Role of Cilostazole and Aspirin in Peripheral Vascular Disease in Diabetics

N BARLAS A S KHAN
Department of Medicine, Fatima Memorial Hospital, Lahore
Correspondence to Dr.Nazeefa Barlas, Senior Registrar Email:drnazeefa6@yahoo.com

Objective: Comparison of Cilostazole and Aspirin in treatment of peripheral vascular disease in diabetics. **Design:** Comparative study. **Place and duration of study:** Fatima Memorial Hospital, Shadman, Lahore from October 2005 to July 2006. **Subjects and methods:** Fifty five diabetics patients were included in the study, regardless of presence or absence of symptoms and signs of peripheral vascular diseases. Complications of diabetes such as neuropathy, retinopathy, diabetic amytrophy and foot deformities were assessed in detail. Patients who had peripheral vascular diseases with (Doppler) ankle brachial index measurement were divided randomly given cilostazole, (pletaal) and aspirin. Ankle brachial index measurement was again done after three months of therapy. **Results:** One way Anova was used to test the efficacy of aspirin and cilestazole. The F ratio ($P<0.05$) showed a significant difference between three groups and post HOC test showed cilostazole is more effective. **Conclusion**: Cilostazole, phosphodiestrase III inhibitor improves symptoms, signs and ABI measurements in diabetic patients when given for three months. However aspirin had no significant effect on improvement of such parameters.

Key words: Intermittent claudication, diabetes peripheral vascular disease

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis in which arterial lumen is occluded by atherosclerotic plaque[1]. The most common symptom of PAD is intermittent claudication, defined as pain cramping, aching in calves, thighs or buttocks that appears reproducibly with walking exercise and is relieved by rest. More extreme presentations include rest pain, tissue loss-gangrene, called collectively as critical links ischemia (CLI).

Intermittent claudication is currently under recognized as a marker for increased coronary and cerebrovascular risk[2].

There have been increasing evidences of vascular implication in pathogenesis of diabetic mono and polyneuropathy[3,4]. IC affects upto 5% of population aged 55-74 years, while 8% of subjects have PAD at the time of diagnosis of diabetes and it raised to 45% by 20 years of duration of diabetes. The common risk factors for IC are as follow and are generally associated with systemic arterhosclerosis[5,6].

Risk factors for development of IC

Cigarette smoking
Diabetes mellitus
Impaired glucose tolerance
Hypertension
Dyslipidaemia
Haemorrhagic factors (elevated fibrinogen level blood)
Hyperhomocystenemia
Age

Diagnosis of peripheral vascular disease is made by history and physical examination aided by specialized investigation measures. The sensitivity of Rose questionnaire for detecting PAD is 9% and 20% of those with PAD had no exercise half pain at rest. These low values are explained by PAD in posterior tibial artery[7,8].

The lower extremities are inspected and examined for pulses, bruits, foot ulcers, edema, gangrene, atrophy dry skin and cool temperature[9,10]. Dorsalis pedis pulse is absent in 4-32.5% subjects[11]. However, the absence of posterior tibial pulse is always abnormal[12]. The ankle brachial index (ABI) is a simple inexpensive, noninvasive tool that correlates with angiographic disease severity and functional symptoms[13,14]. The ABI normally is between 1.0 and 1.3, ABI less than 0.9 is considered diagnostic of PAD[15].

Patients and methods

It is an original research study, carried out as a pilot study at Fatima Memorial Hospital, Lahore. The patients were recruited from outpatients of internal medicine starting from October 2005 till July 2006 according to the following inclusion and exclusion criteria.

Inclusion criteria

1. Diabetic patients
2. Both type I and II diabetes
3. Duration of diabetes >3 years.
4. Age >20 years
5. Both sex groups
6. Uncontrolled diabetes
7. Peripheral neuropathy
8. Smokers and non smokers both
9. Body mass index ranging from healthy to obese
10. All patients with positive Doppler results

Exclusion criteria

1. Severe neurological deficit leading to bedridden condition.
2. Scheduled for major surgery.
3. Severe renal or hepatic insufficiency.

