THE IMPROVEMENT IN CLAUDICATION DISTANCE 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) with regards to improvement in the Claudication Distance (CD)

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 did not receive Cilostazol. The effect of intervention was noted at the timed study points at 4 weeks, 6 weeks and 12 weeks. The anti-platelets were used in the group B as a control.

Results: The CD improvement at the end of the study in the cilostazol treated group was marked compared with the control group. The study participants included 65 males in group A and 74 males in group B, while females made up of 35 number in group A and 26 in group B. the overall total improvement in CD with a P value of 0.0001 was noted in the cilostazol treated group. The results showed marked improvement in the male, diabetic and hypertensive subsets of the study, moderate improvement in the smoker subset and a mild less marked response in the obese category.

Conclusion: Cilostazol produces significantly improvement in the claudication distance. Its use in the indicated population group should be encouraged to improve the management and the prevent the complications of PAD especially in the diabetic and hypertensive patients with this disease.

Keywords: Atherosclerosis, Claudication distance, Peripheral arterial disease, Cilostazol

INTRODUCTION

Atherosclerosis by definition is a response to the injury of the endothelium.[1] Throughout the world it is a recognized as a major cause of the death and disability.[2]

Diabetes mellitus, hypertension, obesity and smoking are its established risk factors.[3] Male gender, sedentary life style, lack of exercise and smoking also predispose to atherosclerosis. Additionally estrogen deficiency, metabolic syndrome, a raised serum homocystiene, fibrinogen, C Reactive Protein (CRP) and asymmetric dimethyl arginine are its other putative risk factors.[4]

The clinical presentations of atherosclerosis can be micro vascular and macro vascular diseases.[5] The macro vascular complications include coronary artery disease (CAD), cerebrovascular accidents (CVA) and peripheral arterial disease (PAD) while retinopathy, peripheral neuropathy and autonomic dysfunction are its the micro vascular complications.[6]

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PAD refers to the atherosclerosis of the lower limb vessels especially those of the leg and feet.[7]

PAD affects more than 25 million people world over,[7] its exact prevalence in Pakistan is not known.[8] The prevalence of PAD increases with age and the presence of cardiovascular risk factors.[9] The age adjusted increase in PAD can be as high as 12% in adult population and 20% in the geriatrics.[10] PAD alone has more chances of being missed than CAD and despite being an independent cardiovascular risk factor it is less intensively managed in medical practice[11,12] the simple knowledge among the general public that could lead to amputation is unfortunately very scanty.[13] There is a 1.5 to 2 fold increase in risk for every 10 years increase in the age.[14]

There is a consensus that PAD is 11 times more prevalent in diabetics[15] and it results in a17 fold increase in the risk of gangrene compared to a 5 fold risk when PAD is not associated with diabetes.[16-18] In the west, values incidence of PAD among diabetics as high as 41% in various studies have been reported.[19] Lack of medical care makes these figures for diabetics even more frightening for Pakistan.[20] Smokers likewise have double the risk of disease progression, limb amputation and mortality as compared with the non-smokers which adds on to the PAD.[21]

Intermittent claudication(IC) is the typical and severe manifestation of PAD with prevalence of 1-7%

(10-30% of the cases of PAD), it is more common in men than in the women.[22] Typically the patients give history of severe pain after walking a certain distance. This travelled distance is called Claudication Distance (CD) or the mean walking distance (MWD). The more severe the PAD, the lesser the CD. About two third of patients with IC also have CAD and 30-50% will have a history of prior stroke.[23] A very small minority of the patients with IC progresses to rest pain or ischemic ulcers (critical limb ischemia).[24] The typical signs in the PAD include Pallor, Poikilothermia (coldness), Pulselessness, Paraesthesia and Paralysis (5 Ps).

