EFFECTIVENESS OF PROSTAGLANDIN E1 IN THE PAIN MANAGEMENT OF PATIENTS WITH CRITICAL LIMB ISCHAEMIA- A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

BACKGROUND

Critical Limb Ischaemia (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 ischaemic rest pain or ischaemic skin ulcers or gangrene.[1] This term of CLI should only be used in patients with chronic ischaemic 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. Observational studies have shown that one year after diagnosis of CLI, 25% of patients experience a major amputation, 25% had died and only 50% survived without requiring a major amputation, though some have rest pain, ulcer or gangrene persisting. The primary goals in treating CLI are to relieve claudication pain and rest pain, to heal the ulcer, to prevent amputation of limbs, to improve quality of life and to prolong survival.

The aim of the study is to study the improvement of claudication pain, rest pain and improvement of the level of amputation in patients with diffuse peripheral arterial disease (CLI) after administration of PGE1.

MATERIALS AND METHODS

From June 2013 to November 2014, a total of 45 patients having advanced CLI (Fontaine's grade III and IV) not suitable for angioplasty and stenting or bypass procedures received different courses of 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 (alprostadil 100mcg) over 10 hours a day for 5 days in one month (1course). The reduction in claudication and rest pain, improvement in level of amputation and complications were assessed.

RESULTS

In all cases, there was reduction in pain scale and Fontaine's grade irrespective of the courses of PGE1 taken. 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.

CONCLUSION

PGE1 is an alternative treatment for amputation in patient presenting with advanced CLI and it is effective in reducing the claudication pain, rest pain and improving the level of amputation.

KEYWORDS

Critical Limb Ischaemia, Rest Pain, Prostaglandin E1.

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BACKGROUND

Critical Limb Ischaemia (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 ischaemic rest pain or ischaemic skin ulcers or gangrene.[1] This term of CLI should only be used in patients with chronic ischaemic disease defined as presence of recurring rest pain that persists for more than 2 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. Observational studies have shown that one year after diagnosis of CLI, 25% of patients experience a major amputation, 25% had died and only 50% survived without requiring a major amputation,

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though some have rest pain, ulcer or gangrene persisting. The primary goals in treating CLI are to relieve claudication pain and rest pain, to heal the ulcer, to prevent amputation of limbs, to improve quality of life and to prolong survival.

Aims and Objectives

To study the improvement of claudication pain and rest pain of POVD patients after the administration of prostaglandin E1 (PG E1).

MATERIALS AND METHODS

This study 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 at Government Medical College, Kottayam, over a period of 15 months, between June 2013 and November 2014 with 45 CLI patients. Diagnosis of disease was made on the basis of clinical examination and Doppler study. Fontaine's grading system was used to grade the symptoms of patient. Parameter taken into account was pain (6 grades).

Inclusion Criteria

All cases of peripheral occlusive vascular disease with diffuse atherosclerotic changes not suitable for angioplasty and stenting or bypass procedures who present during the study period and who have not received PG E1 treatment.

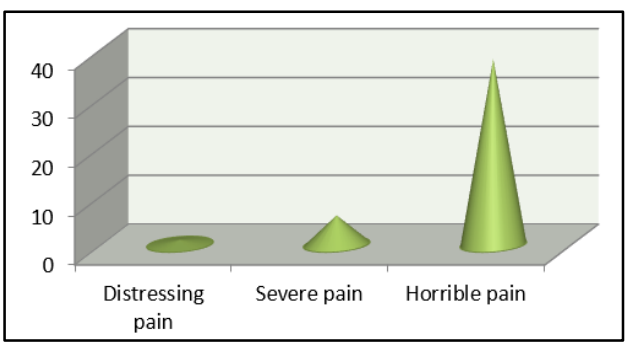
Exclusion Criteria

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

PG 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 treatment available. One ampoule contains 500 micrograms of PG E1. It is diluted with 9 mL of normal saline in a 10 mL syringe. 2 mL (equivalent to 100 micrograms) is put in 500 mL of normal saline and given as continuous intravenous infusion with microdrip set at 50 microdrops/minute to be completed in 10 hours. If given rapidly, it can induce myocardial ischaemia due to coronary steal effect produced by peripheral vasodilatation. The results were analysed using Microsoft Excel, Chi-square test and T-test.

Data Analysis

The research work was done on 45 patients, 30 (66.7%) males and 15 (33.3%) females. The most common age group affected is 60-70 years. Patients usually present to outpatient department with complaints of recurring rest pain that persists for more than 2 weeks requiring regular analgesics. Visual analogue pain scale was used to assess the pain scale of the patient when they were admitted to the hospital (Table 1). The same pain scale was used to compare the reduction in the pain scale after PG E1 administration.[2] Majority of the patients describe the pain as a horrible pain, which wakes them from sleep and typically is relieved on hanging the leg by the side of the bed.



Graph 1

*Majority of the patients describe the pain as a horrible pain.

