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The Effect of Prostaglandin Therapy on Ankle Brachial Index in Non-Reconstructable Symptomatic Peripheral Artery Disease Patients- Retrospective Analysis

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Abstract

Background: Prostaglandin E1 has been reported to benefit patients with significant peripheral vascular disease and limb threatening ischemia. The present retrospective study attempts to assess the effect of Prostaglandin E1 on ankle brachial index in non reconstructable symptomatic peripheral artery disease patients.

Objectives: To study the effect of Prostaglandin E1 on ankle brachial index in non reconstructable symptomatic peripheral artery disease patients.

Methods: Case records of 40 patients who had completed at least six cycles of injection were obtained from medical records of vascular surgery. The demographic data and the ankle brachial index of these patients were recorded at baseline and at the end of six cycles of the drug.

Results: The average ABI of both the limbs changed significantly from baseline to the end of study after six cycles of Prostaglandin E1 injection ($p<0.05$). There was significant increase in Ankle brachial index for the symptomatic limb from baseline whereas the contra lateral limb did not show a significant change. There was a significant increase in Ankle brachial index of both limbs as well as the average Ankle brachial index in the patients without any co-morbidities conditions than those with the presence of co-morbidities.

Conclusion: Prostaglandin E1 therapy increases the ankle brachial index in symptomatic limb of patients with non reconstructable symptomatic peripheral artery disease patients.

Keywords: Prostaglandin E1; Ankle brachial index; Nonreconstructable symptomatic peripheral artery disease patients.

Introduction

The overall prevalence of Peripheral arterial disease (PAD) in Indian population is 3% [1] and among diabetic patients it is as high as 14% [2]. Up to 20% of elderly individuals have PAD upon non-invasive testing [3]. PAD comprises those entities which result in obstruction to blood flow in the arteries, exclusive of the coronary and intracranial vessels. Intermittent claudication is the earliest and the most frequent presenting symptom in patients with lower extremity PAD. In the late stages of PAD, tissue hypoperfusion progresses to ischaemic ulceration and gangrene, and major amputation is eventually required in more than a third of these patients. PAD is a marker of systemic atherosclerosis and is found more frequently among persons with well-known cardiovascular risk factors, especially older age, smoking, or diabetes mellitus, or those with atherosclerosis in other vascular beds. An "anklebrachial index" (ABI) is the objective method of defining PAD using color doppler with an index of less than 0•90 in either leg.

Patient management should include lifestyle modification, focusing on smoking cessation, daily exercise (30 min/day), normal body mass index (≤ 25 kg/m^2), and a diet control. Pharmacological treatment can be added for blood pressure control and a lipid-lowering treatment to achieve LDL cholesterol, 2.5 mmol/L (100 mg/dL) with an option of 1.8 mmol/L (70 mg/dL) if feasible. In diabetic patients, glucose control should be obtained, with the target glycated haemoglobin (HbA1c), 7%. Site-dependent therapy and revascularization strategy are discussed in the respective sections. It must be emphasized that the management of patients with PAD should always be decided after multidisciplinary discussion [4].

Treatment of the patient's lower extremity symptoms should be chosen on the basis of the severity of the symptoms. Invasive intervention for symptomless disease is never appropriate, but the presence of even symptomless disease should serve as a marker of generalized atherosclerosis and therapy should be directed at primary prevention of the systemic complications such as myocardial infarction and stroke. Similarly, patients with mild or moderate claudication symptoms are best treated with conservative measures such as the institution of an exercise programme.

Pharmacotherapy for intermittent claudication can be added as adjunctive treatment to improve walking, although no agent has provided sufficient efficacy to gain widespread acceptance. Although patients with chronic limb-threating ischemia are best served with surgical revascularisation, pharmacotherapy can be considered when, for whatever reason, a surgical procedure is impossible. PGE1 is a potent vasodilator as well as an inhibitor of platelet aggregation. PGE1

has been evaluated in a number of studies and a small but statistically significant increase in walking distance was seen in some of these.

Long-term, intermittent intravenous infusion of prostanoids, such as prostaglandin E1 or more stable prostacyclin analogues such as iloprost have been shown to reduce rest pain and heal ischaemic ulcerations in masked, placebo-controlled trials, but results have not been consistent [5]. With the growing evidence that both platelets and white blood cells are involved in the pathogenesis of peripheral arterial occlusive disease clinical investigators have begun to focus attention on the use of prostaglandins as treatments for intermittent claudication [6]. The present study attempts to investigate the role of prostaglandins on the ankle brachial index, which is a validated objective measurement of PAD.