The diagnosis of PAD is by ankle brachial pressure index (ABPI or ABI).[25] An accurate diagnosis is essential.[26] Further investigations include **Functional Studies {**Pulse volume record Segmental blood pressure monitoring Toe brachial Index (TBI)} and **Structural Studies {**Doppler ultrasound Magnetic resonance angiogram (MRA) Computerized tomography angiogram (CTA) and Conventional contrast angiography}

Therapies devised to modify the course of disease are focused on the stabilization and regression of plaques, which indirectly improves the blood flow and ameliorates the symptoms.[27-29]

The pharmacotherapy for PAD include the labeled use of Aspirin, Clopidogrel, Pentoxiflylline, Cilostazol, Ticlopidine, Dipyridamole and Naftidrofuryl.[30-37] These drugs were formally recommended in the NICE (National Institute of Health and Clinical Excellence) 2011 guidelines for IC based on Scottish Inter-collegiate Guidelines Network (SIGN) study.[38]

The non-labeled pharmacotherapy for PAD include Macrolide antibiotics, Prostaglandins(Beciplast, Iloprost, Alprostadil), α-Tocopherol (Vitamin), Gingko biloba, Garlic, Propionyl levocarnitine, Chelation therapy (EDTA), Hyperbaric Oxygen and Cinnarazine.[39-43] The emerging therapies include molecular, genetic and cellular approaches to augment the growth of new and collateral vessels.[44] The cytokines tumor necrosis factor α (TNF-α) and interleukin 1b (IL_{1b}) also have a possible role in attenuating and arresting the progression of atheroma and are subject of research at present.[45]

Cilostazol is a phosphodiesterase III inhibitor. Cilostazol also promotes the formation of prostacyline, which is vasodilator.[46] The increase in cAMP and vasodilatation both result in an increase in the pain threshold and an improved walking distance. It also promotes collateral blood vessel formation through the stimulation of angiogenesis. ilostazol also has a favorable effect on the serum lipid profile in patients with PAD.[47] Its 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 the evidence of peripheral tissue necrosis. Its recommended dose for PAD is 100mg twice daily. Launched in USA in 1988, it was first approved by FDA for IC in 1999 (in Japan for this indication in 1988). In Japan it is now also approved for secondary prevention of stroke.[38] In United Kingdom it was first approved for IC in 2002and is a ACC/AHA guideline grade I_A drug for this indication. The most common adverse effects of cilostazol are headache, dizziness, palpitations, tachycardia and transient edema, which reverse upon discontinuation.[48]

Ankle brachial pressure index (ABPI or ABI) is simple, inexpensive and can be carried out with the versatility in the physician office.

It is calculated by

ABI (lower limbs) right or left =

Higher systolic pressure in dorsalis pedis or posterior tibial artery

Higher systolic pressure in either right or left brachial artery

It is 90% sensitive and 98% specific for significant (more than 50%) stenosis[49] it is the intra observer reliability, which results in unnecessary referrals to the specialist centers.[50-53] The ABI is the recommended ACC/AHA guideline for the diagnosis of symptomatic patients with PAD and is widely used in angiogrpahically confirmed PAD.

The normal range for ABI is taken as 0.9 to 1.3. Values more than 1.3 suggest non compressible vessels and warrant further studies like Doppler flow ultrasound, pulse volume studies and TBI. ABI is not reliable in this condition. ABI Values less than 0.9 suggest PAD and are described as mild (with ABI 0.71 – 0.9), moderate (with ABI 0.41- 0.7) and severe (with ABI less than or equal to 0.4). ABI values of less than 0.4 suggest critical limb ischemia and usually need surgical treatment. Medical treatment is warranted for values between 0.41 and 0.9.[54]

CD less than 200 meters indicates severe claudication. The improvement in walking following the treatment can be measured by simple counting of the steps or by noting the distance covered in meters. A device called pedometer can also objectively assess the CD. This employs the principle of a motion sensor, which responds to vertical acceleration of hip during gait cycles. These pedometers can be influenced by body size and speed of locomotion and are insensitive to cycling, swimming, walking an incline or weight lifting.

METHODOLOGY

Based on the "null hypothesis", this study was carried out in the medical OPDs of post graduate medical institute (PGMI) Peshawar. It was an interventionist, Prospective, open label clinical trial with randomized allocation into study group and control group. Its end point classification was an Efficacy Study. Cilostazol 100mg twice daily was given to the PAD patients of group A, while the control group B received anti plate-

lets and not the cilostazol. The study population had an uninterrupted treatment and included those patients who had ABI values (measured by the elaborated formula) by the use of ABI machine falling in the range of 0.41 to 0.9. The CD/MWD was noted with counting of the steps and pain free walking distance at the start of the study and 4 weeks, 6 weeks and 12 weeks after the start of the study both conventionally as well as with the use of pedometer in the selected cases. Patients were recruited randomly into the two groups on the basis of strict inclusion and exclusion criteria.

