A Combined Treatment Effect of Cilostazol and Pentoxifylline in the Treatment of Peripheral Vascular Disease

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ABSTRACT

Background: In past comparative studies in peripheral vascular disease (PVD) showed Cilostazol was efficient in relieving intermittent claudication as compared to Pentoxifylline.

Objectives: The present study was planned to assess the effect the combination of cilostazol (50 mg BD) and pentoxifylline (400 mg TDS) therapy in patients with PVD. Additionally, the adverse effects and economic burden of the combination was taken in to account.

Methodology: An Observational antegrade study was done among 100 patients. A Patient with PVD visited to OPD of the vascular department was enrolled in the study. Data was collected as per the Case Record Form.

Results: The mean age was found to be 58.4 ± 11.3 years of total 100 patients. An improvement in a Doppler testing (follow-up at the time interval after 1 month, 3 months and 6 months) and increased in peak systolic velocity in distal vessels as well as collaterals were observed in all patients. The PVD was prevalent in 50 to 60 years of age groups and hypertension and smoking were the most common risk factors present in PVD patients. There was more than 70% increase in...
walking distance after 24 weeks of treatment. Headache 24 (36.4%) and Dizziness 9 (13.6%) were observed as common side effect of therapy. The total cost of the combination therapy was affordable with improved quality of life.

**Conclusion:** The combination treatment showed symptomatic improvement in peripheral vascular disease in the study. The peak systolic velocity gradually increased in the distal vessel and the combination was found to be cost-effective.

**Keywords:** Peripheral vascular disease; cilostazol; pentoxifylline; cost-effectiveness; Doppler test.

## 1. INTRODUCTION

PVD is the third most common condition overall among atherosclerotic cardiovascular disease, according to the World Health Organization (WHO) [1]. Lower limb peripheral vascular disease (PVD) is a blood flow disorder brought on by plaque build-up in the walls of the arteries, which causes a reduction in blood flow to the lower limb's muscles and tissues [2]. The clinical symptoms of lower limb arterial disease include intermittent claudication and the absence of peripheral pulses in the lower leg and foot [3]. Intermittent claudication, Critical Limb Ischemia (CLI), and Acute Limb Ischemia are further clinical manifestations of PVD (ALI) [4]. The risk factors for PVD include age, tobacco use, diabetes mellitus, asthma, hyperlipidaemia, chronic kidney disease, obesity, and race [5]. Intermittent claudication (IC) is a condition marked by discomfort, aching, cramping, or muscle exhaustion in the affected extremity. Approximately 5% of men and 2.5% of women 60 years of age or older have IC [6].

Several diagnostic techniques, including Doppler ultrasonography [7], magnetic resonance angiography (MRA) [8], and computed tomography angiography (CTA), were employed to identify peripheral vascular disease [9]. In the majority of PVD cases, atherosclerotic plaques reduce the arterial flow lumen, restricting blood flow to the distal extremity. Walking may result in thigh or calf pain from acute leg muscle ischemia brought on by decreased blood supply [10]. The development of blood clots inside the arteries is significantly influenced by platelets. The most efficient anti-platelet therapy regimen for PVD is still unknown, despite the fact that percutaneous revascularization therapies have advanced significantly thanks to improvements in interventional devices and methods [11].

The only FDA-approved medication with an AHA/ACC class IA recommendation is cilostazol [12]. It has been proven to be safe, although elderly co-morbid patients should use it with caution to reduce the risk of side effects [13]. The FDA has also given pentoxifylline approval to treat the symptoms of lower extremity claudication. It enhances blood vessels' microcirculation [14]. It has immunomodulatory properties that prevent the production of inflammatory cytokines like tumour necrosis factor-alpha [15]. Few research [16] were conducted on this combination, and the major findings were reported that cilostazol is more effective than pentoxifylline in promoting intermittent claudication or the medicines are provided to a different group of patients with lower extremity PVD.

Therefore, the goal of the current study was to evaluate the effects of treating PVD patients with cilostazol (50 mg BD) and pentoxifylline (400 mg TDS) together. The adverse effects and financial burden of the combination were also taken into account.

## 2. METHODOLOGY

After receiving approval from the Institutional Ethics Committee (IEC), CHARUSAT (Letter No-CHA/IEC/ADM/20/07/622) for a 2-month observational antegrade study, it was conducted at the Department of Vascular Surgery, Sheth H.J Mahagujarat Hospital, Nadiad. According to the study's criteria, individuals with peripheral vascular disease who visited the OPD of the Vascular department were enrolled in the study.