Materials and methods

This is a retrospective observational study conducted in department of vascular surgery, Nizams Institute of Medical Sciences, a tertiary care hospital. Case records of patients who are undergoing treatment for peripheral arterial disease from the year 2009 to 2012 were retrieved from medical records section of department of vascular surgery. The case records of those patients who had completed at least six cycles of injection prostaglandins were enrolled in the study. The baseline characteristics and the ankle brachial index (ABI) at the baseline and at the end of 6 monthly injections of prostaglandin were recorded in a case record form.

Statistical Analysis

The variables are expressed as mean ± SD. Paired t test was done for change in ABI from baseline to the end of the treatment in the patients. The change in ABI for symptomatic and contra lateral limb was done by Mann Whitney U test. All analyses were performed in SPSS version 19 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided with a level of significance defined as a P-value <0.05.

Results

Characteristics	Baseline value
Age in years, mean ± SD	46.65 ± 15.24
% of males	35 (87.5%)
Limb involvement, Right: Left	23:17
% with HTN	14 (35%)
% with DM	9 (22.5%)
% with CAD	2 (5%)
Mean ABI (both limbs)	0.65 ± 0. 2

Table 1: Baseline Characteristics of the Patients.

Case records of 40 patients who had completed at least 6 months of monthly prostaglandin injection for treatment of peripheral arterial disease were analyzed. The baseline characteristic of the patients is given in Table 1.

ABI of left limb and the average ABI of both the limbs showed highly significant increase compared to baseline, however increase in ABI of right limb narrowly missed the significance level (Table 2).

Mean ABI of patients	Before treatment	After 6 months of treatment	p
Right limb	0.66 ± 0.32	0.72 ± 25	0.07
Left limb	0.62 ± 0.26	0.72 ± 22	0.001
Average of both limbs	0.64 ± 0.20	0.72 ± 15	0.001

Table 2: The ABI of right, left and average ABI of both the limbs before and after 6 months of treatment.

The change in ABI values of the patients for the symptomatic limb and the contra lateral limb was again analyzed using t test which showed significant increase in ABI for the symptomatic limb from baseline whereas the contra lateral limb did not showed a significant change (Table 3).

Mean ABI of patients	ABI at baseline	ABI at the end of 6 months	p
Symptomatic limb	0.47 ± 0.24	0.60 ± 0.20	0.0001
Contra lateral limb	0.81 ± 0.23	0.85 ± 0.20	0.25

Table 3: The ABI of the symptomatic limb and contra lateral limb at baseline and at the end of 6 months of treatment.

The Mann Whitney U test showed that the ABI values at the end of treatment were significantly higher than baseline values for the symptomatic limb (p=0.04), whereas the contra lateral limb did not showed significant difference in ABI values at the end of treatment compared to baseline values (p=0.46).

The response to the treatment in patients with co morbidities such as diabetes, coronary artery disease or ulceration of limb was compared with those without these co morbidities. There was a significant increase in ABI of both limbs as well as the average ABI in the patients without any of these associated conditions than those with the presence of co morbidities (Table 4).

The ABI of symptomatic, contralateral and average of both limbs in diabetic patients showed improvement, although not significant statistically. Vascular calcification with stiffness of the distal vessels of the lower limb often gives a spurious high pressures at the level of ankle and high ABI. In those circumstances, we prefer to calculate toe brachial index to quantify the severity of the PVD (Table 5).

The patients having either of lower limbs or both the lower limbs with ABI less than 0.5 showed significant difference at the end of treatment when compared to baseline. (0.36 to 0.54; p<0.05) whereas the patients with average ABI more than 0.5 at baseline did not showed significant change at the end of treatment (0.84 to 0.81; p is NS).

