original article

Comparison of efficacy and tolerability of pentoxifylline and cilostazole on peripheral arterial disease.

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Abstract:

Aim: To compare the efficacy and tolerability of cilostazole and pentoxifylline in patients with moderately severe peripheral arterial disease.

Material and Methods: It is a prospective, randomized, open label parallel study conducted in Postgraduate Department of Pharmacology and Therapeutics in collaboration with Cardiothoracic and Vascular Surgery Department, Govt. Medical College Jammu for a period of one year.

Results: out of 53 patients with grade I chronic limb ischemia, 26 patients were assigned pentoxifylline 400mg, and 28 patients were given cilostazole 100mg. Both pentoxifylline as well as cilostazole raised initial as well as absolute claudication distances significantly from baseline, but on comparison, cilostazole was significantly more effective compared to pentoxifylline. Cilostazole also had significant beneficial effect on lipid profile (decreasing triglycerides and raising HDL-Cholesterol), whereas pentoxifylline was lacking such effect. There were no differences in patient's assessment, physician's assessment as well as side effects between two groups.

Conclusion: cilostazole is found to be an effective treatment for patients of peripheral arterial disease with intermittent claudication. It also has favorable effect on lipid profile. However, long term randomized trials are required to further substantiate our findings.

Introduction:

Peripheral arterial disease is any pathological process causing obstruction to blood flow in arteries except those of coronary and cerebral vessels. It is the major cause of morbidity and mortality especially affecting the elderly population. If affects approximately 20% of adults older than 55 years, and only 3% of people younger than this age group[1]. There is no gender difference in prevalence, but it increases with age and prolonged exposure to smoking, hypertension and diabetes. Initially patient may present with intermittent claudication, but latter with increasing severity, leg ulceration, gangrene or critical limb ischemia (in diabetics) may occur. Although progress has been seen in surgical and interventional techniques, which are appropriate for patients who have significant lifestyle limiting symptoms, pharmacological management and risk factor (smoking, diabetes, hypertension and hyperlipidemia) control may be sufficient during initial less severe disease. US-FDA has approved only two drugs, pentoxifylline and cilostazole for treatment of peripheral arterial disease. Pentoxifylline increases absolute claudication distance by approximately 38%[2] and cilostazole has been shown to improve absolute claudication distance by 40-50%[3] compared to placebo. A comparative trial of cilostazole versus pentoxifylline has found that cilostazole increases absolute walking distance more compared to pentoxifylline[4]. No such study comparing cilostazole versus pentoxifylline has been conducted in our setup, so we carried out this study in our hospital, which will provide beneficial data for future studies and guide the physician working in this setup.

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Keywords:
Peripheral arterial disease, Pentoxifylline, Cilostazole, Initial claudication distance

Material and Methods:

This was a prospective randomized open label parallel study conducted in postgraduate department of pharmacology and therapeutics, in collaboration with cardiothoracic and vascular surgery department government medical college Jammu for a period of one year. Permission from the institutional review board was taken. Written informed consent was obtained from all the patients. Adult patients of either sex, 40 years or above having clinically and/or angiographically proven moderately severe occlusive peripheral arterial disease were included in the study. Patients with severe peripheral arterial disease (e.g. rest pain, ulceration or gangrene), surgical or endovascular arterial reconstruction of lower limbs, sympathetectomy, recent myocardial infarction, deep vein thrombosis, uncontrolled hypertension or diabetes, concomitant disease, substance abuse and gross obesity were excluded. Patients fulfilling above criteria were divided into groups after proper randomization. Group-1 was administered tablet pentoxifylline 400mg. Group -2 was administered tablet cilostazole 100mg. Clinical evaluation was done by complete history, complete general physical examination, complete systemic examination, all basic lab investigations and special investigations including lipid profile, color Doppler and angiography of the lower limb vessels. Claudication distances (initial as well as absolute) were done on treadmill. Patients were re-evaluated every 2, 4, 6, 8, 10 and 12 weeks and following parameters were noted: Initial claudication distance, absolute claudication distance, patients assessment, physicians assessment, lipid profile and any other adverse effects due to drugs. All the parameters were noted in a well-designed proforma. Student's t-test and ANOVA were applied for intragroup and intergroup comparisons respectively. Patients and physicians assessments and adverse effects were analyzed by chi-square test.