Patients with age more than 40 years; with ABI values in the mild to moderate PAD category as described above in any one lower limb or both; with symptomatic 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 one minute after claudication limiting walking exercise; with all the four predisposing etiologies of PAD i.e diabetes mellitus, hypertension, smoking and hypercholesterolemia (obese subject) alone or in any combination; and with the absence of gangrene or ulcer, were included in the study. It was ensured in the history that th symptoms were stale in the last 3 to 6 months and patients were willing to cooperate and follow up who were included in the study. Patients with ABI of less than 0.4; with traumatic arterial insufficiency; with congestive cardiac failure, symptomatic angina, 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 disease/renal failure; with malignancy or use of anti cancer drugs; having undergone recent surgery, were excluded from the study. Patients who were non- consenting and non cooperating, with age less than 40 years, females over 40 years with pregnancy and male patients with Buerger's disease; those with concomitant use of warfarin, SSRIs and anti fungal drugs were also excluded from the study. Cases of attrition due to non follow up were replaced to get the number right as was decided in the study sample.

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

Other statistical values used in this study include the simple mean, ratio, percentage & proportion and prevalence.

RESULTS

A net total of 200 patients were enrolled in the study for which the whole data as suggested in the proforma was collected. In group A there were 65 males

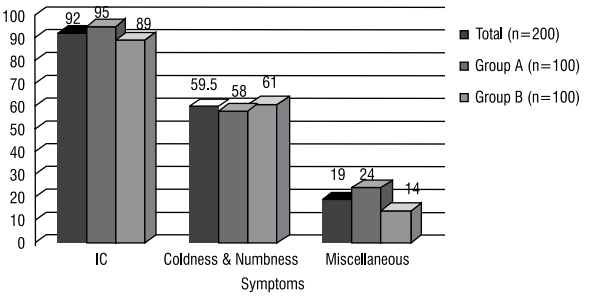

Figure 1: Percentages of presenting symptoms in group A, group B and in both the groups combined.

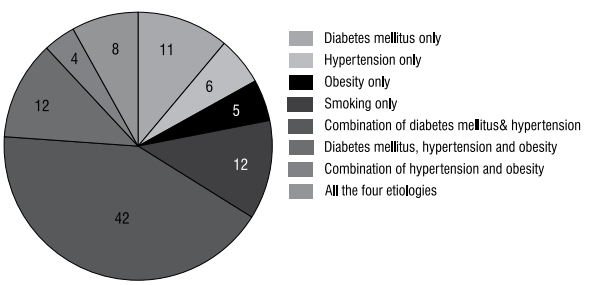

Figure 2: Percentages of etiological presentations alone and in combination in group A

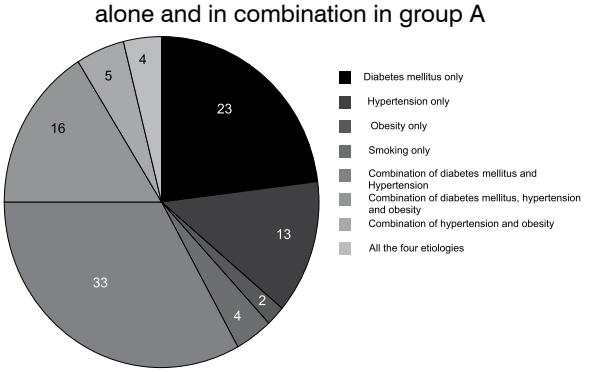

Figure 3: Percentages of etiological presentations alone and in combination in group B

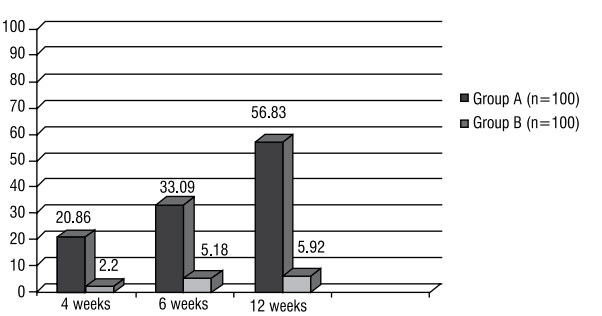

Figure 4: The mean percent increases in the claudication distance at all the study time points, when compared with the start study time point in both the groups

