A Clinical Study Of Peripheral Vascular Diseases With Special Reference To Phosphodiesterase Inhibitors

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Abstract:

Introduction: *Peripheral artery disease (PAD) is underdiagnosed, undertreated, poorly understood, and much more common than previously thought. Various modalities of treatment are been conventially tried recent study on phosphodiesterase inhibitors have proven to be effective in improving the clinical symptoms and outcome.*

Methods: *Study was done on the patients who were suspected for PVD. A diagnosis of PAD was confirmed in each patient on the basis of a resting ankle-brachial index (ABI) of ≤0.90. The enrolled patients were randomized in two groups of 50 each (n=100), Group I who were treated by Pentoxyphylline, Group II who were treated by Cilostazole. The findings were compared and correlated with clinical data and patient outcome.*

Results: *Out of a total 100 patients included for study, mostly 70 (70%) were in the age range of 31-60 years. Males are more prone to disease than females. 52 (52%) patients had their BMI, >25 kg/m^2 while remaining 48 (48%) patients had their BMI<25 kg/m^2. This study shows 58 (58%) patients were current smokers and other risk factors included 52 (52%) diabetics, 42(42%) had Dyslipidemia, 24 (24%) had Hypertension and 25 (25%) had developed Heart Diseases. On comparison of the efficacy of two different drugs the cilostazol drug was more superior in relieving pain while walking than Pentoxifylline drug.*

Conclusion: *The findings of present study coupled with earlier reports indicate Cilostazole as an effective treatment for patients of Peripheral arterial disease with intermittent claudication. Cilostazole was more superior to pentoxyphylline in improveing the overall outcome in patients of Peripheral Vascular Diseases.*

I. Introduction

Peripheral vascular disease (PVD) also known as peripheral artery disease (PAD), is narrowing of the arteries other than those that supply the heart or the brain[1]. It is a nearly pandemic condition that has the potential to cause loss of limb or even loss of life. Peripheral artery disease (PAD) is underdiagnosed, undertreated, poorly understood, and much more common than previously thought[2-3]. In the current study, the term peripheral artery disease is used to denote vascular diseases caused by atherosclerosis of the abdominal aorta, iliac, and lower-extremity arteries leading to stenosis or occlusion. Risk factors for PVD include smoking, hyperlipidemia, diabetes mellitus, and hyperviscosity. Other etiologies for developing PVD may include phlebitis, injury or surgery, and autoimmune disease, including vasculitis, arthritis, or coagulopathy. The PAD is clinically significant for two important reasons. First, patients with PAD may experience many problems, such as claudication, ischemic rest pain, ischemic ulcerations, repeated hospitalizations, revascularizations, and limb loss[4]. These lead to a poor quality of life and a high rate of depression[5-6] Even patients who have no leg symptoms have a poorer functional performance, poorer quality of life, smaller calf muscle area, and less calf muscle fat than an age-matched group of patients without PAD[7]. Second, patients with PAD have a greater likelihood of experiencing a myocardial infarction (MI), stroke, and cardiovascular death and have a higher rate of all-cause mortality compared with patients without PAD[8,9,10]

Various modalities of treatment are been conventially tried recent study on phosphodiesterase inhibitors have proven to be effective in improving the clinical symptoms and outcome[11-12]

In view of the above facts the present study was been conducted to study epidemiology and risk factors of peripheral vascular disease. To study various modes of presentations of peripheral vascular diseases. To assess the role of phosphodiesterase inhibitors in management of peripheral vascular disease and the clinical outcome.

II. Methods

This prospective study was conducted during September 2013 To August 2015 on patients attending OPD or admitted with symptoms and signs of peripheral arterial disease. Sample size was 100 patients. Patients who gave informed consent for participation in study were included. The enrolled patients were randomized in two groups of 50 each (n=100) using random number table. Group I(n=50): who was treated by Pentoxyphylline, Group II(n=50): who were treated by Cilostazole

A diagnosis of PAD was confirmed in each patient on the basis of a resting ankle-brachial index (ABI) of ≤0.90 in the symptomatic leg or for diabetic patients with non-compressible vessels (ABI>1.30), a toe-brachial index (TBI) of ≤0.70. The ABI was calculated with the higher of the 2 systolic blood pressures measured in the upper extremity and the higher of the measured dorsalis pedis or posterior tibial pressures measured in each leg.