4. History of systemic bleeding.
5. History of thrombocytopenia or neutropenia.
6. History of aspirin sensitivity.
7. Women of child bearing age not using reliable contraception.
8. Previously done/entered in clopidogrel studies.
9. Geographical factors leading to impractical participation.

Peripheral neuropathy was assessed by symptoms such as pain, numbness, burning sensation and by logmonofilament usage to assess sensory loss in 10 points on dorsal and planter aspect. The scoring was done to find out the loss of sensory appreciation on feet due to development of neuropathy. Vibrating tuning fork of 128Hz frequency was used to assess early sensory loss at pony prominence of feet and upper limbs. Loss of deep tendon reflexes by clinical hammer was also done to aid in diagnosing peripheral neuropathy.

Lower extremities especially feet were examined for ulcers, deformities, amputation, clawing of toes, gangrene and skin changes were noted. Foot ulcers were graded from I to V.

Grade I superficial ulcers involving full thickness of skin
Grade II deep ulcers involving ligaments and muscles
Grade III deep ulcers with cellulites, abscess formation often complicated by osteomyelitis
Grade IV localized gangrene
Grade V extensive gangrene involving entire foot

Peripheral vascular disease was identified not only on basis of history and physical examination but by also Doppler to assess presence of vessel occlusion. Pulses both dorsalis pedis and posterior tibial were palpated and graded from grade 0-2 as absent, difficult to palpate and easily palpable respectively.

Doppler ultrasonography to find out the ABI was done with hand held ultrasound Doppler device Hunt Leigh Health Care UK Super Dopplex-II Model No. SD2, Probe: 8mHz recommended for arteries.

The same blood pressure cuffs used for the arm were used for ankle pressures. The higher systolic pressures in both upper and lower limbs on same side and lower limb pressures were divided by brachial pressures generating the ABI.

The ratio calculated this way relate the ankle and arm pressures taken closed together in time and are therefore more meaningful.ABI values ranging from 0.00 to >1.30 were grades as

Normal	0.91-=1.30
Mild to moderate PAD	0.41-0.9
Severe	0.00-0.40
Non compressible	>1.30

The patients with positive Doppler or ABI indicating PAD were divided in three groups and were given cilostazole 50mg twice a day and the other group was given aspirin 75mg PO OD for three months and one group was given placebo which was control group. These groups were followed after 3 months of therapy to repeat the Doppler and to assess any change in ABI.

Results

A total of 55 patients were included in this study from outpatients department of internal medicine. Table I shows their distributions in various groups. Equal number of patients were distributed in Loprin pletaal and control group that is 15 in each group. However, 10 patients were lost to follow up.

Table II shows the demographic features of study. 28 patients were male and 27 female. Among them their ages range from 29-85 years. Mean age was 54 years x±S.D 10.23. The lowest percentage (10%) was from 43 years and 90% were 66 years of age.

Table I: Distribution of patients (n=55)

Distribution	=n
Loprin (aspirin) group	15
Pletaal (cilostazole) group	15
Control group	15
Lost to follow up	10

Table II: Demographic feature (n=55)

Demographic features	=n
Male patients	28
Female patients	17
Age range 29-85 years (mean 54 yrs)	
10%	43
25%	50
50%	55
75%	61
90%	66

Table III shows the distribution of cases depending upon severity of disease into premedication and post medication groups.

The patients prior to giving loprin were 15and all of them were having mild to moderate PAD. 1 patient had non compressible vessels out of 15 patients who were be given cilostazole. The controlled group included 15 patients who all belonged to mild to moderate peripheral arterial disease group.

The post medication cases distribution showed that only 2 patients got normal ABI and 1 got severe PAD who were given loprin for 3 months while 12 of the patients remained in mild to moderate category of PAD while 13 patients got normal ABI after 3 months of cilostazole therapy and only 2 had persistent mild to moderate PAD after therapy with cilostazole.

However the 15 patients who were included in the control group and were given placebo therapy remained in the mild to moderate category of PAD disease.

