THE IMPROVEMENT IN THE ABI INDEX FOLLOWING 3 MONTH TREATMENT WITH CILOSTAZOL IN PATIENTS WITH MILD TO MODERATE PERIPHERAL ARTERIAL DISEASE

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ABSTRACT

Objective: To study the effects of cilostazol in patients with mild to moderate peripheral arterial disease (PAD) using the improvement in ankle brachial pressure index (ABI).

Methodology: This hospital based interventionist study was a prospective, open labeled clinical trial. After the baseline data collection cilostazol was given to the group A, while the group B didn't receive cilostazol. The effect of intervention was noted at the timed study points at 4, 6 and 12 weeks .The antiplatelets were used in the group B as a control.

Results: The ABI improvement at the end of the study in the cilostazol treated group was marked compared with the control group. The group A had 65 males and 35 females, while the group B had 74 males and 26 females. The total ABI improved in the right and left lower limb with a P value of 0.001 each. The ABI results were better in the male, diabetic and hypertensive subsets of study as compared with female, obese and smoker.

Conclusion: Cilostazol significantly improves ABI in PAD. Its use in the indicated population group should be encouraged to improve the management and prevent the complications.

Key Words: Atherosclerosis, Ankle brachial pressure index, Peripheral arterial disease, Cilostazol

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INTRODUCTION

Atherosclerosis is defined as "a response to the injury of the endothelium"[1]. It is a major cause of the death and disability throughout the world[2]. All the risk factors for the arthrosclerosis act at the endothelium to initiate the cardiovascular complication[2]. The four major risk factors include diabetes mellitus, hypertension, obesity and smoking[3]. Male age is an additional risk factor. Other putative risk factors include estrogen deficiency, metabolic syndrome associated with insulin resistance, a high blood level of homocystiene, fibrinogen, C Reactive Protein (CRP) and asymmetric dimethyl arginine[4]. The complications of atherosclerosis can be micro vascular and macro vascular[5]. The micro vascular complications include retinopathy, peripheral neuropathy and autonomic dysfunction, while the macro vascular complications include coronary artery disease (CAD), cerebrovascular accidents (CVA) and peripheral arterial disease (PAD)[6]. Peripheral arterial disease (PAD) refers to the atherosclerosis of the lower limb vessels especially those of the leg and feet[6, 7].

PAD affects about 10 million people in the United States of America (USA)[8]. The exact prevalence in Pakistan is not known but for those with diabetes mellitus the incidence is reported to be 31.6% in a recent multicentre study[9]. The major complication of PAD related to diabetes mellitus is a 17 fold increase in the risk of gangrene compared to a 5 fold risk when PAD is not associated with diabetes[10-12]. Intermittent claudication(IC) is the typical and severe manifestation of PAD. It is more common in men than in the women[13, 14]. A very small minority of the patients with IC progresses to rest pain or ischemic ulcers (critical limb ischemia)[15].

The diagnosis of PAD is by ankle brachial pressure index (ABPI or ABI)[16]. The management plan for PAD can be summarized by three strategies: risk factor modification, exercise and pharmacotherapy. The drugs used include aspirin, clopidogrel, pentoxifylline, cilostazol, ticlopidine, dipyridamole and naftidrofuryl[17-26].

Non-labeled use includes macrolide antibiotics, prostaglandins, α-Tocopherol,Gingko biloba, garlic, propionyl levocarnitine, chelation therapy (EDTA), hyperbaric oxygen and cinnarazine[27-29.]

ABI is 90% sensitive and 98% specific for significant (more than 50%) stenosis[30] and has a prognostic value for cardiovascular morbidity and mortality[31]. A low ABI has a high specificity and a low sensitivity for the subsequent cardiovascular outcome[32]. ABI can be interpreted as a marker of PAD in terms of Mild (0.71 – 0.9) and Moderate (0.41- 0.7).

ABI values of less than 0.4 suggest critical limb ischemia and need surgical treatment. Cilostazol's main indication is for the improvement of the maximal and total pain free walking distance in patients with IC in the absence of rest pain or evidence of peripheral tissue necrosis[33]. Although the exact mechanism of action of cilostazol is not known its most well-known action is phosphodiesterase III (PDE III) inhibition[34]. Cilostazol also promotes the formation of prostacyline, which is a vasodilator[35, 36]. The increase in cAMP and vasodilatation both result in an increase in the pain threshold and an improved walking distance. It also has anti-proliferative, anti-platelet and anti-lipid effects[37- 45].