### 2.1 Inclusion Criteria

1) All patients with peripheral vascular disease who were managed conservatively. 2) All patients who were operated for PVD with distal vessel disease and needs aggressive medical management. 3) All patients with PVD who were operated and not completely relived by surgery.

### 2.2 Exclusion Criteria

All those peripheral vascular disease patients who were completely recovered by the surgery were excluded from the study.
2.3 Data Collection Method

The participants in this study were the Antegrade and Retrograde PVD patients who visited the vascular department’s OPD and had their diagnoses made by a treating physician. As stated in the case record form, data was gathered (CRF). Baseline and treatment-related examinations, such as changes in symptoms like rest discomfort, claudication distance, and gangrene, were thoroughly monitored. Following the completion of the treatment period, one month, three months, and six months later, a follow-up Doppler test was conducted and documented. In parallel, the rise in peak systolic velocity in distal vessels and collaterals was investigated and compared with pre-treatment procedures.

2.4 Statistical Analysis

Details of tables, tests and other statistical analysis were done by using t test in Microsoft office excel. Descriptive statistics was also used.

3. RESULTS

The inclusion criteria were used to screen a total of 100 patients. There were 100 patients, of which 90 (90%) were men and 10 (10%) were women. The average age was 58.4 ± 11.3 years. The risk of PVD was shown to be reduced in age groups under 30 to 40 years and to be higher in those between 50 and 60 and 60 and 70. Women were now more likely than males to have lower extremity PVD as they get older, but men were still more likely to be affected. PVD blockage bifurcation in all patients were categorised as represented in Fig. 1.

Out of 100 patients, majority of patients are found to have intermittent claudication (100%) and gangrene (20%). Only 4 (4%) patients had complaint of critical limb ischemia, 24 (24%) of patients had complaint of pre-gangrene and 52 (52%) of patients had complaint of pain (rest pain). Out of 100% of intermittent claudication patients, 5 (5%) comprised of female patients of age group 60 to 70 years. Moreover, out of 20% gangrene patients, 45% patient population were females. Majorities of the PVD patients had hypertension (70,28.6%) and diabetes (55,22.4%) as associated condition and nearly 80 (32%) patients had smoking history (Table 1).

In the study, 30% of patients were treated surgically, and the remaining 70% were managed with medicinal intervention. Out of 100 patients with intermittent claudication, 29% demonstrated improvement following one month of receiving treatment, 52% within three months, and 73% improved after six months of receiving treatment.

A total of 20 patients out of 100 developed gangrene signs. Out of these 20 patients, six (30%) patients showed improvement in gangrene within one month of starting treatment, ten (50%) patients improved after three months, and fifteen (75%) patients improved after six months.

Similar to this, out of 100 patients, 52 percent of patients experienced rest discomfort; of these, 19 (36.5%) patients improved after one month, 26 (50%) patients improved after three months, and 42 (80.8%) patients improved within six months. All PVD patients received clopidogrel alone, aspirin alone + atorvastatin, simvastatin, or rosvastatin as adjuvant therapy in addition to these medicines. It subsequently turned out to be helpful in preventing blood clotting and clearing artery plaque. In PVD patients, a steady improvement in the doppler test was also noted (Tables 2 & 3).

A total of 94 (94%) patients were found to have followed their treatment plans exactly. Observations of compliance were made through patient follow-ups at the hospital. All PVD patients experienced the negative effects throughout their treatment. The majority of them (24,36.4 percent) reported headaches. Despite the fact that all of the complaints were minor, the vascular surgeon handled them all well (Table 4).

The total cost of tablet cilostazol (Zilast) 50 mg (twice daily) was ₹60.52 for 10 tablets and tablet pentoxifylline (Trental and Kinetal) 400 mg prescribed thrice a day and cost for ₹30.45 and ₹26.52 respectively. The combination treatment regimen showed better quality of life (QoL) in approximately 80% of the PVD patients with good symptomatic improvement and manageable side effects.

4. DISCUSSION

The present antegrade study enrolled 100 patients of lower extremity peripheral vascular disease. Out of 100 patients, male (90%) predominance was observed. Likewise, a meta-analysis study by Gaddi AV et al reported similar findings. The female PVD patients were found to be less as compared to male [17]. The age group 50 to 70 years was found to be at high risk of
lower extremity PVD. In present study, the mean age was found to be 58.4 ±11.3 years. A similar mean age difference was found in the previous study [17].

