics and with ulceration or gangrene of the foot or toes. These criteria correspond to stage 3 and 4 of Fontaine's classification of POVD.[4]

Observational studies have shown that one year after diagnosis of CLI, 25% of patient experiences a major amputation, 25% had died and only 50% survived without requiring a major amputation though some have rest pain, ulcer or gangrene persisting and it is also associated with excessively high risk for cardiovascular events including myocardial infarction and death.[2,5]

PGE1, known pharmaceutically as Alprastodil. Although widely used, the exact mechanism of the known beneficial effects is not completely understood.[6] PGE1 therapy increases the blood flow by peripheral vasodilatation and by inducing angiogenesis. The anti-ischemic effect mechanisms of PGE1 in POVD patients are complex and clearly not limited to a direct vasodilator action alone. Effects of PGE1 therapy has been described on cellular factors in the blood, haemostasis and fibrinolysis and endothelium. PGE1 improves the endothelial function in patients with CLI and also inhibits monocytes and neutrophil function suggesting that PGE1 has anti-inflammatory effects.[7] A more recent meta-analysis of the administration of PGE1 for patients with POVD stage III or IV not eligible for arterial reconstruction shows that it not only has significant beneficial effects over placebo on ulcer healing and pain relief, but also increases the rate of patients surviving with both legs after 6 months follow up.[8,9] The quality of life evaluation and the cost analysis indicated a benefit of preserving limbs in some studies.[10,11] The side-effects of therapy include headache (4%), erythema and pain of injected vein (8%). All these transient side effects never led to the interruption of therapy.[12]

The total number of cases involved in the research study was 45. The most common age group affected is the 60-70 years group. Males are more commonly affected. Hypertension in association with diabetes was the most common co-morbid condition for CLI.

All patients had claudication pain or rest pain. Majority of patients (36 patients -80%) had associated gangrene of limbs/ toes of which 14 patients (31.11%) had non-healing ulcers as well.

Clinical examination with Doppler study was done to diagnose a patient with CLI.[12,13] 22 patients (48.88%) presented with claudication pain, rest pain and gangrene of toes while 14 patients (31.11%) had non-healing ulcer in addition to the pain and gangrene of toes (Fontaine's grade IV). 9 patients (20%) had claudication pain and rest pain only, putting them in Fontaine's grade III.[4] Patients who had gangrene of limbs/ toes underwent amputation (Ray amputation/ Above Knee/ Below Knee amputation)

PGE1 therapy showed improvement in pulsations in the lower limb and the level of amputation also improved with PGE1 therapy (Figure 3). Only 7 patients (15.6%) needed higher amputation but ultimately had a healthy amputated stump. In the follow up periods, 7 deaths were observed but never related to the therapy.

This research proves the beneficial effects of PGE1 in reducing the pain as well as in Fontaine's grade in 45 patients with CLI. 7 patients (15.6%) required higher amputation due to ascending gangrene and deterioration of wound while 24 patients (53.3%) after having undergone an amputation did not have progression of the disease after starting PGE1 therapy. The side effects of the therapy (2.2%) were insignificant. It became clear that PGE1 is a real alternative in preventing progression to higher disability where no other alternative medical management is available.[13-15]

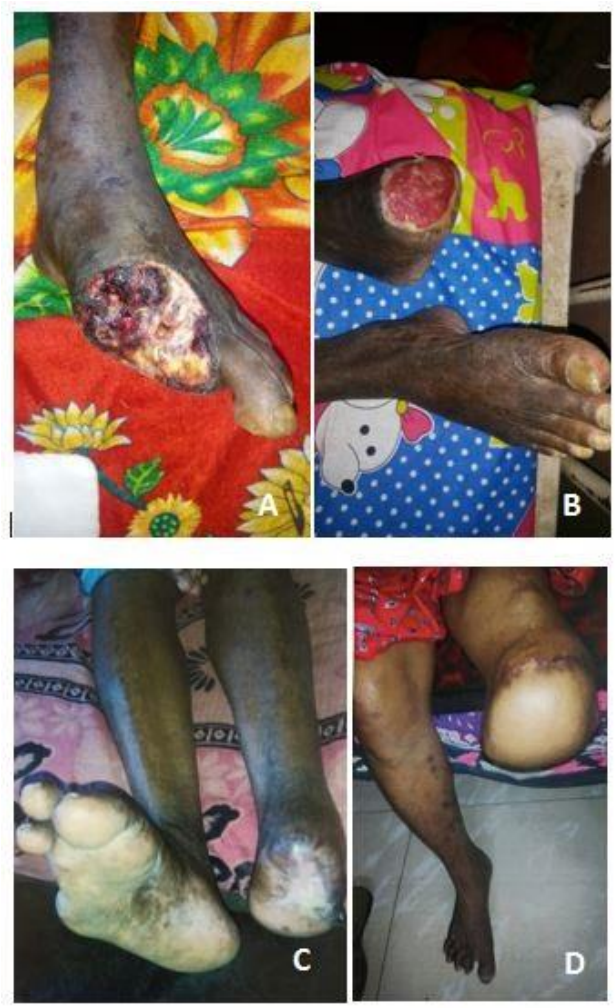

Figure 3: Clockwise from above left; (A) 72-year-old male patient was admitted with gangrene of the left big toe and the second toe. He underwent ray amputation of the left big toe and the second toe. After first course of PGE1, gangrene of the wound was found ascending and hence mid-tarsal amputation done. On the third course, the wound is showing healing red granulating wound; (B) Wound was completely healed at the end of 6th course; (C) a female patient who took 5 courses, after 3year follow up; (D) healthy BK stump after 2years follow up.

After diagnosing a patient with advanced CLI where angioplasty and stenting or bypass procedures are not possible, aggressive treatment for the non-healing ulcer, amputation of gangrenous limbs or toes and starting the PGE1 therapy early not only arrest the progression of POVD but even reverses it to some extent. Limitations of study include only a few surgical units practicing the use of PGE1 for advanced CLI cases and ignorance of patients for follow up.

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Ethical approval: The study was approved by the institutional ethics committee

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