Results:

Out of 53 patients with grade-II chronic limb ischemia[5] 26 were assigned pentoxifylline, 400mg and 28 patients were given cilostazol 100mg. Basic characteristics of subjects enrolled are summarized in Table 1.

Table 1: Patient characteristics at baseline.

Characteristics	Pentoxifylline (n=26)	Cilostazole (n=28)
Age (years) (mean. S.E.M)	62±8	59±7
Sex: Male Female	 26 0	 27 1
Weight (Mean±S.E.M)	72±2.9	68±2.38
Ankle/Brachial index	0.68±0.03	0.69±0.02
Initial claudication distance	82.57±2.03	79.71±1.65
Absolute claudication distance	155.96±2.44	151.80±1.71
Lipid profile(mg/dl) (Mean±S.E.M) • Triglycerides • Total cholesterol • LDL-C • HDL-C	 172.30±2.51 195.15±2.77 115.92±2.82 44.42±1.38	 179.53±2.71 207.53±2.90 132.17±3.11 39.78±1.28

Pentoxifylline shows progressive increase in both initial as well as absolute claudication distance from baseline up to 12 weeks (Table 2) which are statistically significant at $p<0.001$.

Table 2: effect of pentoxifylline on claudication distan

Follow up (weeks)	Initial claudication distance (m) (Mean±SEM)	Absolute claudication distance (m) (Mean±SEM)
Baseline	82.57±2.03	155.96±2.44
2 Week	90±2.13***	172.03±2.39***
4 Week	100.88±2.24***	188.76±2.10***
6 Week	106.45±2.51***	196.79±2.58***
8 Week	109.65±2.67***	202.82±2.81***
10 Week	113.65±2.67***	209.86±2.94***
12 Week	116.86±2.57***	220±3.38***

***statistically significant at p<0.001 (compared to baseline)

Cilostazole also increased initial as well as absolute claudication distance distances from baseline up to 12 weeks (Table 3), which are also statistically significant. However, comparative to pentoxifylline, cilostazole shows more rise in both initial as well as absolute claudication distances which are statistically significant at 12 weeks (Table 4&Table 5).

Table 3: Effect of cilostazole on claudication distances.

Follow up (Weeks)	Initial claudication distance (m) (Mean±SEM)	Absolute claudication distance (m) (Mean±SEM)
Baseline	79.71±1.65	151.80±1.71
2 Week	89.16±1.61***	174.89±1.74***
4 Week	100.81±1.69***	206.66±1.76***
6 Week	106.71±1.69***	210.77±4.83***
8 Week	112±1.69***	217.09±5.02***
10 Week	115.49±1.67***	216±7.26***
12 Week	122.10±1.77***	226.18±7.74***

***statistically significant at p<0.001 (compared to baseline)

Table 4: Percentage change in initial claudication distance from baseline in pentoxifylline group vs cilostazole group.

Time (Weeks)	Pentoxifylline Meters (%)	Cilostazole Meters (%)	P-value
2 Week	7.43±2.08 (8.99%)	9.45±1.63 (11.85%)	0.44
4 Week	18.31±2.13 (22.17%)	21.1±1.67 (26.47%)	0.30
6 Week	23.88±2.27 (28.92%)	27±1.67 (33.87%)	0.26
8 week	27.08±2.35 (32.79%)	32.29±1.67 (40.509%)	0.07
10 Week	31.08±2.35 (37.64%)	35.78±1.66 (44.887%)	0.10
12 Week	34.29±2.3 (41.52%)	42.39±1.71 (53.18%)	0.006*

****statistically significant at p<0.01

Table 5: Percentage change in absolute claudication distance from baseline in pentoxifylline group vs cilostazole group.