In this study, out of 100 patients, 9% (42 to 73 years age range) of male patients wherein 3% (47 to 65 years age range) females had bilateral affected lower limbs. Three types of PVD blockage bifurcation were observed in this study which involves aorto-iliac bifurcation, femoropopliteal PVD, and Bilateral Tibial Peroneal Trunk (B.T.P.T) PVD. Out of it, B.T.P.T.PVD was most common among both genders. Additionally, more than one blockage was also reported among the patients. Total 31 male and 1 female were having femoro-popliteal as well as B.T.P.T blockage, 8 males and 4 females had aorto-iliac and B.T.P.T blockage, 4 males had aorto-iliac, femoropopliteal as well as B.T.P.T blockage and 2 males had aorto-iliac and femoropopliteal blockage. Inclusive, 137 different blockages were identified, out of which 21(15.3%) aorto-iliac PVD type, 48 (35%) femoro-popliteal PVD and 68 (49.6%) B.T.P.T PVD. Among 68 (49.6%) patients had B.T.P.T PVD blockage (type c blockage) represented 59 (86.7%) males and 9 (13.2%) females. A total of 48 (35%) patients were identified with Femoro-popliteal PVD (type b blockage) whereas 47 (97.9%) males were affected by this blockage. Lastly, 21(15.3%) aorto-iliac (type a blockage) was identified among 19 (90.4%) males and 2 (9.5%) females.

In the present study, PVD patients had 245 types of associated co-morbidities and risk factors were identified. Among these, smoking 80 (32.6%) followed by hypertension 70 (28.6%) and diabetes55 (22.4%) were the major root causes of disease. Additionally, more than two risk factors were identified in the study. A similar study observation was reported by Mann et al. [18].

Intermittent claudication (IC) was found as the most common symptom among all (100%) PVD patients followed by gangrene (20%) and (4%) critical limb ischemia. On the other hand, pre-gangrene symptoms were also found in the 24 (24%) patients. According to a previous study, cilostazol was beneficial in reducing lipid profiles in PVD patients along with intermittent claudication [19].

<table>
<thead>
<tr>
<th>Associated aetiology</th>
<th>Total Number of Patients N (%)</th>
<th>Number of Male Patients (N)</th>
<th>Number of Female Patients (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>70 (28.6%)</td>
<td>68</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>55 (22.4%)</td>
<td>52</td>
<td>3</td>
</tr>
<tr>
<td>Smoking</td>
<td>80 (32.6%)</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>Obesity</td>
<td>20 (8.2%)</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Alcohol</td>
<td>15 (6.1%)</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Trauma</td>
<td>5 (2%)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>245 (100%)</td>
<td>232</td>
<td>14</td>
</tr>
</tbody>
</table>

Fig. 1. Patients having types of blockages at different sites of the lower limb

Table 1. Number of patients with associated aetiology
Table 2. Symptomatic improvement and follow-ups at different time intervals

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Drug prescribed cilostazol 50 mg (B.D) + Pentoxifylline 400 mg (T.I.D)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After 1st month</td>
</tr>
<tr>
<td>Improvement in Claudication distance</td>
<td>29 (29%)</td>
</tr>
<tr>
<td>Improvement in Gangrene</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>Improvement in rest pain (as per the Visual Analogue Scale (VAS) Score)</td>
<td>19 (36%)</td>
</tr>
</tbody>
</table>

Table 3. Improvement in Doppler’s test

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Parameters for Doppler test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak systolic velocity(PSV) from Baseline</td>
<td>25-32 cm/sec</td>
</tr>
<tr>
<td>2</td>
<td>PSV after 1 month of giving treatment via cilostazol and pentoxifylline</td>
<td>30-36 cm/s</td>
</tr>
<tr>
<td>3</td>
<td>PSV after 3 months of giving treatment via cilostazol and pentoxifylline</td>
<td>40-45 cm/s</td>
</tr>
<tr>
<td>4</td>
<td>PSV after 6 months of giving treatment via cilostazol and pentoxifylline</td>
<td>44-50 cm/sec</td>
</tr>
</tbody>
</table>

Table 4. Side effects of the drug combination in the patients during or after the treatment

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Side effects</th>
<th>Number of patients N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Headache</td>
<td>24 (36.4%)</td>
</tr>
<tr>
<td>2</td>
<td>Dizziness</td>
<td>9 (13.6%)</td>
</tr>
<tr>
<td>3</td>
<td>Abnormal stools</td>
<td>8 (12.1%)</td>
</tr>
<tr>
<td>4</td>
<td>Pharyngitis</td>
<td>4 (6.1%)</td>
</tr>
<tr>
<td>5</td>
<td>Peripheral edema</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>6</td>
<td>Tachycardia</td>
<td>3 (4.5%)</td>
</tr>
<tr>
<td>7</td>
<td>Palpations</td>
<td>6 (9.1%)</td>
</tr>
<tr>
<td>8</td>
<td>Nausea</td>
<td>8 (12.1%)</td>
</tr>
<tr>
<td>9</td>
<td>Vomiting</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>66 (100%)</td>
</tr>
</tbody>
</table>