This study was conducted to study the effects of cilostazol in patients with mild to moderate peripheral arterial disease (PAD) using the improvement in ankle brachial pressure index (ABI).

METHODOLOGY

The study was conducted in the medical OPDs of the postgraduate medical institute (PGMI) Peshawar. Cilostazol 100mg twice daily was given to the PAD patients in the study group (A), while the control group (B) received antiplatelets and not the cilostazol. The study population had 12 weeks of uninterrupted treatment. ABI machine was the main tool of the study with which ABI was measured at 4, 6 and 12 weeks after the start of the study. For each of the 100 patients in both the groups strict inclusion and exclusion criteria were employed.

Patients with age more than 40 years; with ABI less than 0.9 and more than 0.4 in any one lower limb or both; with smptomatic PAD with an ABI of 0.9-1 in the resting state in which there is a 20% reduction in the arterial pressure in at least one of the extremities when the measurement is recorded 1 minute after claudication limiting walking exercise; with all the four pre-disposing etiologies of PAD i.e. diabetes mellitus, hypertension, smoking and hypercholesterolemia alone or in any combination; and with the absence of gangrene or ulcer, were included in the study. Patients with ABI of less than 0.4; with traumatic arterial insufficiency; with Congestive cardiac failure, arrhythmia, poorly controlled diabetes mellitus; with Stroke/TIA in the last six months; with history of deep venous thrombosis; with severe anemia, thrombocytopenia, hemorrhagic diathesis, chronic liver/renal failure; with malignancy or use of anti-cancer drugs; having undergone recent surgery, were excluded from the study.

Ankle Brachial Pressure Index (ABPI or ABI) is used for the diagnosis of PAD by using the following formula.

$$\text{ABI (lower limb) right or left} = \frac{\text{Higher systolic pressure in dorsalis pedis or posterior tibial artery}}{\text{Higher systolic pressure in either right or left brachial artery}}$$

The data collected through the proforma in this study was analyzed using statistical package for social sciences 16 (SPSS) version16. In this study, "independent sample t-test" was used. The ABI value was the dependant variable, while gender, diabetes mellitus, hypertension, obesity and smoking were the independent variables. A P value of less than 0.05 was considered statistically significant.

RESULTS

Total of 200 patients were enrolled in the study, in group A, 65 were male and 35 were female, while in the group B 74 were male and 26 were female. In the age category 29% in group A and 34% in group B were in the 6th (51-60 years) decade, while 57% in group A and 62% in group B were in the 7th (61-70 years) decade age group. The mean ages in the two groups were 61.53±2.6 years in the group A and 62.50±2.3 years in group B. District Peshawar was the major residential address in the majority of patients in both the groups (83% patients in group A and 79% patients in group B).

At the start of the study, mean ABI results in the right lower limb were 0.65±0.002 for the 100 patients in the study group (A) and 0.69±0.001 for the 100 patients in control group (B). The corresponding values for the left lower limb were 0.66±0.001 and 0.71±0.002 in the group A and group B respectively (Figure 1 and 2).

There is total and percent increase in the mean ABI values at 4, 6, 12 weeks study time as compared to the start study time (Table 1)

Figure 1: Right lower limb ABI values at different study times.