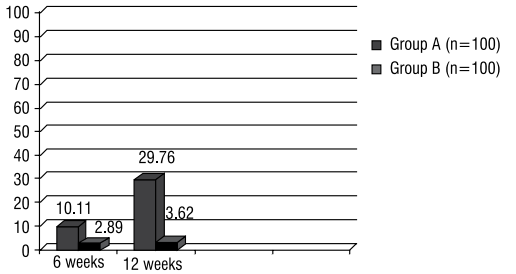

Figure 5: The percent increase in the mean claudication distance (CD) in both the groups at 6 and 12 weeks study time points, when compared with the CD at 4 weeks study time point taken as a baseline

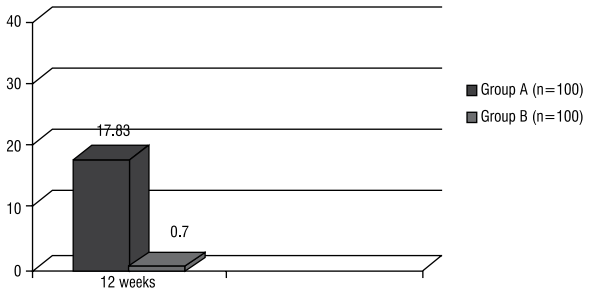

Figure 6: The percent increase in the mean claudication distance (CD) in both the groups at 12 weeks study time point, when compared with the CD at 6 weeks study time point taken as a baseline

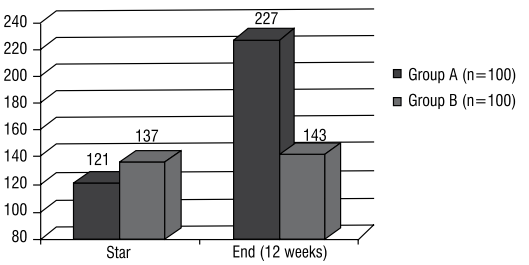

Figure 7: The mean claudication distances at the start and at the end study time points in the male gender in both the groups

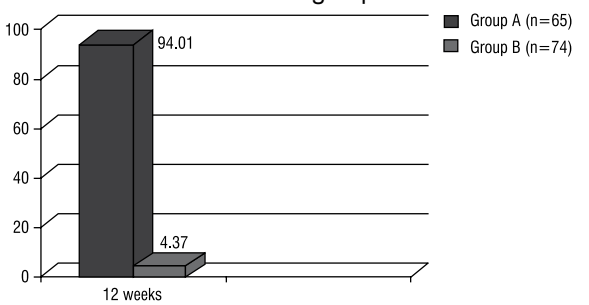

Figure 8: The percent increase in the mean claudication distance (CD) in male gender at the end study time point, when compared with the CD at start study point in both the groups

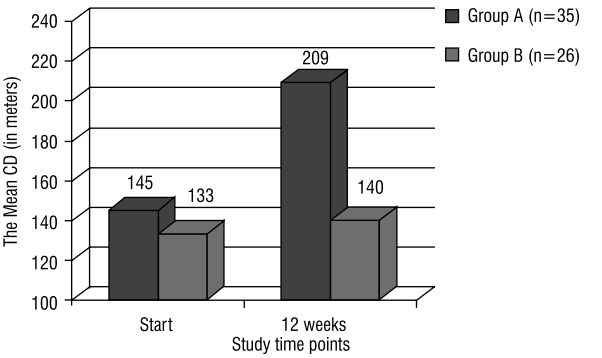

Figure 9: The mean claudication distances at the start and at the end study time points in the female gender in both the groups

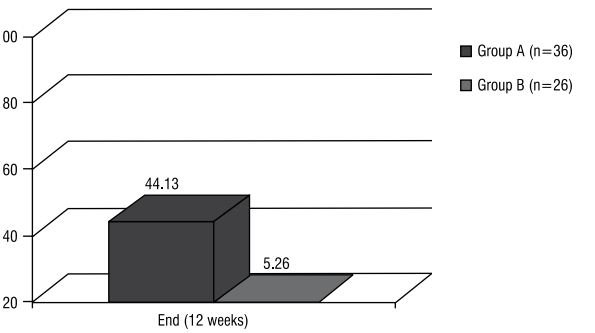

Figure 10: The percent increase in the mean claudication distance (CD) in the female gender at the end study time point, when compared with the CD at start study point in both the groups