Procedures

Each patient gave written, informed consent to participate in the study and the study protocol was approved by the institutional review board including ethical issues. A detailed history was obtained from each patient. This included age, gender, smoking, alcohol intake, diabetes mellitus – duration, treatment; hypertension – duration, treatment; symptoms of coronary artery disease; family history of diabetes, coronary artery disease, hypertension or cerebrovascular accident.

Anthropometric measurements included height and weight measurements and BMI was determined according to kilogram per meter square. A fasting blood sample was taken, 75 g glucose was given orally with 200 ml water to all of the individuals excluding known diabetic subjects, and a 2-h post glucose sample was then collected.

All of the Doppler studies were performed by a single observer using the M/S Appleo Toshiba. Blood pressure recordings were made of the brachial pulses in the upper limb. Similar recordings were made of the dorsalis pedis and posterior tibial pulses in the lower limb by inflating the cuff proximal to the ankle, and the mean of these 2 readings was taken as the ankle pressure. The ankle-brachial index (ABI) ratio was calculated in every subject. A criterion for diagnosis of PVD was an ABI<0.9.

The focus of PAD treatment was 1) to reduce symptoms and improve quality of life, and 2) to reduce overall cardiovascular morbidity and mortality.

Treatment typically included lifestyle modifications which were stopping smoking, commit to a regular exercise program that included walking, eating a balanced diet with proper nutrition, lose weight, treatment of conditions such as diabetes, high blood pressure, or high cholesterol.

Medical therapy included treatment with phosphodiesterase inhibitors like cilostazole 100mg twice daily dose another group included patients treated with pentoxyphylline 400mg thrice daily dose.
The two groups were compared and resuts were tabulated

Statistical analysis

The results obtained in the study were presented in a tabulated manner as Mean ± SD and were analyzed using with Statistical Package for Social Sciences (SPSS 20.0)and chi-square tests was used for comparison of frequencies. Multiple logistic regression analyses were performed using PVD as the dependent variable and age, sex, smoking, BMI, hypertension, glucose intolerance, serum cholesterol, serum triglycerides, HDL cholesterol, LDL cholesterol, and serum creatinine as independent variables. P value of <0.05 was considered statistically significant.

III. Results

Out of a total 100 patients included for study, mostly 70 (70%) were in the age range of 31-60 years. Males are more prone to disease than females. 52 (52%) patients had their BMI, >25 kg/m^2 while remaining 48 (48%) patients had their BMI<25 kg/m^2. Obesity has been linked with complications of PAD.

This study shows 58 (58%) patients were currently smokers and other risk factors included 52 (52%) diabetics, 42(42%) had Dyslipidemia, 24 (24%) had Hypertension and 25 (25%) had developed Heart Diseases among studied patients. Hyperglycemia, as well as smoking, dyslipidemia, and blood pressure are potentially modifiable risk factors for the development of PVD.

While on left side 83 cases were severe, 12 were moderate, 4 were mild and only 1 case was within normal limits of ABI. On the right side, 74 were severe,19 were moderate,5 mild and 2 were found to be under normal limits of ABI. It was shown that the ABI is an indicator of atherosclerosis at other vascular sites and can serve as a prognostic marker for cardiovascular events and functional impairment

The findings of present study coupled with earlier reports indicate Cilostazole as an effective treatment for patients of Peripheral arterial disease with intermittent claudication. Also by favorably affecting the ABI, it can prevent one of risk factors responsible for increased prevalence of this disease. Cilostazole was more superior to pentoxyphylline in improveing the overall outcome in patients of Peripheral Vascular Diseases.

IV. Discussion

Peripheral arterial disease (PAD) is the occlusive disease of arteries distal to the aortic bifurcation. The prevalence of PAD in the lower limbs in a general population >55 years of age is between 10% and 25% and it increases with age. Majority of affected population have asymptomatic disease. Peripheral arterial disease, whether symptomatic or asymptomatic, is a risk factor for non-fatal and fatal coronary disease and cerebrovascular events. Patients with PAD alone have the same relative risk of death from cardiovascular cause as those with coronary or cerebrovascular disease. Risk of death in patients of PAD within 10 years is 4 times more than those without the disease.