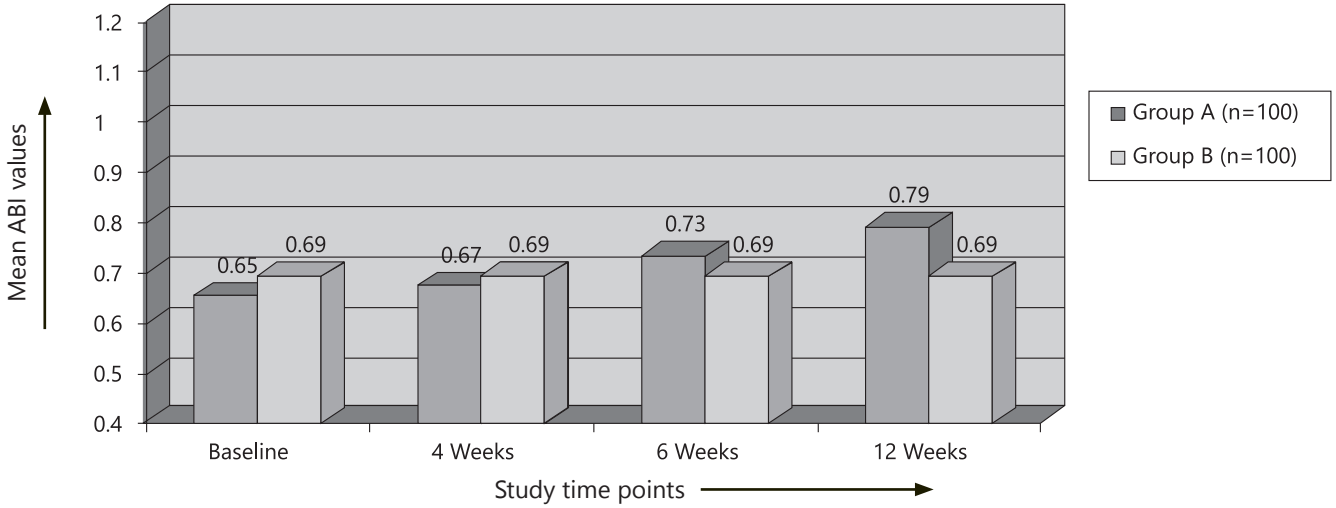

Figure 2: Left lower limb ABI values at different study

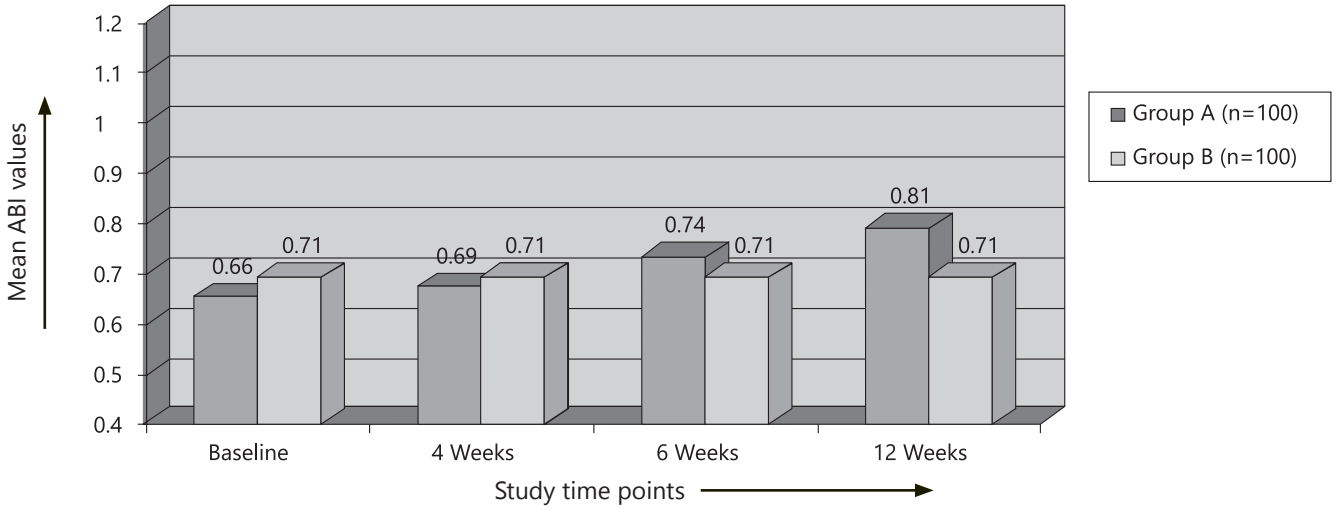

Figure 3: The mean ABI values in the male gender in both the groups and in both the lower limbs at the start and at the end study time points