Time (Weeks)	Pentoxifylline Meters (%)	Cilostazole Meters (%)	P value
2 Week	16.07± 2.41 (10.30%)	23.09±1.72 (15.21%)	0.01*
4 Week	32.8±2.27 (21.03%)	54.86±1.75 (36.13%)	<0.001**
6 Week	40.83±2.51 (26.17%)	58.97±3.27 (38.84%)	<0.001**
8 Week	46.86±2.62 (30.04%)	65.29±3.36 (43.01%)	<0.001**
10 Week	53.9±2.69 (34.56%)	64.2±4.48 (42.29%)	0.160
12 Week	64.04±2.91 (41.06%)	64.38±4.72 (42.41%)	0.95

**highly significant, *significant at p<0.05

Pentoxifylline did not produce any statistically significant changes in lipid profile (Table 6), but cilostazole did decrease triglycerides, decrease LDL-Cholesterol (initially up to 4 weeks) and increased HDL-Cholesterol which were statistically significant (Table 7).

Table 6: Effect of pentoxifylline on lipid profile.

Follow up (Weeks)	Triglycerides (mg/dl) (Mean±SEM)	Total cholesterol (mg/dl) (Mean±SEM)	Low density lipoprotein - cholesterol (mg/dl) (Mean±SEM)	High density lipoprotein-cholesterol (mg/dl) (Mean±SEM)
Baseline	172.30±2.51	195.15±2.82	115.92±2.82	44.42±1.38
2 Week	179.42±2.58	197.84±2.75	115.65±2.76	46±1.39
4 Week	183.26±2.52	200.23±2.74	115.84±2.81	45.15±1.34
6 Week	168.53±2.99	193.07±2.92	110.15±3.05	43.84±1.45
8 Week	168.19±4.34	188.76±3	111.80±3.14	41.84±1.53
10 Week	171.26±3.52	188.07±3.01	110.03±3.13	42.46±1.56
12 Week	167±3.62	191±3.03	112.46±3.12	42.57±1.55

Table 7: Effect of cilostazole on lipid profile.

Follow up (Weeks)	Triglycerides (mg/dl) (Mean±SEM)	Total cholesterol (mg/dl) (Mean±SEM)	Low density lipoprotein-cholesterol (mg/dl) (Mean±SEM)	High density lipoprotein-cholesterol (mg/dl) (Mean±SEM)
Baseline	179.53±2.71	207.53±2.90	132.17±3.11	39.78±1.28
2 Week	128.07±2.05***	204.64±2.87	127.85±3.22*	42.82±1.27*
4 Week	119.44±2.08***	201.55±2.91	130.44±3.35**	46.74±1.33**
6 Week	125.42±2.23***	198.26±3.03	128.03±3.51	46.84±1.32**
8 Week	122.84±1.98***	203.76±3.01	128.19±3.46	45.53±1.33**
10 Week	123.53±2.04***	201.96±3	128±3.42	45.80±1.33**
12 Week	125.29±2.30***	198.08±3.17	130.41±3.48	46.20±1.33**

***p<0.001, **p<0.01, *p<0.05 (compared to baseline)

There was no statistically significant difference observed between pentoxifylline and cilostazole on physician's assessment (Table 8), patient's assessment (Table 9) and observed adverse effects (Table 10).

Table 8: Physicians assessment.

Assessment	Pentoxifylline (n=26)	Cilostazole (n=28)	P value
Much better	1 (3.8%)	3 (10.7%)	0.65
Better	9 (34.6%)	11 (39.2%)	0.29
Unchanged	16 (61.5%)	14 (50%)	0.39
Worse	0	0	
Much worse	0	0	

Table 9: Patients assessment.

Assessment	Pentoxifylline (n=26)	Cilostazole (n=28)	P-value
Much better	4 (15%)	6 (21%)	0.18
Better	7 (26.9%)	10 (35.7%)	0.13
Unchanged	14 (53.8%)	12 (42.8%)	0,10
Worse	1 (3.8%)	0	0.97
Much worse	0	0	

Table 10: Commonly reported adverse events.

