ORIGINAL

# Effect of Cilostazol on Claudication Distances and Lipid Profile in Patients with Occlusive Peripheral Arterial Disease: A Placebo Controlled Trial

**Singh Surjeet, M.D.**

Assistant Professor, Department of Clinical Pharmacology SKIMS Srinagar

## ABSTRACT

**Objective(s):** To study the efficacy and tolerability of cilostazol in patients with moderately severe peripheral arterial disease.
**Study Design:** Randomized, open label, placebo controlled parallel study
**Methods:** This study was 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. Patients fulfilling the eligibility criteria were divided into two groups; Group A patients received cilostazol 100mg orally BD and group Breceived placebo tablet twice daily. Clinical evaluation was done by complete history, gen. physical examination, systemic examination, baseline investigations (hemogramme, LFT, KFTG, ECG) and lipid profile. Special investigations like color Doppler study and angiography of lower extremity vessels was also done. Follow up was done every 2, 4, 6, 8, 10 and 12 weeks.
**Results:** Out of 53 patients fulfilling the inclusion criteria, 28 patients were assigned cilostazol 100mg twice daily, and 25 patients were given placebo twice daily. Cilostazol significantly raised both initial as well as absolute claudication distance, which was well sustained throughout all weeks of follow up, whereas placebo raised he claudication distance for initial few weeks, but decreased it below baseline subsequently. Cilostazol also had significant beneficial effect on lipid profile compared to placebo. There was almost no significant difference in patient's assessment, physician's assessment as well as side effect between two groups.
**Conclusion:** Cilostazol can 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 on large scale are required to further substantiate our findings. JMS 2017; 20 (2):77-81
**Key words:** Initial claudication distance, absolute claudication distance, peripheral arterial disease, cilostazol

## INTRODUCTION

Peripheral arterial disease is any pathological condition, which leads to the obstruction to blood flow in arteries, except those of cerebral and coronary vessels. It affects approximately 20% of adults of 55 or older age group, and only 3% patients 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[2]. Symptoms of peripheral arterial disease range from intermittent claudication to rest pain, leg ulcerations and gangrene. Critical leg ischemia with rest pain and skin ulcerations can sometimes occur in diabetic patients. Although surgery is treatment of choice in patients with severe disease having significant lifestyle limiting symptoms, pharmacological management along with the modification of risk factors like smoking cessation, control of hypertension, diabetes and hyperlipidemia may suffice in less severe condition[2]. US-FDA has approved only two drugs, pentoxifylline (approved in 1984) and cilostazol (approved in 1999) for the treatment of intermittent claudication. Cilostazol have been found to be superior in efficacy compared to pentoxifylline[3,4].Cilostazol is a phosphodiestrase type III inhibitor that increases intracellular cAMP levels. Increased cAMP in turn inhibits platelet aggregation by inhibiting thromboxane $A_2$ production by inhibiting phospholipase and cyclooxygenase enzymes[6]. Cilostazol has been found to be 10-30 times more potent than aspirin in inhibiting platelet aggregation induced by ADP, collagen, epinephrine or arachidonic acid[9]. Further, cilostazol does not inhibit prostacyclin synthesis from endothelium[10]- thus

***Correspondence***
Dr. Surjeet Singh, M.D.
Assistant Professor, Department of Clinical Pharmacology
Sher-i-Kashmir Institute of Medical Sciences Srinagar
E-mail: surjeet.singh@skims.ac.in

potentiating antiaggregatary effect on platelets. Very few studies have been carried out for determining efficacy and tolerability of cilostazol on peripheral arterial disease in northern India, particularly J & K state. So, considering the scarcity of data available and high morbidity and disability associated with the disease, this study was carried out in our hospital, which will provide beneficial data for future studies and guide the physicians working in this setup.

## METHODS

This prospective, randomized placebo controlled parallel study was carried out in the postgraduate department of pharmacology and therapeutics, in collaboration with cardiothoracic and vascular surgery department, govt. medical college associated hospital Jammu, for a period of one year. Due permission from institutional review board was sought. After obtaining written informed consent, adult patients of either sex, 40 years and above having clinically and/or angiographically proven moderately severe occlusive peripheral arterial disease were included in the study.