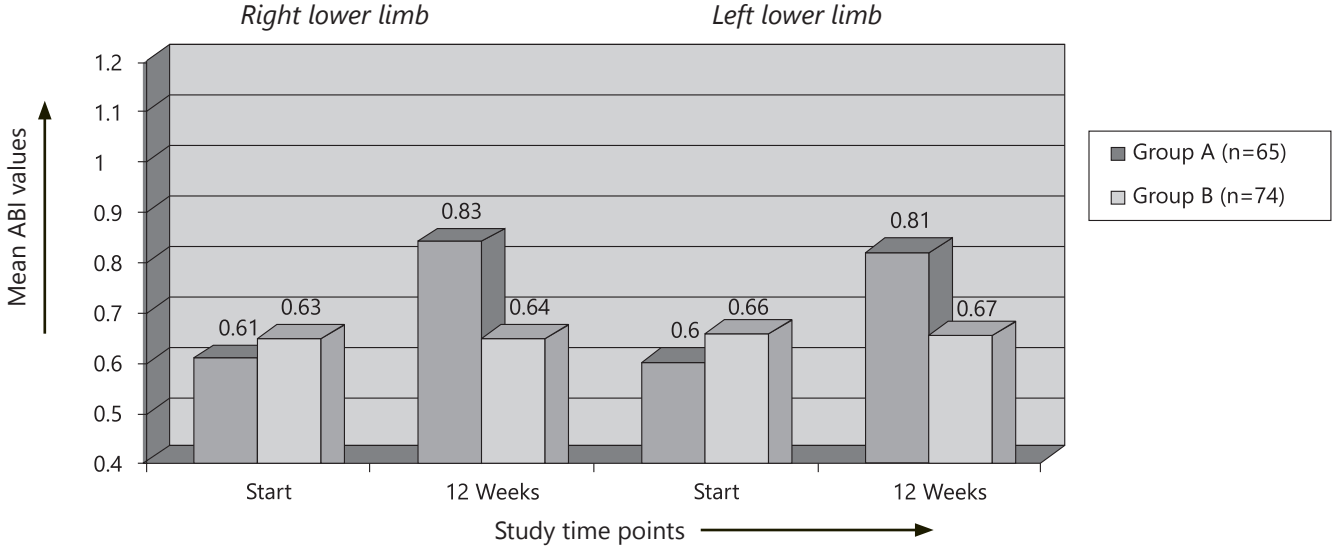

Figure 4: The mean ABI values in the female gender in both the groups and in both the lower limbs at the start and at the end study time points