Adverse events	Pentoxifylline (n=26)	Cilostazole (n=28)	P-value
Headache	4 (15.3%)	8 (28.5%)	0.26
Diarrhea	2 (7.6%)	5 (17.8%)	0.40
Musculoskeletal pain	3 (11.5%)	3 (10.7%)	0.98
Abnormal stools	2 (7.6%)	4 (14.2%)	0.66
Dizziness	1 (3.8%)	3 (10.7%)	0.65
Peripheral edema	0	2 (7.1%)	0.91
Pharyngitis	6 (23%)	0	
Nausea	7 (26.9%)	2 (7.1%)	0.06

Discussion:

Peripheral arterial disease is a highly prevalent manifestation of atherosclerosis that is associated with a substantial risk of illness and death and a marked reduction in ambulatory capacity and quality of life. Such patients have three times higher mortality due to cardiovascular events compared to matched controls[6].

Present study shows a significant increase in initial and absolute claudication distance in pentoxifylline group. This is consistent with other previous studies[7,8]. This may be due to the fact that pentoxifylline and its metabolites improve blood flow by decreasing blood viscosity, improving erythrocyte flexibility and blood filterability and by reducing serum fibrinogen level[9]. It also inhibits platelet aggregation[10]. Therefore, by increasing blood flow to the affected musculature, it improves tissue oxygenation and perfusion. Present study also shows significant increase in initial and absolute claudication distances with cilostazole. This is consistent with other studies[3,11,12,13]. Comparing the two drugs, cilostazole is shown to be more effective in increasing claudication distances compared to pentoxifylline. This observation is also consistent with other studies[4,9]. Cilostazole is phosphodiestrase type III inhibitor, which increases intracellular cAMP levels, which in turn inhibits thromboxane A2 production and platelet aggregation by inhibiting phospholipase and cyclooxygenase[11]. Cilostazole is 10-30 times more potent than aspirin in inhibiting platelet aggregation induced by ADP, collagen, epinephrine or arachidonic acid[14].Further, cilostazole does not inhibit prostacyclin synthesis; so that endothelium derived prostacyclin potentiates platelet antiaggrigation effect of cilostazole[15]. In addition to antiplatelet effects, cilostazole acts as an arterial vasodilator, probably through its direct action on vascular smooth muscle. Intracellular cAMP blocks release of calcium ions from intracellular storage granules within the smooth muscle cells, thus inhibiting the function of contractile proteins. Cilostazole also affects smooth muscle cell proliferation. This effect may also be mediated through increased cAMP levels in smooth muscle cells[11].

Physicians assessment and patients assessment are slightly better in cilostazole group than pentoxifylline group, but this difference is not statistically significant as reported earlier[8,11,13]. However, cilostazole shows beneficial effect on serum lipid levels compared to pentoxifylline, which is statistically significant. This is consistent with previous studies[16,17,18,19] which have shown the beneficial effects of cilostazole on many parameters of lipid profile, i.e. lowering of triglycerides, LDL-cholesterol, total cholesterol and raising HDL-cholesterol levels. Effects of cilostazole on lipoproteins are a result of its ability to inhibit cyclic nucleotide phosphodiestrase and thereby elevate intracellular cyclic AMP. cAMP in turn reduces hepatic triglyceride (VLDL) secretion[20].

Present study reported headache, diarrhea and abnormal stool more in cilostazole treated group, whereas nausea and pharyngitis are reported more in pentoxifylline group. These observations are in agreement with previous studies[4,21].Overall both drugs were well tolerated.

Conclusion:

The findings of present study coupled with earlier reports indicate that cilostazole can be an effective treatment for patients with peripheral arterial disease with intermittent claudication. Also, by favorably affecting the lipid profile, it can prevent from one of the risk factors responsible for prevalence of this disease. Although, this study will prove to be of help when faced with dilemma of choosing one drug over another. However, long term randomized trials can be carried out to further substantiate our findings.

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