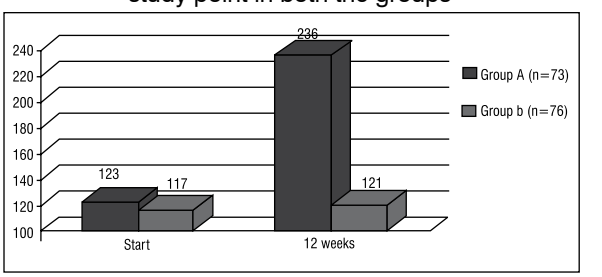

Figure 11: The mean claudication distances at the start and at the end study time points among the diabetics in both the groups

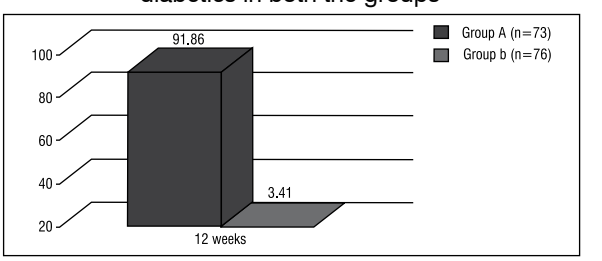

Figure 12: The percent increase in the mean claudication distance (CD) among the diabetics at the end study time point, when compared with the CD at start study point in both the groups

Table 1: Mean claudication distances (in meters) in Group A and Group B at all the study time points

Study time points	Group A (n=100) CD (in meters)	Group B (n=100) CD (in meters)
Baseline	139	135
4 Weeks	168	138
6 Weeks	185	142
12 Weeks	218	143

Table 2: The mean claudication distances and its mean percent increase in group A and group B at the start and end study time points among the hypertensive subset of study subjects

Study time points	Group A (n=72)		Group B (n=71)		P Value
	Mean CD (in meters)	Mean percent increase	Mean CD (in meters)	Mean percent increase	
Start study time point (Baseline)	126	81.15	136	1.43	0.008
End study time point (12 weeks)	227		138		

Table 3: The mean claudication distances and its mean percent increase in group A and group B at the start and end study time points among the smoker subset of study subjects

Study time points	Group A (n=20)		Group B (n=8)		P Value
	Mean CD (in meters)	Mean percent increase	Mean CD (in meters)	Mean percent increase	
Start study time point (Baseline)	130	65.38	140	3.57	0.04
End study time point (12 weeks)	215		145m		

Table 4: The mean claudication distances and its mean percent increase in both the groups at the start and end study time points among the obese subset of study subjects

Study time points	Group A (n=25)		Group B (n=22)		P Value
	Mean CD (in meters)	Mean percent increase	Mean CD (in meters)	Mean percent increase	
Start study time point (Baseline)	150	26	156	4.48	0.05
End study time point (12 weeks)	189		163		

and 35 females while in group B there were 74 males and 26 females. 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 of the two groups 61.53+-2.6 years in group A and 62.50+-2.3 years in group B. District Peshawar was the major residential address in both the groups (83% in group A and 79% in group B).

The major presenting symptom in both the groups was features of intermittent claudication (IC) as shown in Figure 1.

Figure 1 reveals that IC is the main presenting complaint in 95% (n=100) in group A, 89% (n=100) in group B and 92% (n=100) when both the groups are combined. Coldness and numbness were reported in 58% (n=100) in group A, 61% (n=100) in group B and 59.5% (n=200) when both the groups are combined.

In group A (n=100) 11% had diabetes mellitus only, 6% had hypertension only, 5% had morbid obesity only and 12% presented with a history of smoking only as their possible etiological cause of PAD. In the same group 42% had a combination of diabetes mellitus and hypertension, 12% had a combination of diabetes mellitus, hypertension and obesity, 4% had hypertension and obesity, while all the four etiologies were present

in only 8% of patients (see Figure 2).