Table IV shows ankle brachial index measured pot medication (after 3 months of therapy) of right side. It showed F ratio 5.441 ($P<0.05$) when comparison between cilostazole, loprin and control group was done which is

shown by post boc tests. The post boc tests show the multiple comparison between pletaal and loprin was 0.18867 abd significance was 0.003. The comparison between loprin and control group showed sig diff at .410. No sig diff

Table III: Premedication postmedicatioan distribution of cases according to severity of peripheral vascular disease.

	Mild–moderate	Severe	Non-Compressible
Loprin	15	0	0
Cilostazole	14	0	1
Control	15	0	0

Postmedication distribution

	Mild – moderate	Severe	Non-Compressible	Normal
Loprin	12	01	0	02
Cilostazole	02	0	0	13
Control	15	0	0	0

Table IV:

	Sum of squares	Df	Mean square	F	Sig
Between groups	.287	2	.144	5.441	.008
Within group	1.108	42	.026		
Total	1.396	44			

Data	Mean Difference	Std. Error	Sig	95% confidence interval	
				Lower bound	Upper bound
Pletal					
Loprin	.18867	.05932	.003	.0690	.3084
Control	.13933	.05932	.024	.0196	.2590
Loprin					
Pletaal	-.18867	.05932	.003	-3084	-.0690
Control	-.04933	.05932	.410	-.1690	`.0704
Control					
Pletal	-.13933	.05932	.024	-.2590	-.0916
Loprin	.4933	.05932	.410	-.0704	.1690

Table V

	Sum of squares	Df	Mean square	F	Sig
Between groups	.324	2	.166	7.970	.001
Within group	.852	42	`.020		
Total	1.176	44			

Data	Mean Difference	Std. Error	Sig	95% confidence interval	
				Lower bound	Upper bound
Pletal					
Loprin	.18733	.05202	.001	.0823	.2923
Control	.17133	.05202	.002	.0663	.2763
Loprin					
Pletaal	-.18733	.05202	.001	-.2923	-.0823
Control	-.01600	.05202	.760	-.1210	.0890
Control		.05202			
Pletal	-.17133	.05202	.002	-.2763	-.0663
Control	.01600	.05202	.760	-.0890	.1210

Table V one way analysis of variance applied for ankle brachial index on left side. The F ratio is 7.970 ($P<0.05$) which show that cilostazole has a significant effect on improvement of peripheral arterial disease.

Similarly the post hoc test showed the multiple comparison for left side between three groups. When pletaal was compared with loprin the mean difference was significant at 0.001 when pletaal and control group was compared the mean difference was significant at .002. However the control and loprin when compared showed sig of .760 which is not significant.

Discussion

Peripheral arterial disease is a disorder typically caused by atherosclerosis that limits blood flow to the limbs. Most patients with PAD are either asymptomatic or complain of intermittent claudication. A minority however develop CLI whereby the integrity of the limb is jeopardized. In this sceneraio, PAD is complicated by ischaemic rest pain, non healing ulcers, or gangrene. Without restoration of limb perfusion the patient who has PAD and critical limbs ischemia is at high risk for limb lost. Yet revascularization might not be technically possible. As a result pharmacotherapy is used as a last resort for improving the manifestations of chronic critical limb ischemia. This current study performed exclusively on diabetic patients shows the comparison of two drugs cilostazole and aspirin and their effect upon outcome of PAD in patients who had PAD ranging from mild moderate, severe and incompressible vessels when ankle brachial index was performed prior to giving medications and three months after giving treatment.

The treatment approaches for PAD include glycemic control, adequate hypertension control and dyslipedemia therapy. The pharmacological treatment options include antiplatelet therapy with either aspirin or clopidogrel and cilostazole an oral phosphodistrase type III inhibitor.

The antiplatet trialist collaboration reviewed 145 randomized studies in an effort to evaluate prolonged treatment with antiplatelet agents[16]. This metaanalysis combined data from >100,000 patients including in 70,000 high risk patients with evidence of cardiovascular disease. A 27% reduction in odds ratio (OR) in the composite primary end point (MI, stroke and vascular death) was found form high risk patients compared with control subjects. However, when a subset of >3,.000 patients with claudication was analysed effects of antiplatelet was not significant[17]. Thus the use of aspirin to prevent cardiovascular death in patients with PAD is considered equivocal.