Patients with severe peripheral arterial disease as manifested as rest pain, ulceration, or gangrene, or who have undergone endovascular reconstruction surgery of lower extremity, sympathetectomy in preceding six months; uncontrolled hypertension and diabetes, recent myocardial infarction, recent deep vein thrombosis, severe concomitant disease, substance abuse, gross obesity were excluded.

Patients fulfilling the criteria were divided into two groups, one of whom were administered cilostazol 100mg orally BD and another group was administered tab placebo twice daily. Clinical evaluation was done by complete history, gen. physical examination, systemic examination, baseline investigations (hemogramme, LFT, KFTG, ECG) and lipid profile. Special investigations like color Doppler study and angiography of lower extremity vessels was also done. Follow up was done every 2 week, 4 week, 6 week, 8 week, 10 week and 12 weeks and patients were re-evaluated for following parameters: initial claudication distance (distance that patient can walk without feeling claudication pain, i.e. pain-free walking distance), absolute claudication distance (maximum distance patient can walk after feeling initial claudication pain, i.e. maximum painful walking distance), patients assessment, physicians assessment, lipid profile and any adverse reactions due to these agents. Present study is the post hoc analysis of original study[17], where we have compared cilostazol group with placebo. Intragroup comparisons were analyzed by student's t-test, whereas intergroup comparisons were analyzed by ANOVA. Chi$^2$ test was applied for patient's assessment, physician's assessment and adverse effect comparisons.

## RESULTS

Out of 53 patients fulfilling the inclusion criteria, 28 patients were randomly assigned tab. Cilostazol 100mg twice daily, whereas 25 patients were administered placebo twice daily. Baseline characteristics of subjects enrolled are summarized in Table 1.

**Table 1:** Baseline characteristics of patients.

| Characteristics | Cilostazol (n=28) | Placebo (n=25) |
|---|---|---|
| Age (years) (mean± S.E.M) | 59±7 | 60±9 |
| Sex:<br>Male<br>Female | <br>27<br>1 | <br>25<br>0 |
| Weight (Mean±S.E.M) | 68±2.38 | 75±1.35 |
| Ankle/Brachial index | 0.69±0.02 | 0.70±0.03 |
| Initial claudication distance | 79.71±1.65 | 89.08±2.08 |
| Absolute claudication distance | 151.80±1.71 | 165.24±2.74 |
| Lipid profile(mg/dl) (Mean±S.E.M)<br>• Triglycerides<br>• Total cholesterol<br>• LDL-C<br>• HDL-C | <br>179.53±2.71<br>207.53±2.90<br>132.17±3.11<br>39.78±1.28 | <br>173.28±3.35<br>199.08±3.27<br>120.04±3.68<br>43.92±1.53 |

### Effect on claudication distances:

Cilostazol increased both initial as well as absolute claudication compared to baseline from 2$^{nd}$ week to 12 weeks. This increase was statistically significant on all weeks of follow up (Table 2).

Placebo also showed statistically significant increase in initial claudication distance as well as absolute claudication distance up to 6 weeks, but thereafter there was a decline, which was even below baseline at 12 weeks (Table 2).

**Table 2:** Effect of cilostazol and placebo on claudication distances

| Follow up (weeks) | Cilostazol | | Placebo | |
|---|---|---|---|---|
| Baseline | Initial claudication distance (m) (Mean±SEM) | Absolute claudication distance (m) (Mean±SEM) | Initial claudication distance (m) (Mean±SEM) | Absolute claudication distance (m) (Mean±SEM) |
| 2 week | 79.71±1.65 | 151.80±1.71 | 89.08±2.08 | 165.24±2.74 |
| 4 week | 89.16±1.61*** | 174.89±1.74*** | 93.28±2.21*** | 173.4±2.66*** |
| 6 week | 100.81±1.69*** | 206.66±1.76*** | 96.28±2.21*** | 180.96±2.65*** |
| 8 week | 106.71±1.69*** | 210.77±4.83*** | 99.88±2.43*** | 184.36±2.68*** |
| 10 week | 112±1.69*** | 217.09±5.02*** | 98.16±2.46*** | 179.36±2.76*** |
| 12 week | 115.49±1.67*** | 216±7.26*** | 90.16±2.51 | 159.48±3.57 |

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

Comparing the two, there is significantly more and well sustained rise in initial claudication distance as well as absolute claudication distance in cilostazol treated patients compared to placebo administered group (Table 3).

