OPD management of Peripheral Arterial Disease patients in a Tertiary Care hospital: Does Aspirin and Cilostazol help

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Abstract

Background: Cilostazol is the first-line drug for peripheral arterial disease (PAD) because it improves the symptoms and quality of life. The treatment of PAD involves the prevention of cardiovascular events plus relief of symptoms including intermittent claudication (IC). The objective of this study was to evaluate the efficacy of aspirin and cilostazol in patients suffering from peripheral arterial disease (PAD).

Methods: Patients were evaluated on outpatient department (OPD) basis. Meticulous history was followed by clinical examination and measurement of ankle-brachial index for diagnosing PAD. The patients also underwent duplex imaging, computed tomography angiography or magnetic resonance angiography. The treatment includes lifestyle modification in the form of smoking cessation and exercise; management of atherosclerotic risk factors, including antiplatelets, statins, drugs for hypertension; and agents to improve walking distance, such as cilostazol and enalapril

Results: The mean age of the patients was 47±6.2 years. History of smoking, either past or current, was present in 91% of patients. History of ischemic heart disease was present in 2.17 %, while 26.08% patients were diabetic. Aspirin and cilostazol were prescribed after the diagnosis was made. Symptomatically, all the patients improved. Walking time was improved in all the patients.

Conclusion: The safety profile of aspirin and cilostazol in patients with PAD appears to be acceptable. In addition to risk factor management, treatment with cilostazol should be considered in patients of PAD.

Keywords: OPD, aspirin, cilostazol, peripheral arterial disease, management.

Introduction
Peripheral arterial disease (PAD) is a common disorder which affects arteries of the lower limb and patients mostly present with IC. It is portion of a general cardio-vascular disorder of diffuse atherosclerosis. PAD affects 12-14% of the overall population and its prevalence increases with age affecting up to 20% of patients over the age of 75[1]. Due to the common underlying pathologic process of atherosclerosis, coronary artery disease (CAD) and/or cerebrovascular disease (CVD) is also present in PAD patients.
PAD is said to be the third leading cause of atherosclerotic cardiovascular morbidity, following CAD and stroke\cite{2}. Patients of PAD have a 6.6 fold increased risk of death from CAD\cite{3}. In addition to quitting smoking and exercise, cilostazol\cite{4} and statins\cite{5} have been demonstrated to decrease claudication in PAD patients. In addition, these patients are also advised to receive antiplatelet therapy to prevent major adverse cardiovascular events (MACE) including myocardial infarction (MI), stroke and death\cite{6-10}. Evidence shows that single antiplatelet therapy is associated with a 25% odds reduction in MACE in arrange of high-risk patients with cardiovascular diseases\cite{11}. This includes patients with an acute or previous MI, acute or previous ischemic stroke, stable or unstable angina, and atrial fibrillation\cite{11}. Hence, patients with symptomatic PAD usually receive single antiplatelet therapy with daily aspirin. The present study was done to assess the patterns of PAD in our population and its management.

**Material and Methods**

Data were collected prospectively from patients attending cardiothoracic and vascular surgery OPD with diagnosis of atherosclerotic PAD from March 2016 to January 2019. Meticulous history was followed by clinical examination and measurement of ankle-brachial index for diagnosing PAD. All the patients were analysed for presence of risk factors for atherosclerosis (history of smoking, hypertension, diabetes, dyslipidemia, renal insufficiency, history of ischemic heart disease or cerebrovascular disease). Ankle brachial index (ABI) was documented. Doppler imaging of lower limbs was done in all the patients. More detailed anatomic information from computed tomography angiography and magnetic resonance angiography, is usually unnecessary unless endovascular or surgical intervention is being considered, or if abdominal aortic aneurysm or popliteal aneurysm need to be excluded. The treatment includes lifestyle modification in the form of smoking cessation and exercise; management of atherosclerotic risk factors, including antiplatelets, statins, drugs for hypertension; and agents to improve walking distance, such as cilostazol and enalapril. The surgical interventions including endovascular ones are usually reserved for lifestyle limiting IC which does not respond to conservative management, and for critical limb ischaemia. Inclusion criteria were: aged 20 years or older with symptomatic PAD for 6 months and no significant change in severity for a minimum of 3 months. Exclusion criteria were: rest pain, ischemic tissue necrosis, surgical or endovascular procedures within the past 3 months, unstable coronary artery disease, symptomatic cardiac arrhythmias, recent (3 months) DVT, conditions that limited exercise capacity other than IC. The minimum duration of follow-up had to be one month.