The clopidogrel versus aspirin in patients at high risk of ischemic events (CAPRIE) study evaluated aspirin versus clepidogrel in >10,000 patients with recent stroke, MI,. or stable PAD. The study showed that 75mg of clopidogrel per day was associated with a relative risks reduction of 8.7% compared with the benefits of 325mg of

aspirin per day for a composite end point (MI, ischemia, stroke, vascular death). More strikingly in a subgroup analysis of >6,0000 patient with PAD, clopidogrel was associated with a risk reduction of 24% compared with aspirin. Clopidogrel was as well tolerated by patients as aspirin. Based on these results, clopidogrel was approved by Food and Drug Administration (FDA) for reduction of ischemic events in all patients with PAD. In the CAPRIE study above one third of the patients in the PAD group had diabetes. In those patients clopidogrel was also superior to aspirin therapy[18].

Pentoxifylline, a hemorrhagic agent was approved by FDA in 1984 for claudication. The results of post approval trials, however, suggest clinically meaningful extent.

Ciloctazole, an oral phosphodiestase type III inhibitor was the second drug to gain FDA approval for treating intermittent claudication. Significant benefit has been demonstrated in increasing maximal walking time in six of eight randomized controlled trials in addition to improving functional status and health related quality of life[19].

In a single trial pentoxyfylline was inferior when compared with treatment with cilostazole[20]. Based on the above cilostazole is the drug of choice of pharmacological therapy is necessary for management of PAD in patients with diabetes.

Anticoagulants, antiplatelet therapy defibrinogenating agents, rheologic drug and prostanoids have been used for CLI, but unfortunately none of these agents have produced major long term improvement in CLI. In their recent consensus document, TASE working group meted, because the results are unconvincing or negative. Current drug cannot be recommended in patients with CLI. In one study the efficacy of cilostazole 100mg twice a day was evaluated in a mixed cohert of patients after 6 weeks 48% of patients showed marked improvement and only 19% worsened. The authors concluded that cilostazole might be useful in the treatment of skin ulceration caused by vascular disease[22]. In a group of 26 patients with arterial occlusive disease from varying causes cilostazole 200mg each day for 3 months improved ulcer healing and rest pain in 50% of the patients[23]. Money et al documented a significant increase in post treatment ankle brachial index when cilostazole was compared with placebo (0.64-0.70 in the cilostazole group vs 0.68-0.69 in the placebo group, P<.0125)[24].

In study of 9 patients with peripheral arterial disease, cilostazole administered for 2 weeks increased the mean ankle blood flow by 16.2% (P<0.5 vs baseline)[25]. Ohashi et al compared 100mg with 200mg of cilostazole each day for 6 weeks in 10 patients with peripheral arterial disease. Significant increase in skin temperature and blood flow were documented in 7 of the 10 patients only when higher dose was used[26].

Our study including 55 of total patients out of which 10 were lost to follow up and remaining 45 patients were distributed into 3 groups equally. Premedication ankle brachial index measures and after 3 months of therapy with two drugs post medication ankle brachial index measures were assessed to judge the efficacy of cilostazole and loprin.

Fifteen patients were included in loprin, cilostazole and control group. The control group was given placebo treatment. The ankle brachial index after 3 months of therapy was assessed for both right and left limnbs. The ratio was 5.441 for right limbs postmedication (P<0.05) shown by analysis of variance (ANOVA). Multiple comparison shown by post boc test between loprin (aspirin) and control group showed no statistical difference, which means that no improvement was seen if either placebo or loprin was given to patients with deranged ABI. But when cilostazole was given 100mg twice a day to patients with peripheral vascular disease and results were compared with loprin the statistical significance was 0.003.

The ABI index of left limb showed F=7.91 by one way ANOVA and post boc tests showed comparison between cilostazole, loprin and control group showed clearly that cilostazole had a significant effect on improvement of ABI.