**Table 3:** Percentage change in initial and absolute claudication distance from baseline in cilostazol group vs placebo group

| Time (weeks) | Cilostazol ICD difference from baseline, meters (%) | Placebo ICD difference from baseline, meters (%) | P-value | Cilostazol ACD difference from baseline, meters (%) | Placebo ACD difference from baseline, meters (%) | P-value |
|---|---|---|---|---|---|---|
| 2 week | 9.45±1.63 (11.85%) | 4.2±2.14 (4.71%) | 0.05 | 23.09±1.72 (15.21%) | 8.16±2.7 (4.93%) | <0.001* |
| 4 week | 21.1±1.67 (26.47%) | 7.2±2.14 (8.08%) | <0.001* | 54.86±1.75 (36.13%) | 15.72±2.69 (9.51%) | <0.001* |
| 6 week | 27±1.67 (33.87%) | 10.8±2.25 (12.12%) | <0.001* | 58.97±3.27 (38.84%) | 19.12±2.71 (15.57%) | <0.001* |
| 8 week | 32.29±1.67 (40.50%) | 9.08±2.27 (10.19%) | <0.001* | 65.29±3.36 (43.01%) | 14.12±2.75 (8.54%) | <0.001* |
| 10 week | 35.78±1.66 (44.88%) | 1.08±2.29 (1.21%) | <0.001* | 64.2±4.48 (42.29%) | -5.76±3.15 (3.48%) | <0.001* |
| 12 week | 42.39±1.71 (53.18%) | -2.24±2.32 (2.51%) | <0.001* | 74.38±4.72 (42.41%) | -19.44±3.44 (11.76%) | <0.001* |

*highly significant

### Effect on lipid profile

There is astatistically significant decline in triglycerides and an increase in HDL-cholesterol level in cilostazol treated group whereas no statistically significant changes were observed in placebo group (Table 4).

**Table 4:** Effect of cilostazol and placebo on lipid profile

| Follow up (weeks) | Triglycerides mg/dl (Mean±SEM) | | Total cholesterol mg/dl (Mean±SEM) | | LDL-cholesterol mg/dl (Mean±SEM) | | HDL-Cholesterol mg/dl (Mean±SEM) | |
|---|---|---|---|---|---|---|---|---|
| | Cilostazol | Placebo | Cilostazol | Placebo | Cilostazol | Placebo | Cilostazol | Placebo |
| Baseline | 179.53±2.71 | 173.28±3.35 | 207.53±2.90 | 199.08±3.27 | 132.17±3.11 | 120.04±3.68 | 39.78±1.28 | 43.92±1.53 |
| 2 week | 128.07±2.05*** | 180.36±3.14 | 204.64±2.87 | 201.88±3.30 | 127.85±3.22* | 119.72±3.75 | 42.82±1.27* | 45.8±1.53 |
| 4 week | 119.44±2.08*** | 182.2±3.12 | 201.55±2.91 | 203.08±3.38 | 130.44±3.35** | 120.4±3.83 | 46.74±1.33** | 45.96±1.52 |
| 6 week | 125.42±2.23*** | 176.84±2.96 | 198.26±3.03 | 205.52±3.42 | 128.03±3.51 | 123.68±4.06 | 46.84±1.32** | 45.2±1.59 |
| 8 week | 122.84±1.98*** | 165.4±3.07 | 203.76±3.01 | 199.64±3.53 | 128.19±3.46 | 122.68±4.21 | 45.53±1.33** | 44.2±1.57 |
| 10 week | 123.53±2.04*** | 168.84±3.06 | 201.96±3 | 192±3.61 | 128±3.42 | 117.04±4.30 | 45.80±1.33** | 43.6±1.55 |
| 12 week | 125.29±2.30*** | 170.88±3.12 | 198.08±3.17 | 194.88±3.57 | 130.41±3.48 | 119.64±4.16 | 46.20±1.33** | 43.76±1.53 |

***p<0.001, **p<0.01, *p<0.05 statistically significant compared to baseline

### Patient's assessment and physician's assessment

Although, many patients felt much better and better with cilostazol compared to placebo (where some patients were worsened on both patients assessment as well as physicians assessment) (Table 5), but the difference was not statistically significant.

### Adverse effect profile

No statistically significant difference was observed between cilostazol group and placebo group on majority of commonly reported adverse effects (Table 5).