**Results**

A total of 46 patients were diagnosed of having PVD. The mean age of the patients was 47±6.2. Male/female ratio was 29/17 (Table 1). Forty two patients gave history of current or past history of smoking. Twelve patients were diabetic and 37 patients had history of hypertension. Twenty six patients had deranged lipid profile (Table 2). Thirty one percent of patients had all 4 risk factors, 38% had any 3 risk factors and 74% had any two risk factors.ABI was measured in all the patients. Based on ABI value, mild to moderate PAD (ABI 0.41-0.90) was present in 42(91.3%) patients while 4(8.69%) patients had severe PAD (ABI ≤0.40). All the current smokers were advised to quit smoking. Nicotine replacement therapy (chewing gum) was advised to current smokers. All patients were advised regular walking and exercises. All patients were prescribed aspirin (75 mg once daily) and cilostazol (50 mg twice daily). Atorvastatin was prescribed to 26 patients while ACE inhibitor (Enalapril) was prescribed to 24 patients. Beta blocker was prescribed to 8 patients (Fig 1). Two patients had past history of myocardial infarction.
Two patients needed embolectomy for acute on chronic vascular obstruction. The patients were examined monthly on OPD basis and were asked to continue treatment for 3 months. On completion of three months, patients had improvement in symptoms and signs of PAD (Fig 2).

**Table 1: Baseline characteristics of patients**

<table>
<thead>
<tr>
<th>Number of patients studied</th>
<th>46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years±SD</td>
<td>47±6.2</td>
</tr>
<tr>
<td>Males/Females</td>
<td>29/17</td>
</tr>
<tr>
<td>Rural/urban</td>
<td>30/16</td>
</tr>
</tbody>
</table>

**Table 2: Risk Factors in the studied population**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smokers</td>
<td>36 (78.2%)</td>
</tr>
<tr>
<td>Past smokers</td>
<td>6 (13.04%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (26.08%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37 (80.43%)</td>
</tr>
<tr>
<td>Abnormal lipid profile</td>
<td>26 (56.52%)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2 (4.34%)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>1 (2.17%)</td>
</tr>
<tr>
<td>Patients who needed embolectomy for acute on chronic vascular obstruction</td>
<td>2 (4.34%)</td>
</tr>
</tbody>
</table>

**Fig 1: Bar Diagram showing medicines prescribed to the studied subjects**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>44</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>44</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>30</td>
</tr>
<tr>
<td>Enalapril</td>
<td>20</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>10</td>
</tr>
</tbody>
</table>

**Fig 2: Pie chart showing symptomatic relief in patients after completion of three month medical management**

- **Marked improvement in symptoms**: 44
- **Mild improvement in symptoms**: 2
Discussion