The corresponding values for all these categories in group B (n=100) were 23%, 13%, 2%, 4%, 33%, 16%, 5% and 4% respectively (see Figure 3).

The overall mean CD at the start of the study was found to be 139 meters in group A and 135 meters in group B. This value increased to 168 meters in group A and 138 meters in group B at 4 weeks study time point. At six weeks study time point it was 185 meters in group A and 142 meters in group B. The final values were 218 meters in group A and 143 meters in group B at the 12 weeks study time point. (Table 1)

Table 1 and Figures 4, 5 and 6 clearly demonstrate a significant increase in the overall mean CD in group A from the 139 meters at the start to 218 meters at the conclusion of the study at 12 weeks (56.83%) with a P value of 0.0001.

In group A the baseline CD value of 139 meters, with an increase of 29 meters at 4 weeks (20.86%) compared with the same values in the control group B (2.2%) produced a P value of 0.004. There was a likewise rise in the mean CD of 33.09% (total=46 meter) at 6 weeks in group A compared to 5.18% rise in group B with a P value of 0.002 and P value of 0.0001 at 12 weeks.

The data in the male category showed a start study CD of 137 meters increasing to 227 meters in the group A at 12 weeks with a corresponding value of 121 meters and 143 meters in group B (Figure 7)

This translates into a percent improvement of 94.01% at the end study time point (12 weeks), the improvement in group A was compared with just 4.37% in group B. This represented a P value of 0.0001 for group A versus group B.(Figure 8)

The data in the female category showed a start study CD of 145 meters increasing to 209 meters in the group A at 12 weeks with a corresponding value of 133 meters and 140 meters in group B (Figure 9)

This shows that in the female subset of the study population at 12 week study time there is 44.13% (64 meters) improvement in group A compared with 5.26% (7 meters) in group B, with a P value of 0.04 (Figure 10)

The mean CD values in the diabetic subsets in both group A and group B are listed in Figure 11. From the baseline values of 123 meters and 117 meters in group A and group B respectively and values of 236 meters in group A and 121 meters in group B rise at 12 weeks showing 91.86% in group A as compared to the 3.41% in group B yielding a statistically significant P value of 0.008 for the diabetic subset of this study. (Figure 12)

The mean CD values in the hypertensive subsets in both group A and group B are listed in Table 2. From the baseline values of 126 meters and 136 meters in group A and group B respectively and values of 227 meters in group A and 138 meters in group B rise at 12 weeks showing 80.15% in group A as compared to the 1.43% in group B yielding a statistically significant P value of 0.008 for the hypertensive subset of this study

Table3 describes he mean CD values in the smoker subsets in both group A and group B with a P value of 0.04 for group A.

Table 4 describes he mean CD values in the obese subsets in both group A and group B with a P value of 0.05 for group A

DISCUSSION

In geriatric population with special reference to the diabetic and hypertensive subset of population Peripheral Arterial Disease represent a major challenge to management in the light of co-morbid medical illness in that age group. 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 for patients with PAD. The very fact that anti platelet drugs can reduce the death risk due to cardiovascular complications has led to their recommendation for treatment of patients with PAD.

Regarding the role of utility of the ABI, Hakeem et al concluded that both the PAD and CAD have independent course of clinical history and that a log linear relationship exists between the ABI result and the CAD risk and this risk continues to decline as the ABI values increase above 1.0.[55-56] Further studies by Mc-Dermott et al clearly established a link between the subclinical cardiac and carotid studies and the abnormal ABI.[51] 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[30]. While these aspects are beyond the scope of our study's, aims and objectives it reaffirms our results that Cilostazol has an ability to subjectively improve the quality of life.