**Table 5:** Patient's assessment, physician's assessment and adverse effect profile of cilostazol group vs placebo group

| Assessment scale | Patient's assessment | | | Physician's assessment | | | Adverse effects | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cilostazol | Placebo | p-value | cilostazol | placebo | p-value | Adverse effect | Cilostazol | Placebo | p-value |
| Much better | 6 (21%) | 1 (4%) | 3.48 | 3 (10.7%) | 0 | 2.87 | Headache | 8 (28.5%) | 3 (12%) | 2.2 |
| Better | 10 (35.7%) | 3 (12%) | 3.99 | 11 (39.2%) | 5 (20%) | 2.33 | Diarrhea | 5 (17.8%) | 2 (8%) | 1.11 |
| Unchanged | 12 (42.8%) | 18 (72%) | 4.55 | 14 (50%) | 17 (68%) | 1.74 | Musculoskeletal pain | 3 (10.7%) | 3 (12%) | 0.02 |
| Worse | 0 | 2 (8%) | 2.37 | 0 | 3 (12%) | 3.57 | Abnormal stool | 4 (14.2%) | 2 (8%) | 0.5 |
| Much worse | 0 | 1 (4%) | 1.19 | 0 | 0 | - | Dizziness | 3 (10.7%) | 0 | 2.87 |
| Much better | 6 (21%) | 1 (4%) | 3.48 | 3 (10.7%) | 0 | 2.87 | Peripheral edema | 2 (7.1%) | 1 (4%) | 0.32 |

## DISCUSSION

Peripheral arterial disease is a highly prevalent manifestation of atherosclerosis that is associated with a substantial risk of morbidity and mortality, and a marked reduction in ambulatory capacity and quality of life. There is three times higher mortality due to cardiovascular events in these patients compared to age matched controls[5]. Numerous drugs have been studied for the treatment of intermittent claudication (main symptom of moderately severe peripheral arterial disease), including prostaglandins, vasodilator agents, anticoagulants and antiplatelet drugs[2]. However, US-FDA has approved only two drugs, pentoxifyllin and cilostazol for treating claudication in patients with peripheral arterial disease. Cilostazol, a quinolone derivative was approved in 1999. Present study suggests that cilostazol significantly increased initial as well as absolute claudication distance from baseline at 12 weeks (intragroup comparisons), which was also significantly more compared to placebo (intergroup comparisons). This observation is similar to other reports[3,6,7,8] which agree with present study. Increased cAMP induced by cilostazol inhibits platelet aggregation by blocking thromboxane A2 production due to inhibition of phospholipase and cyclooxygenase enzymes[6]. Further, cilostazol does not inhibit prostacyclin synthesis from endothelium10- thus potentiating antiaggregatary effect on platelets. In addition to antiplatelet effects, cilostazol 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. Cilostazol also affects smooth muscle cell proliferation which may be mediated through increased cAMP levels[6].

On patient's assessment, 56.7% patients felt better or much better in cilostazol group compared to only 16% in placebo group. Moreover, none felt worse in cilostazol group compared to 3 (12%) patients in placebo group. Similarly, on physician's assessment, 49.9% subjects were judged as better or much better with cilostazol compared to 20% in placebo group. Again, none was judged as worse with cilostazol, whereas 3 patients (12%) worsened in placebo group. These results are almost similar to previous reports[6,8].

Cilostazol has been found to have beneficial effects on serum lipids, and present study shows a significant triglyceride lowering (30% from baseline) and HDL-cholesterol raising (17% from baseline) effect in cilostazol treated group compared to placebo group. These results are consistent with previous studies[6,11,12,13,14]. Our results are more similar to a multicenter, randomized double blind trial[15], where plasma triglycerides were lowered by 15% and HDL-cholesterol raised by 10% with cilostazol. Effects of cilostazol on lipoproteins are a result of its ability to inhibit phosphodiestrase III, thereby raising intracellular cAMP levels which in turn reduces hepatic triglyceride (VLDL) secretion either directly or indirectly by potentiating the effect of glucagon. Elevated cAMP also promotes the release of lipoprotein lipase from adipocytes which could reduce plasma triglycerides[15].

Present study reported headache, diarrhea and abnormal stool more in cilostazol treated group compared to placebo. This is similar to previous studies[4,16], except that no drug withdrawal was reported due to side effects in our study, whereas headache was responsible for drug withdrawal in Dawson et.al. 2000. Reason could be due to short period of follow up and less number of patients included in our study compared to previous large scale studies. Overall, drug was well tolerated.