Of the 45 patients, 20 (44.4%) completed 6 full courses, 3 patients completed 5 courses (6.7%), 5 patients (11.1%) completed 4 courses, 4 patients (8.9%) completed 3 courses, 4 patients (8.9%) completed 2 courses and 9 patients took only one course. Three patients dropped out of this study after taking the first course. The main reason given by the patients for non-completion of the course is due to absent pain (relief of pain) and 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 pain scale for the patients irrespective of the course completed was 156 and reduction in Fontaine's grade was 110. The overall reduction in pain scale was 3.46 and that of Fontaine's grade was 2.44(Table 2).P-value is significant in all the comparisons (Table3), i.e. pain scale before and after PGE1 administration and Fontaine's grade before and after PGE1 administration.

Descriptive Statistics						
	N	**Minimum**	**Maximum**	**Sum**	**Mean**	**Std. Deviation**
Reduction in pain scale	45	0.00	4.00	156.00	3.4667	0.86865
Reduction in Fontaine's grade	45	0.00	3.00	110.00	2.4444	0.86748
Valid N (list wise)	45					

Table 1. Overall Reduction in Pain Scale and Fontaine's Grade

** Overall reduction in pain scale and Fontaine's grade.

		t	**df**	**Sig. (p-value)**
Pair 1	Visual analogue pain scale - Pain scale after prostaglandin E1 administration	26.772	44	0.000
Pair 2	Fontaine's grading-Before- Fontaine's grading-After	37.195	44	0.000

Table 2. Significant Table (p-value)

***Significant table (p-value).

In the follow up period, 1 death each were registered in the patient group receiving 6 full courses and in patient group receiving 5 courses. Two patients died after receiving 2 courses and 3 deaths were registered in patients receiving only one course of PGE1. All these deaths were registered after the end of PGE1 treatment and none were related to the administration of PGE1.

So, this research study and analysis justify the role and use of PGE1 in the treatment of advanced cases of critical limb ischaemia for reduction of pain as an alternative treatment option for those in whom angioplasty, stenting and bypass procedures are not possible.[3,4,5]

DISCUSSION

Diffuse Peripheral Vascular Disease (POVD) involving the lower limb is a debilitating illness with high incidence of morbidity and mortality. The highest incidence of critical limb ischaemia was seen in the 60-70 age groups with a mean age incidence of 65.23 years.[6] The incidence of CLI is more common in males. Hypertension in association with diabetes was the most common comorbid condition for CLI. Early diagnosis and intervention is the key to successful outcome.

Clinical examination with Doppler study was done to diagnose a patient with CLI.[3] 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[2,7] which was used to assess the pain status at the time of admission as well as after the administration of PGE1.

Increase of blood flow in the ischaemic leg is believed to represent the main action of PGE1 in the therapy of POVD. PGE1, known pharmaceutically as alprostadil increases the blood flow by peripheral vasodilatation and induces angiogenesis and also improves the endothelial function.[8] The anti-ischaemic effect mechanisms of PGE1 in POVD patients are probably complex and clearly not limited to a direct vasodilator action alone.[8] In addition to the known effects of PGE1 on blood flow, platelet aggregation, fibrinolysis and viscosity, it also inhibits monocytes and neutrophil function suggesting that PGE1 has anti-inflammatory effects. Prostaglandin E1 improves the endothelial function in patients with CLI. Several randomised trials have now been completed and combined in meta-analysis with proven improved outcomes after PGE1 in CLI. The transient side effects of PG E1 therapy, which never led to interruption of therapy include headache (4%), erythema and pain of injected vein (8%).[9]In a nutshell, intravenous PGE_1infusion is effective and safe in the treatment of outpatients with intermittent claudication.[9]

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.[5,10] After treatment with PGE1, some studies noted a significant reduction in analgesic use and in pain score.[5]

Though PGE1 is used for treatment of advanced CLI by Indian doctors, studies have so far not been published about the effects of PGE1 on the reduction of pain after administration amongst Indian population. Among our 45 patients, 20 patients (44.4%) completed 6 full courses, 3 patients completed 5 courses (6.7%), 5 patients (11.1%) completed 4 courses, 4 patients (8.9%) completed 3 courses, 4 patients (8.9%) completed 2 courses and 9 patients took only 1 course. Three patients dropped out of this study after taking the first course. The main reasons given by the patients for non-completion of the course are relief of pain and wound healing.

The overall reduction in pain scale is 3.46 and that of Fontaine's grade is 2.44.P-value is significant in all the comparisons (Table3), i.e. pain scale before and after PGE1 administration and Fontaine's grade before and after PGE1 administration. In the follow up periods, 7 deaths were observed. All deaths were registered after the end of PGE1 therapy, but never related to the therapy.

So, our study justifies the role and use of PGE1 treatment in advanced cases of critical limb ischaemia for reduction of pain as an alternative treatment option.[6,7,11] The cost analysis and the quality of life evaluation done by some studies indicated a benefit of preserving limbs.[12,13] Limb salvage will continue to be the primary goal for most patients undergoing vascular therapy.[14,15]

CONCLUSION

This study proves the beneficial effects of PGE1 in reducing the pain as well as Fontaine's grade in patients with CLI. Short duration of the study, limited number of surgical units practicing the use of PGE1 for advanced CLI cases and defaulters are the limitations of this study.

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