Intermittent claudication of limbs is due to insufficient blood flow to meet the metabolic demands and presents as painful aching, cramping or tightness of muscles during exercise. IC manifests in the calf muscles when the infrainguinal arteries are affected. It may also present in the thighs and buttocks if there is aortoiliac disease. Some patients with PAD, particularly the elderly who have additional co-morbidities that limit walking such as arthritis, spinal stenosis, heart failure, and pulmonary disease may not experience symptoms of PAD. Data were collected prospectively from patients attending cardiothoracic and vascular surgery OPD with diagnosis of atherosclerotic PAD from March 2016 to January 2019. Meticulous history and clinical examination helps us in diagnosing PAD. All the patients were analysed for presence of risk factors for atherosclerosis (history of smoking, hypertension, diabetes, dyslipidemia, renal insufficiency, history of ischemic heart disease or cerebrovascular disease). For atypical exertional leg pain, post-exercise ABI was measured. This is usually done following treadmill exercise (typically performed walking at 3 km/h). If a treadmill is not available, then the walking exercise may be performed by walking up and down the hallway or by climbing stairs\[8\]. Active pedal plantar flexion compares favourably with treadmill exercise and should be considered an appropriate alternative\[8\]. Ankle brachial index (ABI) was documented. ABI is defined as the ratio of the highest systolic pressure at the ankle divided by the brachial systolic pressure\[8\]. In normal people, ankle systolic blood pressure is 10-15 mm Hg higher than brachial systolic blood pressure and thus the normal ABI value is more than 1. A value of ABI less than or equal to 0.90 is diagnostic of PAD with values between 0.41 and 0.90 confirms mild to moderate PAD and values less than or equal to 0.40 reflects severe PAD. It has been widely accepted that an ABPI of less than 0.9 is up to 95% sensitive and 99% specific in detecting peripheral arterial disease that would be detected on angiography\[12,13\]. This non-invasive bedside test is a reliable tool in assessing the presence and severity of PAD rather than relying solely on a clinical diagnosis. An ABPI of less than 0.9 is associated with an increased risk of cardiovascular and cerebrovascular events\[14\]. The benefit of early diagnosis by screening for asymptomatic PAD (defined by a ABPI of 0.9), is debated but remains to be established \[15\]. More detailed information about PAD is required to exclude abdominal aortic aneurysm (which can occur in up to ten percent of patients with PAD, or popliteal aneurysm and to plan surgical management including endovascular interventions. The aneurysmal disease can be diagnosed on physical examination and the imaging procedures are required if endovascular or open surgical intervention is planned. Doppler examination is a non-invasive investigation used to see the sites of occlusion or stenosis, and is often the only imaging which is required. Doppler examination is also useful investigation for during follow up of vascular interventions. Every patient was subjected to doppler study of both lower limbs. Both computed tomography angiography (CTA) and magnetic resonance angiography (MRA) have good sensitivity and specificity. Patients were subjected to CTA and magnetic MRA as and when required. The patients should undergo renal functions before CTA or MRA as contrast nephropathy and nephrogenic systemic fibrosis has been associated with exposure to gadolinium based MRI contrasts. Patients were advised for smoking cessation and advised regarding exercise. The twin priorities in the medical management of PAD are symptom relief and the prevention of cardiovascular events. Both require treatment of the causes and consequences of atherothrombosis but some strategies are more effective for one goal than the other. The association between smoking and PAD is very strong with over 80% of patients being current or ex-smokers\[16\]. Furthermore, the association is dose dependent; increasing exposure to cigarette smoke is associated with earlier onset
of symptoms and more severe PAD\cite{17}. Finally, smoking cessation in patients with PAD is associated with a reduction in severity of IC and risk of developing rest pain\cite{18}. Intermittent claudication is almost twice as common in patients with diabetes compared to those with normal glycemic control\cite{8}. Intensive glycemic control reduces the impact of microvascular complications of diabetes, but there is little evidence that it changes the course of macrovascular disease causing PAD\cite{19}. Neuropathy, local microvascular changes in the foot and PAD all contribute to diabetic foot problems and screening for these has been advocated\cite{20}. Regular exercise is not only beneficial for cardiovascular health among the general population\cite{21} but also for patients with PAD in whom it reduces mortality and cardiovascular events\cite{22}. Exercise is also beneficial in improving maximum walking time and walking ability\cite{23}. Patients with IC should be advised about a supervised exercise programme. Consider providing a supervised exercise programme for people with intermittent claudication which involves 30 to 40 min in sessions performed at least 3 times per week for a minimum of 12-16 weeks, encouraging people to exercise to the point of maximal pain. The regular exercise programme is seen to decrease cardiovascular risk in this high risk population. After diagnosing PAD, drugs were prescribed for modification of atherosclerotic risk factors (aspirin and lipid lowering drugs) and for intermittent claudication (cilostazol). Eligibility of drugs was decided based on ACC/AHA and TASC-II guidelines for management of patients of PAD\cite{8,16}. All patients were eligible for aspirin, lipid lowering drugs, ACE inhibitors and cilostazol. The patients with history of ischemic heart disease were considered eligible for beta blockers. Antiplatelet therapy (chiefly aspirin) reduces the relative risk of major cardiovascular events among those at risk of atherothrombosis, including those with IC, by about 25\cite{24}. The lipid lowering agents reduce total cardiovascular events and improve pain-free walking distance. Adding simvastatin (40 mg/day) to existing treatments reduces the rates of myocardial infarction, stroke and revascularization\cite{25}, chiefly by reducing overall risk of major vascular events rather than blood lipid concentrations alone. Statins are the only type of lipid lowering drug for which consistent, clear evidence of a beneficial effect is available for total cardiovascular events, total coronary events and stroke\cite{26}. Cilostazol is a phosphodiesterase 3 inhibitor which has vasodilator and antiplatelet properties. It has been shown to improve maximal walking distance by upto 60\% after 12-24 weeks of treatment\cite{27}. Apart from these effects, cilostazol has been shown to increase HDL cholesterol and decrease plasma triglyceride levels\cite{28}. It is recommended in the patients of IC in the absence of heart failure. Previous reports have established the relative safety of cilostazol and an acceptable low risk of serious side effects and no increase in bleeding events over placebo\cite{29,30} but polypharmacy and compliance are concerns in this patient population, as medication regimens become increasingly complex. Palpitations, headache and diarrhoea are most common adverse effects of cilostazol, which may be responsible for underuse of this drug. Hypertension has been reported to be a risk factor for PAD in some but not all studies\cite{8,31}. Although there are few data based on patients with PAD, drug treatment of hypertension reduces cardiovascular risk\cite{32,33}. The HOPE study and other large trials have established that angiotensin-converting enzyme (ACE) inhibitors significantly reduce the risk of cardiovascular related events in patients with symptomatic and asymptomatic PAD\cite{34}. There is currently no proof that the use of beta-blockers adversely affects walking distance in patients with IC\cite{35}, so that if a beta-blocker is required for cardio-protection, then it should be used. Calcium channel blockers protect against cardiovascular and cerebrovascular disease mortality of any etiology\cite{36}. The evidence of the effects of various antihypertensive drugs in
patients with PAD is poor but this should not detract from the compelling evidence of its benefit in lowering blood pressure in patients[37].