Discussion

Prostaglandins are still being studied for the treatment of peripheral arterial disease. In studies they have often been used in people with severe symptoms and who can't have surgery. In the meta analysis of randomised controlled prostaglandin E1 studies in peripheral arterial occlusive disease stages III and IV, PGE1 therapy 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 [7]. The mechanisms of anti-ischemic effects

of PGE1 in patients with Peripheral Arterial Occlusive Disease (PAD) are probably complex and clearly not limited to a direct vasodilator action. In addition to the known effects on blood flow, viscosity, fibrinolysis and platelet aggregation, the compound also inhibits monocyte and neutrophil function, suggesting that PGE1 will also have anti-inflammatory effects, inhibition of expression of adhesion molecules (E-selectin, ICAM-1, and VCAM-1), release of inflammatory cytokines (TNFalpha, MCP-1), matrix components and decrease endothelin-1 levels 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 [8].

ABI of patients without associated conditions mentioned above	ABI at baseline	ABI at the end of the study	P	ABI of patients with associated conditions mentioned above	ABI at baseline	ABI at the end of the study	P
ABI for right limb	0.65 ± 0.30	0.76 ± 0.22	0.008	ABI for right limb	0.75 ± 0.35	0.72 ± 0.31	0.55
ABI for left limb	0.66 ± 0.26	0.74 ± 0.23	0.01	ABI for left limb	0.55 ± 0.23	0.65 ± 0.19	0.06
Average ABI for both limbs	0.66 ± 0.20	0.75 ± 0.15	0.009	Average ABI for both limbs	0.65 ± 0.21	0.69 ± 0.15	0.34

Table 4: The ABI of both limbs and average ABI at baseline and at the end of study for patients without any of the associated co morbidities such as diabetes, CAD or ulceration compared to those with these associated conditions.

ABI	Baseline	End of treatment (6 months)	p
ABI ≤ 0.3	0.25	0.46	P<0.03
ABI 0.3-0.5	0.4	0.58	P<0.001
ABI ≥ 0.5	0.84	0.81	NS

Table 5: The ABI of symptomatic, contralateral and average of both limbs in diabetic patients.

Vascular inflammation is a complex biological response trigged by chemical and mechanical injuries as well as by infectious stimuli. Inflammation is observed to various degrees in major cardiovascular diseases including atherosclerosis, myocardial infarction, congestive heart failure, and aortic aneurysm. A critical step of vascular inflammation is the recruitment of circulating leukocytes including monocytes and T lymphocytes into the vascular wall. The recruitment process is primarily the result of coordinated expression of vascular adhesion molecules as well as proinflammatory chemokines and cytokines. As a major component of the arterial wall, vascular smooth muscle cells (VSMCs) [2] are critical in maintaining normal physiological functions of blood vessels as well as in modulation of pathological processes taking place in the vascular wall. Numerous studies have shown that VSMCs can be an important source of cytokines in the vessel wall [9].

Patients with peripheral arterial disease may be asymptomatic or present with a spectrum of symptoms including atypical leg pain, classic claudication, rest pain, and critical limb ischemia with gangrene. PAD is diagnosed by assessing the ankle-brachial blood pressure index (ABI), a rapid and simple non-invasive diagnostic technique. Exercise and drugs such as PGE1, cilostazol, and angiotensin II type 1 (AT1) receptor blockers improve the symptoms of PAD. In general, these drugs increase flow in capillary vessels and do not affect the main arterial tract. Thus, most reports have shown that these therapies improve symptoms, but do not influence ABI.

In the present study we found a significant increase in ABI at the 6 months on monthly treatment with prostaglandin in patients with PAD. The average of both limbs and left limb showed significant increase in ABI, more number of patients had symptoms in right limb which could be the reason for missing significance (n=23).

The level of ABI also correlates with Lower Extremity Arterial Disease severity with high risk of amputation when the ABI is 0.50. An ABI change 0.15 is generally required to consider worsening of limb perfusion over time, or improving after revascularization [8].

In the present analysis we found that the prostaglandin increased the mean ABI of the symptomatic limb from 0.47 ± 0.24 to 0.60 ± 0.20 with the difference in mean ABI of 0.13, which satisfies minimal change expected after revascularization.

PAD patients with more severe disease with ABI less than 0.5 in either or both lower limbs showed highly significant increase in ABI of 1.8. Thus the patients with critical limb ischemia are more suitable for prostaglandin therapy which can serve as an alternative option to revascularization procedures.

The lack of improvement in patients with diabetes or other co morbidities explains its role in buergers disease or pure peripheral arterial disease without co morbidities.

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