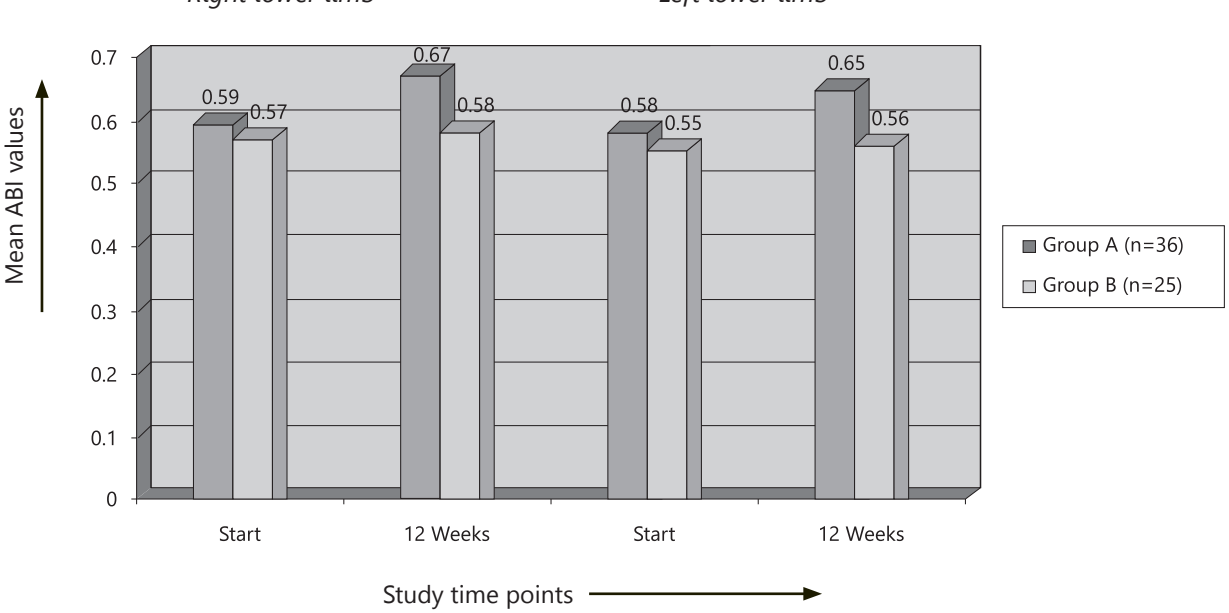

Table 1: The total and percentage increase in the mean ABI value at the 4th, 6th and 12th week study time points in both the groups and in both the lower limbs, when compared with the start of the values taken as baseline

Study time points	Right lower limb					Left lower limb				
	Group A (n=100)		Group B (n=100)		P values	Group A (n=100)		Group B (n=100)		P values
	Total increase in mean ABI	Percent increase in mean ABI	Total increase in mean ABI	Percent increase in mean ABI		Total increase in mean ABI	Percent increase in mean ABI	Total increase in mean ABI	Percent increase in mean ABI	
4 weeks	0.019	2.91	0.001	0.14	0.007	0.03	4.68	0.001	0.14	0.05
6 weeks	0.079	12.11	0.002	0.29	0.002	0.078	12.40	0.001	0.14	0.006
12weeks	0.14	21.47	0.003	0.42	0.001	0.15	22.69	0.002	0.28	0.001

For the gender category that is an independent variable in this study, the ABI values are considered only at the start and end study time points of the study

The percentage increase in the ABI in the male gender at the completion of the study is thus 36.49% in group A and 1.42% in group B in the right lower limb. For left lower limb these values stand at 34.92% in group A and 1.2% in group B (Figure 3). The P values thus obtained for the study group A in both the right and left lower limb were significant i.e. 0.0001 for each lower limb.

Females, who constituted 35% (n=35) in group A had a mean start study time point (baseline) ABI value of 0.59±0.001 in the right lower limb and 0.58±0.002 in the left lower limb. These values increased to 0.67±0.001 in the right lower limb and 0.65±0.001 in the left lower limb in at the conclusion of the study at 12 weeks. In the group B from the start of the study to the end of the study time point mean ABI values were 0.57±0.002 and

0.58±0.001 for the right lower limb and 0.55±0.003 and 0.56±0.002 in the left lower limb.

The percentage increase in the mean ABI among the female population of the study thus revealed, in the group A 13.53% improvement in the right lower limb and 11.85% improvement in the left lower limb. There, however, was only 1.57% improvement in the group B in the right lower limb and 1.62 % improvement in left lower limb. This yielded a P value of 0.04 for group A in the right lower limb and a P value of 0.045 in the left lower limb (Figure 4).

For the mean ABI values in the diabetic subset in both the group A and group B the results are listed in Table 2. The P value in the diabetic subset of group A is more pronounced in the left lower limb (0.0003) than the right lower limb (0.0009).

The P value in the hypertensive subset like that in diabetics is more pronounced in the left lower limb (0.0001) than the right lower limb (0.0004). Table 3 describes the data amongst the hypertensive subset in this study.

Table 4 describes the mean ABI values among the smoker subset of the study population.

Table 5 describes the increase in the mean ABI values for both the right and lower limbs in the obese subset of study.

Table 2: The total and percent increase in the mean ABI values in both the groups and in both the lower limbs among the diabetic subset at the start and end study time points

Study time points	Right lower limb					Left lower limb				
	Group A (n=73)		Group B (n=76)		P value	Group A (n=73)		Group B (n=76)		P value
	Total increase in mean ABI	Percent increase in mean ABI	Total increase in mean ABI	Percent increase in mean ABI		Total increase in mean ABI	Percent increase in mean ABI	Total increase in mean ABI	Percent increase in mean ABI	
Start study time point (Baseline)	0.61 ± 0.001	26.18	0.60 ± 0.002	1.49	0.0009	0.59 ± 0.002	31.92	0.62 ± 0.001	1.92	0.0003
End study time point (12 weeks)	0.77 ± 0.001 (0.16)		0.61 ± 0.001 (0.009)			0.78 ± 0.001 (0.189)		0.63 ± 0.003 (0.12)		