In present study, for 70 (70%) patients’ medical intervention was preferred with angiography while rest 30 (30%) patients underwent various surgical interventions included as femoro-distal bypass surgery 18 (60%) and 12 (40%) on aorto-femoral bypass surgery in addition to aggressive medication management. The surgical and non-surgical interventions were provided by vascular surgeon as per the clinical presentations of patients.

In this study, cilostazol was considered as first choice of treatment for the patients of intermittent claudication. The statins were prescribed along with pentoxifylline in 24 (24%) PVD patients. In medical intervention, the tablet cilostazol (50 mg) two times a day whereas tablet pentoxifylline (400 mg) thrice daily were included as treatment regimen for PVD. Similar doses of cilostazol were considered earlier in a study [20].

In the present study, it was observed that, after the initial month of treatment, the patients were able to walk between 450 m to 580 m and gradually increased walking distance up to 640 m after 3rd month and 640m to 700 m after 6th month of treatment. In a previous comparative study of cilostazol and pentoxifylline, [21] a mean distance of 107 m increased with cilostazol and mean distance of 67 m was increased with pentoxifylline after 6-month treatment. In the present study, the average walking distance was 150 m after 6 months, which showed better combination therapy effect.

In the study, 29 (29%) patients showed improvement in IC within 1 month of treatment followed by 52 % after 3 months and 21%
within 6 months. It showed total 73% patients had gradual improvement in IC. In the case of gangrene patients (20%), after initiating treatment, 6 (30%) patients showed improvement in gangrene within 1 month, 10 (50%) patients showed improvement in after 3 months and 15 (75%) patients after 6 months.

In the current study, 52 (52%) patients were suffered from rest pain, out of which 19 (36.5%) patient showed improvement in 1 month, 26 (50%) patients showed improvement after 3 months while 42 (80.7%) patients showed improvement within 6 months. Total 94% patients were adhered to their treatment regimen. Compliance status was recorded for the patients file as surgeon recorded the observation based on the patient’s interaction and improvement in laboratory parameters. The reappearance of symptoms was observed in 5% male patients (age 60 years) with presence of smoking and hypertension.

In the present study, the cost of therapy was analysed in order to check the economic burden and improvement in quality of life (QoL) post medical intervention of combination therapy. Tablet cilostazol (Zilast) 50 mg prescribed for twice daily, which had total cost of ₹60.52 for 10 tablets. Hence the total cost for 60 days was ₹1089.36. Tablet Pentoxifylline (400 mg), thrice a day, wherein two brands were prescribed such as Trental (₹30.45) and Kinetal (₹26.52) and which had total costs of ₹822.15 and ₹716.04 for 60 days duration respectively. In the study, statin was prescribed along with combination regimen for prophylactic purpose in PVD patients, [22] and the cost was ₹1227 for 30 days. It represented the better disease control in patients with cost effectiveness.

In this study, side effects of cilostazol and pentoxifylline combination therapy were observed. Total 66 patients reported minor side effects. Out of 66 patients, 24 (36.4%) had headache followed by 9 (13.9%) dizziness, 8 (12.1%) abnormal stools and 8 (12.1%) nausea, a similar study by McDermott, had reported headache, dizziness, diarrhoea and palpitations as major side effects [21].

5. CONCLUSION

In the study, peripheral vascular disease symptoms improved when cilostazol (50 mg) was taken twice daily and pentoxifylline (400 mg) was taken three times daily. Whereas a total of 73 (73%) individuals demonstrated improvements in rest pain, gangrene, and intermittent claudication. The two main co-morbidities/risk factors for PVD patients were hypertension (70%) and smoking (80%). Combining cilostazol and pentoxifylline increases peak systolic velocity in the distal arteries while also reducing intermittent claudication distance. Only 5 patients (5%) under 60 years old experienced recurrence of symptoms following the treatment. Additionally, patients with critical ischemia and gangrene in the severe condition were recommended a combination of any one statin (often atorvastatin or simvastatin) with cilostazol + pentoxifylline.

CONSENT

As per international standard or university standard, patients’ written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