The present study regarding the objective use of Cilostazol is a concrete step toward getting a local data in Khyber Pakhtunkhwa regarding the use of this novel drug for the various clinical manifestation of PAD. Our study equates well with the RACT trial and CREST trial showing the Cilostazol to be an effective anti-platelet agent for PAD and the results of treatment with Cilostazol were comparable to the Dawson DL et al. study results.[57] Money SR et al. study showed only 9% improvement in CD with a P value of 0.0125 due to some restraints of the study.[58] Our study was also comparable to Beebe HG et al. study which showed improvement in MWD with a P value of < 0.001.[59] Elam MB et al. study which focused on the effects of cilostazol on the plasma lipoproteins also demonstrated with the use of cilostazol an increase in treadmill walking distance

by 35% and a rise in ABI of 9%[60] The study of Jaff MR et al.[61] and Strandness DE et al.[62], however, that they failed to find any beneficial effects of cilostazol on the ABI did demonstrated a 50% increase in CD/MWD. Regensteiner JR et al. showed a better community based walking ability (P=0.0001) and an improved quality of life.[63] MiyashitaY et al. study on cilostazol in patients with critical limb ischemia showed improvement in the skin perfusion pressure (SPP) that correlated better with the wound healing.[64-66]

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.[67] The male gender thus has a proven predictive role about the outcome of the disease and the treatment as was shown by the Aboyans V et al. in MESA study.[68] The fact that females have a lower CD values has been validated by our study (94.01% improvement in the mean CD in males versus 44.13% improvement in the mean CD in females).

Diabetic and hypertensive patients were shown in our study to respond more favorably in respect of better improvement in CD compared with the smokers and obese subsets of study subjects.[69] The promotion of new vessel formation and collateral circulation was demonstrated in the diabetic patients by Shror K et al. study.[70] This might be the basis of better results among the diabetics in our study. The results from the hypertensive category in our study were almost at par with that of the diabetics, with an increase in the MWD/CD of 80.15% as compared to 56.83% in the overall category (P value=0.002). These findings suggest that cilostazol works in tandem in the both the diabetic and the hypertensive patients.

The lesser improvement in the mean MWD/CD in the obese subset of our study population considering the fact that cilostazol also has its intrinsic lipid lowering property (Elam et al.[46] Ikeda et al.[65])show that it cannot obviate the need for a proper lipid-lowering agent. The NCEP ATP III guidelines in this regard must be implemented vigorously.

The results for the smoker category in our study again showed less favorable increase in mean MWD/CD compared with the overall category. While Buergers' disease has been on the exclusion criteria of our study the chances of PAD overlapping with the former cannot be excluded explaining this anamoly. It was suggested by Smith FB et al. study that smokers have more non-deformable red cells and elevated plasma fibrinogen in addition to increased platelet aggregation.[71] Pentoxifylline is reportedly better in this regards but a conclusive data on the benefit of cilostazol in the smokers is not available.[72]

Otsuka manufacturers' research group, however, considering all the available research on their brand product have declared Cilostazol to be therapeutically safe and effective in smokers. Our study agrees with the international studies regarding the efficacy of cilostazol in smokers, the degree of response, however, is variable.

In Japan and south East Asia, cilostazol is also used in the secondary stroke prevention but the studies in Europe and America are still not conclusive on this aspect. It will need much more data before its future universal approval as a management guideline for secondary stroke prevention. The effects on CAD and CVA were beyond the domains of our study.

Exciting new data about its effect on the endothelial progenitor cells and revascularization in cerebral ischemia are emerging. Zampetaki A et al. study demonstrated a decreased carotid intima media thickness with cilostazol.[73,74] DAPC (Diabetic Atherosclerosis Prevention by Cilostazol) study from the Far East Asia has already recommended approval of cilostazol for stroke prevention after finding it useful in Japanese study patients. SPAD (The Safety and efficacy of cilostazol in ischemic stroke patients with PAD) 2012 study in Taiwan, CATHARSIS (Cilostazol Aspirin THerapy Against Recurrent Stroke with Intracranial artery Stenosis) study for stoke prevention and WASID (Warfarin Aspirin Symptomatic Intracranial Disease) need further validation. Seen in the light of the American Heart Association (AHA) statistical update cilostazol has promising future for its use in stroke prevention.

While these aspects of the treatment with cilostazol are not the subject of our study, it definitely has opened new vistas for local research.

CONCLUSION

Our study established the efficacy of Cilostazol in improving the claudication distance and thus the quality of life in mild to moderate cases of PAD. ABI which is based on the principles blood pressure monitoring with sphygmomanometer can be modified and incorporated into health care delivery system to improve the management by early diagnosis of PAD. Based on the results the patients can be offered medical and surgical treatments. Cilostazol holds the promising prospects in the medical therapy of PAD by improving the symptoms, arresting the disease progression and preventing the complications.

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