Table 3: The total and percent increase in the mean ABI values in both the groups and in both the lower limbs among the hypertensive subset at the start and end study time point

Study time points	Right lower limb					Left lower limb				
	Group A (n=72)		Group B (n=71)		P value	Group A (n=72)		Group B (n=71)		P value
	Total increase in mean ABI	Percent increase in mean ABI	Total increase in mean ABI	Percent increase in mean ABI		Total increase in mean ABI	Percent increase in mean ABI	Total increase in mean ABI	Percent increase in mean ABI	
Start study time point (Baseline)	0.63 ± 0.003	30.01	0.61 ± 0.002	3.10	0.0004	0.62 ± 0.003	34.99	0.65 ± 0.003	1.37	0.0001
End study time point (12 weeks)	0.82 ± 0.001 (0.118)		0.63 ± 0.001 (0.019)			0.81 ± 0.001 (0.218)		0.66 ± 0.002 (0.009)		

Table 4: The total and percent increase in the mean ABI values in both the groups and in both the lower limbs among the smoker subset at the start and end study time points

Study time points	Right lower limb					Left lower limb				
	Group A (n=20)		Group B (n=8)		P value	Group A (n=20)		Group B (n=8)		P value
	Total increase in mean ABI	Percent increase in mean ABI	Total increase in mean ABI	Percent increase in mean ABI		Total increase in mean ABI	Percent increase in mean ABI	Total increase in mean ABI	Percent increase in mean ABI	
Start study time point (Baseline)	0.56 ± 0.001	16.22	0.58 ± 0.002	0.17	0.01	0.57 ± 0.001	12.60	0.58 ± 0.001	2.06	0.04
End study time point (12 weeks)	0.65 ± 0.002 (0.091)		0.58 ± 0.003 (0.001)			0.64 ± 0.003 (0.072)		0.59 ± 0.003 (0.002)		

Table 5: The total and percent increase in the mean ABI values in both the groups and in both the lower limbs among the obese subset at the start and end study time points

Study time points	Right lower limb					Left lower limb				
	Group A (n=25)		Group B (n=22)		P value	Group A (n=25)		Group B (n=22)		P value
	Total increase in mean ABI	Percent increase in mean ABI	Total increase in mean ABI	Percent increase in mean ABI		Total increase in mean ABI	Percent increase in mean ABI	Total increase in mean ABI	Percent increase in mean ABI	
Start study time point (Baseline)	0.67 ± 0.001	10.43	0.66 ± 0.002	0	0.045	0.68 ±0.001	11.74	0.65 ± 0.001	1.84	0.05
End study time point (12 weeks)	0.74 ± 0.001 (0.07)		0.65 ± 0.001 (-0.001)			0.76 ± 0.001 (0.08)		0.66 ± 0.003 (0.012)		

DISCUSSION

Peripheral Arterial Disease is one of the most common cause of morbidity in elderly hypertensive and diabetic population and is a challenging problem to manage .Our study has shown that study group using cilostazol produces better outcome in PAD while the control group using conventional anti-platelet agents failed to produce those results.

Comparing our study results with that of RACT trial and CREST trial the clinically beneficial effects of cilostazol in PAD are now equated to an effective anti-platelet effect. While the anti-platelet therapy has an established role in the CAD, factors other than anti-platelet effect also seem to be operating in PAD as in spite of proper anti-platelet therapy it could not prevent and treat the intermittent claudication (IC)which is typical and severe manifestation of PAD.

Regarding the role and utility of the ABI, Hakeem et al concluded that both PAD and CAD have an independent course of clinical history and a log linear relationship exists between the ABI result and CAD risk and this risk continues to decline as the ABI values increased above 1.0[45, 46]. Further studies by the Mc-Dermott et al clearly established a link between the sub clinical cardiac and carotid studies and the abnormal ABI[26]. Wild et al in the Edinburg Artery study also proved a low ABI as a great predictor of cardiovascular events independent of the conventional factors and metabolic syndrome[19]. Resnick et al further elaborated the value of high and low ABI in their Strong Heart Study (SHS) report[41]. While these aspects were beyond the scope of our study's aims and objectives we do were able to demonstrate with the use of cilostazol an improved quality of life subjectively.