As with other clinical atherosclerotic syndromes, the etiology of PAD is due to both modifiable (diabetes, smoking, hypertension, and hypercholesterolemia) and non-modifiable (e.g. age, gender, family history) risk factors. The decreased blood flow to the legs caused by PAD may be mild or severe, resulting in a broad range of symptoms. Patients may not suffer recognizable limb symptoms, or they may experience intermittent claudication (IC), or manifest symptoms of severe limb ischemia. IC, the most common symptom of PAD, is defined as fatigue, cramping, or frank pain of the gluteal, thigh, or calf muscles that is consistently provoked by exercise and that is reproducibly relieved by rest. Patients with IC are often limited in their daily activities owing to walking impairment and in turn experience a diminished quality of life. With continued exposure to atherosclerotic risk factors, PAD may progress to critical limb ischemia (CLI), which portends a severe diminution in quality of life, and is associated with a high rate of amputation and a marked increase in short term mortality. Thus, PAD is a common manifestation of atherosclerosis that is associated with a range of symptoms, a variable impact on quality of life, and a heightened risk of cardiovascular ischemic events.

Several studies have shown that the ankle brachial index (ABI), an index for occlusive vascular disease, is now considered as an independent predictor of coronary and cerebrovascular morbidity and mortality.

In managing PAD, it is critically important to deal with the high risk of developing severe and often fatal cardiovascular complications. The first priority is to aggressively modify risk factors that enhance the progression of atherosclerosis and atherosclerotic complications. It is also important, however, to relieve the symptoms of intermittent claudication.

Medications play a key role in the management of intermittent claudication (IC). In addition to pentoxifylline and cilostazol, other medications used include antiplatelet agents, vasodilators, anticoagulants, ketanserin, nifedipine, fish oil, and ethylenediaminetetraacetic acid (EDTA), used for chelation therapy. Before the approval of cilostazol for marketing, pentoxifylline was the only medication whose FDA-approved labeling included the treatment of IC. Pentoxifylline, a trisubstituted methylxanthine derivative, produces dose-related hemorheologic effects, and its metabolites improve blood flow by decreasing blood viscosity and improving erythrocyte flexibility. Cilostazol exhibits its pharmacologic effects via antiplatelet, vasodilatory, and antithrombotic activities. Like pentoxifylline, cilostazol and several of its metabolites exhibit these antiplatelet and vasodilatory actions through the inhibition of phosphodiesterase activity.

When we compare two groups of drugs, more improvement was seen in group Cilostazole regarding ABI, peak walking time, rest pain and claudication onset time respectively. Similar results have been reported by large placebo controlled double blind trials by Dawson DL et al 2000 and Tsung – Ming Lee et al 2001[12] .

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Table 1 Age Distribution

Age	Frequency (%)
<30	4 (4%)
31-40	25(25%)
41-50	30(30%)
51-60	15(15%)
61-70	21 (21%)
71-80	4 (4%)
>81	1 (1%)
Mean±SD	**46.25±15.0**

Table 2 Risk Factors

Gender M : F	72 : 28
BMI >25kg/m^2 : <25kg/m^2	52 : 48
Risk Factors(Current Smokers)	58%
Other Risk Factors	
• Diabetese	52%
• Dyslipidemia	42%
• Hypertention	24%
• Heart Diseases	25%
Clinical Presentation	
• Intermittent Claudication	33%
• Ischemic Rest Pain	70%
• Ulceration	40%
• Gangrene	67%

Table 3 Management

MANAGEMENT	GROUP I (n=50) Pentoxyphylline	GROUP II (n=50) Cilostazole	P VALUE
ABI Improvement			
After 1 month	0.55	0.65	0.19
After 3 months	0.72	0.89	0.03
Claudication onset time (sec)			
After 1 month	210.9	259.9	<0.001
After 3 months	275	375	<0.001
Rest Pain			
After 1 month	20.3	10.1	<0.001
After 3 months	10.2	4.2	<0.001