PAD is one of the manifestations of generalized systemic atherosclerosis and the patients have high risk of adverse cardiovascular events. All these patients need management of risk factors similar to patients of coronary artery disease. Modification of the risk factors and antiplatelet agents are recommended for patients with symptomatic PAD with the aim of reducing the risk of future MACE and improve outcomes in them. Medical therapy improves survival in these patients and the cessation of smoking reduces the cardiovascular risk. Regular exercise should be advised (both home based programmes and supervised). While antiplatelet agents and statins are being used adequately; cilostazol is suboptimal and needs to be increased. Consideration of cilostazol as a medical adjunct in appropriate candidates is warranted to potentially improve limb-related outcomes. The patients should be sent to a vascular surgeon when the diagnosis is doubtful, critical limb ischemia is evident by persistent rest pain, presence of ischaemic ulceration or gangrene, symptoms of claudication which limit lifestyle or work, or there has been no improvement in spite of an exercise program, modification of risk factors and medical management after a 6 month period. Patients with critical limb ischemia (rest pain, tissue loss, or gangrene) usually require revascularisation which prevents limb loss/amputations. The main options available are open surgical reconstruction by peripheral bypass with or without endarterectomy or endovascular angioplasty or stenting. The choice of procedure will depend on the extent of the disease, anatomic location of the stenotic vessel and the patient’s comorbidities.

Conflict of interest: None

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References
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