## CONCLUSION

The findings of present study coupled with earlier reports indicate that, cilostazol can be an effective treatment for patients of peripheral arterial disease with intermittent claudication. Also, by favorably affecting the lipid profile, it can prevent one of the risk factor responsible for increased prevalence of this disease. However, long term randomized trials on large scale are required to further substantiate our findings.

## REFERENCES


1. Graeme J Hankey, Paul E Norman, and John W Eikelboom. Medical treatment of peripheral arterial disease. JAMA 2006; 295: 547-553.
2. Mark A Creager and Libby Peter. Peripheral arterial disease in: Richard Zorab (editor) Heart Disease: A text book of cardiovascular medicine 7th edition 2005; 1437-1461.
3. Money SR, Herd JA and Isaac JL. Effect of cilostazol on walking distance in patients with intermittent claudication, caused by peripheral vascular disease. J Vasc Surg 1998; 28: 267-275.
4. Dawson DL, Cutler BS, Hiatt WR. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med 2000; 109: 523-530.
5. Mc Kenna M, Wolfson S and Kullaer L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. Atherosclerosis 1991; 87: 119-128.
6. Dawson DL, Bruce S Cutler, Mark H Meissner and D Eugene Strandness. Cilostazol has beneficial effects in treatment of intermittent claudication: Result from a multicenter, randomized, prospective double blind trial. Circulation 1998; 98: 678-686.
7. Regensteiner JG, Ware JE, and McCarthy WJ. Effect of cilostazol on treadmill walking, community based walking ability and health related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. J Am Geriatr Soc 2002; 50: 1939-1946.
8. Thompson PD, Zimet R, Forbes WP and Zhang P. Meta-analysis of results from eight randomized, placebo controlled trials: effect of cilostazol on patients with intermittent claudication. Am J Cardiol 2002; 90: 1314-1319.
9. Kimura Y, Tani T, Kanbe T and Watanabe K. Effect of cilostazol on platelet aggregation of experimental thrombosis. Arzneimittelforschung 1985; 35: 1144-1149.
10. Igawa T, Tani T, Chijiwa T, Shiragiku S, Kawamura K,

Sato S, Unemi F and Kimura Y. Potentiation of antiplatelet aggregating activity of cilostazol with vascular endothelial cells. Thromb Res 1990; 57: 617-623.

11. Takazakura E, Ohsawa K and Hamamatsu K. Effect of cilostazol (pletal) on serum lipid levels in diabetic patients: with special emphasis on the effect of increasing serum levels of high density lipoprotein cholesterol. Jpn Pharmacol Therapeutics 1989; 17: 2769-2773.
12. Azuma S, Yoshida Y, Kasuga M, Aoyama N, Doi K, Amano M, Fukud T, Yamakazi T and Baba S. Clinical usefulness of cilostazol in patients with complications due to diabetes: with particular reference to the therapeutic effect on paresthesia, peripheral circulation insufficiency and lipid metabolism disorder. Clinical Report 1990; 24: 5451- 5457.
13. Sekiguchi M, Morikawa A, Nakajima K, Ito H, Takashashi M, Tobishim M and Makino I. Clinical usefulness of cilostazol (pletal) on diabetic neuropathy and serum lipid levels. Jpn Pharmacol Therapeutics 1991; 19: 3273-3277.
14. Noma Y, Hirota M and Shima K. The effects of cilostazol on serum lipid levels in diabetic patients: especially the effects in patients with hyperlipidemia. Clinical Report 1992; 26: 109-113.
15. MB Elam, J Heckman, JR Crouse, DB Hunninghake, JA Herd, M Davidson, IL Gordon, EB Bortey and WP Forbes. Effect of the novel antiplatelet agent cilostazol on plasma lipoproteins in patients with intermittent claudication. Arterioscler Thromb Vasc Biol 1998; 18: 1942-1947.
16. Craig M and Pratt MD. Analysis of cilostazol safety database 2001; 87: 28-33.
17. Surjeet Singh, MD, Harbinder Singh, MS, Arvind Kohli, MCh, Vinod Kapoor, MD, Gurjeet Singh, MCh. Effect of cilostazol and pentoxifyllin on claudication distances and lipid profile in patients with occlusive peripheral arterial disease: A comparative trial. Ind J Thoracic and CardiovascSurg 2009; 25: 45-48.