References

1. Criqul MHJ, Lanbger RD, Fronek A. Large vessel and isolated small vessel disease. In: Fowkes FGR, ed. Epidemiology of Peripheral Vascular Disease. New York NY. Springer-Verlag 1991: 895-89.
2. Davies A. The practical management of claudication. Br Med J 2000; 321: 911-2.
3. Dyek Pj, Hansen S, Karnes J, O'Brien P, Yasuda H et al. Proc Nat Acad Sci USA 82: 2513.
4. Johnson PC, Doll SC, Cromy DC. Ann Neutrol 1986; 19: 450.
5. Murabito JM. D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from the Framingham Hearty Study. Circulation 1997; 96: 44-9.
6. Clarke R, Daly L, Robinson K et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. New Engl J Med 1991;324: 1149-55.
7. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in fluid surveys. Bull World Health Organ 1962; 27: 645-58.
8. Dormandy JA, Rutherford RB. Management of peripheral arterial disease. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg 2000; 31(Suppl)S1-S296.
9. Weitz JI, Byne J et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities a critical review. Circulation 1996; 94: 3026-49.
10. Dormandy J, Heck L, Vig S. Lower extremity arteriosclerosis as a reflection of a systemic process, implications for concomitant coronary and carotid disease. Semin Vasc Suyrg 1999; 12: 118-22.
11. Barhnorst DA, Barner HB. Prevalence of congenitally absent pedal pulses. N Engl J Med 1968; 278: 264-65.
12. Olin JW. Clinical evaluation and office based detection of peripheral arterial disease. Available at

http://www.svmb.org/medpro/cme/p1/cme_part1.html. Accessed November 2, 2000.
13. Hiatt WR, Jones DN. The role of hemodynamics and duplex ultrasound in the diagnosis of peripheral arterial disease. Curr Opin Cardiol 1992; 7: 805-810.
14. Papamichael CM. Lekakis JP et al. Ankle brachial index as a predictor of the extent of coronary atherosclerosis and cardiovascular events in patients with coronary artery disease. Am J Cardio 2000; 86: 615-18.
15. Hatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001; 344: 1608-21.
16. Antiplatelet Trialists, CollaborationCoolaborative overview of randomized trials of antiplatelet therapy. 1: prevention of death, myocardial infarction and stroke by prolonged antiplatelet Br Med J 1994; 308: 81-106.
17. American Diabetes Association. Aspirin therapy in diabetes (Position Statement) Diabetes Care 2003; 26 (Suppl.I): 587-588.
18. Caprie Steering Committee: A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic event (CAPRIE) Lancet 1996; 348: 1329-39.
19. Regensteiner JG, Ware JE Jr, McCarthy WJ, Zhang P et al. Effect of cilostazole on treadmill walking, community-based walking ability and health related quality of life in patients with intermittent claudication due to peripheral arterial disease: metaanalysis of six randomized controlled trials. J Am Geriatr Soc 2002; 50: 1939-46.
20. Dawson DL, Cutler BS, Hiatt WR, Hobson RW. 2nd Martin JD, Bortey EB, Forbes WP, Strandness DE. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med 2000; 109: 523-30.
21. Dormandy JA, Rutherford RB. Management of peripheral arterial occlusive disease. D4, Pharmacotherapy for critical limb ischemia. TASC Working Group. Trans Atlantic Inter-Society Consensus (TASC) J Vasc Surg 2000; 31(1 Pt2):S197-203.
22. Arakawa K, Arada J. Clinical analysis of Pletal for intractable skin ulcer based on vascular damage and cutis symptom. Shin's Yakuato Rinsho Journal of New Remedies & Clinics) 1993; 42(1): 60-8.
23. Numano F, Kishi Y, Ashikaga T. Clinical studies of phosphor disease inhibitors for cardiovascular disease. Adv Second Messenger Phosphoprotein Res 1992; 25: 395-407.
24. Money SR,. Herd JA,. Issacsohn JL et al. Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. J Vasc Sug 1998; 27: 267-75.
25. Kamiya T, Sakaguchi S. Hemodynamic effects of the antithrombotic drug cilostazol in chronic arterial occlusion in the extremities. Arzneimittelforschung 1985; 35(7A): 1201-3.
26. Ohashi S, Iweatani M. Hykuna Y, Morioka Y. Thermographic evaluation of the hemodynamic effect of the antithrombotic drug cilostazol in peripheral arterial occlusion. Arzneimittelforschung 1985; 35: 1203-8.