The evaluation of the demographic and prevalence profile in this study is in consonance with the available international literature. Males in our study constituted 65% in group A and 74% in group B. Scottish Inter Collegiate Guideline Network (SIGN) also reported men to be affected more than the females with a 20% overall prevalence in more than 50 years age group and with the relative death risk 3.5 times more than the general population[14]. The male gender thus has a proven predictive role about the outcome of the disease and the treatment as was shown by the Aboyans et al in MESA study[15].

The fact that females have a lower ABI values has been validated by our study as is the fact that the effect of the therapy is less marked in the female gender. This clearly suggests that although cilostazol produces statistically significant improvement in the ABI in both the genders it is more marked in males as compared with the females

Diabetics and hypertensives responded more favourably to cilostazol in our study. In humans studies of Mitsuhasi et al and Ahn et al tested and approved the anti-proliferative action of cilostazol[48, 49]. The promotion of new vessel formation and collateral circulation was demonstrated in the diabetic patients by Shror et al study[50]. So the anti-proliferative and neo-vascularization effects of the cilostazol in the settings of metabolic syndrome may be responsible for the unusual results among diabetics in our study. The results from the hypertensive category in our study were almost at par with that of the diabetics. These findings suggest that cilostazol works in tandem in the both the diabetic and the hypertensive categories in the study subjects.

While the lowering of the cholesterol by cilostazol has been amply proven in the study by Elam et al and Ikewaki et al study the additional benefits may not be just related with the exercise training or cholesterol lowering as we showed that the "obese category" also responds less well to cilostazol[43, 47].

For the smoker category our study showed that the mean ABI values improved less favorably than in the overall category. While Buergers' disease has been on the exclusion criteria of our study the chances of PAD over lapping with the former cannot be ruled out and this could be the cause of less desirable results among the smokers in our study. It was suggested by Smith et al study that smokers have more non-deformable red cells and elevated plasma fibrinogen in addition to increased platelet aggregation[51]. Pentoxifylline is reportedly better in this regards in improving the ABI values among smokers but a conclusive data compared to cilostazol in the smokers is not available. Otsuka manufacturers' research group, however, considering all the relevant data in their study regarding the use and safety of cilostazol in smokers declared it therapeutically safe and effective[52]. Our study agrees with the international studies regarding the efficacy of cilostazol in smokers. The degree of response, however, is variable.

More research in this field in underway. The changes in intima media thickness in response to cilostazol are currently the subject of DAPC (Diabetic Atherosclerosis Prevention by Cilostazol) study. Shin et al has already recommended approval of cilostazol for stroke prevention after finding it useful in Japanese study patients[53]. SPAD (The Safety and efficacy of cilostazol in ischemic stroke patients with PAD) 2012 is another interventionist study in Taiwan, the data being under publication. CATHARSIS (Cilostazol Aspirin THErapy against Recurrent Stroke with Intracranial artery Stenosis) study is

evaluating both cilostazol and aspirin for stoke prevention. WASID (Warfarin Aspirin Symptomatic Intracranial Disease) study has recommended cilostazol for secondary stroke prevention. Seen in the light of the American Heart Association (AHA) statistical up-date cilostazol may well be that magic drug, which will prevent a major morbidity and mortality related to stroke[54]. As already described while these aspects of the treatment with cilostazol are not the subject of our study, it definitely has paved the first step for others in this regard.

CONCLUSION

Our study proved the efficacy of cilostazol in mild to moderate cases of PAD. Measurement of ABI is simple, by giving basic knowledge for performance of ABI test to paramedical staff and primary physicians we can easily diagnose PAD and effectively treat the patient with cilostazol and can stop disease progression and complication.

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CONTRIBUTORS

SS planned the study, did data analysis and wrote the manuscript. MAS helped in acquisition of data and its interpretation. Both authors contributed significantly to the final manuscript.