Effectiveness of cilostazol in the treatment of peripheral arterial obstruction

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Introduction   The term "peripheral arterial disease" describes a pathological process involving gradual occlusion of the arterial lumen. It does not cover disorders of coronary or cerebral blood vessels.[1]

Most atherosclerotic lesions develop in the arteries of the limbs, especially the lower limbs. In the past, physicians focused on relieving the effects of the disease by means of arterial reconstructive surgery, surgical embolectomy, or surgical bypass. The current approach focuses on the prevention of disease progression by risk-factor reduction or pharmacological treatment. The latter may significantly alleviate disease symptoms and increase the distance of claudication.[2] Physical activity alone, including marching with occasional rest, can positively affect claudication distance; however, the addition of pharmacotherapy provides faster and more permanent results.

Intermittent claudication is described as strong sensation of pain, muscle cramp, or sensation of pressure in the limb. These symptoms occur in various locations depending on the site of atherosclerotic lesions. When the process affects the aortoiliac region, the symptoms occur in the buttocks and thighs, and when it affects the area below the inguinal ligament, the symptoms occur in the calf. In some individuals, especially elderly patients with comorbidities such as posttraumatic osteoarthritis, heart or respiratory failure, degenerative spine disease, and musculoskeletal disorders (decreased mobility for other reasons), claudication may not be noticed by the patient. In such cases, peripheral arterial disease can be diagnosed by measuring the ankle–brachial index. An ankle–brachial index of 0.9 and lower is a predictor of moderate reduction in tissue perfusion, while that of 0.5 and lower is an indication for intensive therapy to avoid limb amputation. Surgery should be strongly considered in patients with a claudication distance of less than 100 meters and an ankle–brachial index around 0.5.

The risk of atherosclerosis increases with age and is higher in smokers and diabetes patients. Less significant risk factors include dyslipidemia, hypertension, and renal failure. All these factors inhibit endothelial nitric oxide synthase (eNOS), which is the main "player" in the relaxation of vascular walls. Endothelial dysfunction is one of the major factors involved in atherosclerosis. Recent studies have shown that impaired endothelial function is an important component of the Virchow's triad because it affects the other components of hemostasis. It is important to develop fully reproducible noninvasive methods to assess endothelial function because it may help better understand the pathological process. One of such methods is an ultrasound assessment of flow-mediated dilation of the brachial artery. Unfortunately, this method is rarely used in clinical practice.[3,4] Only one-third of the patients with atherosclerosis and an ankle–brachial index of less than 0.9 present with the symptoms of intermittent claudication.

In conservative treatment, it is of key importance to eliminate the risk factors. This primarily involves smoking cessation, weight reduction, and an increase in physical activity. Correction of dyslipidemia should start with a modification of diet, and, if ineffective, appropriate drugs should be administered. The next important step in the prevention of peripheral arterial disease is the treatment of diabetes and hypertension.

Therapeutic effects of cilostazol   For more than 40 years, different medications have been used in the treatment of insufficient blood supply to the peripheral tissues with various results. The exception is cilostazol, which has been tested for the past 25 years and reported as safe and effective.

Cilostazol has antiaggregative and relaxing effects on the smooth muscle cells of the arterial wall. These effects are thought to be achieved by the inhibition of phosphodiesteraze 3, which results in an increase in intracellular levels of cyclic

adenosine monophosphate levels. Cilostazol inhibits primary and secondary platelet aggregation as well as aggregation induced by turbulent blood flow (in which case, it is more effective than acetylsalicylic acid).[5] Moreover, it decreases plasma triglyceride levels by an average of 15% and increases high-density lipoprotein (HDL) cholesterol levels by an average of 10%. This mechanism has not been elucidated so far but it might be related to an increased activity of lipoprotein lipase.[6]

An experimental study on mice has shown that cilostazol can promote neovascularization in response to tissue ischemia via an eNOS-dependent mechanism.[7] In 2013, Jiao et al.[8] examined patients with type 2 diabetes with proteinuria. Half of the patients were treated with 200 mg of cilostazol daily (100 mg in the morning and 100 mg in the evening after meal), while the second half received oral vitamin B at a dose of 20 mg daily (in the morning and in the evening). In the cilostazol group, a decrease in the levels of intercellular adhesion molecule 1 and monocyte chemoattractant protein 1 as well as a reduction in proteinuria were observed. This suggests that cilostazol can significantly decrease urinary albumin excretion in patients with type 2 diabetes. Nakagawa et al.[9] have reported recently that cilostazol added to triple antiplatelet therapy in clopidogrel-resistant patients reduces the rate of clopidogrel resistance and suppresses new ischemic lesions without hemorrhagic complications, as compared with standard dual antiplatelet therapy. A Korean study assessing the effects of cilostazol in smoking and nonsmoking patients with coronary artery disease concluded that adverse clinical effects of smoking may be abolished by the addition of cilostazol to dual antiplatelet therapy after drug-eluting stent implantation. This may be due to the fact that smoking enhances the antiplatelet effect of cilostazol.[10] Resnick and Gordon[11] have shown that cilostazol at a dose of 200 mg daily promotes ischemic wound healing.

Effectiveness of cilostazol in intermittent claudication There is a vast number of publications in the literature describing the positive effects of cilostazol on maximum walking distance (MWD), pain-free walking distance (PFWD), pain alleviation, and plasma lipid composition.

In 2002, Thompson et al.[2] published an analysis of 8 phase III, randomized, double-blind trials including 2702 patients with stable disease and intermittent claudication. Circulatory compromise was diagnosed when the ankle–brachial index decreased from 0.9 to 0.7 after the treadmill exercise test. A statistical analysis of data from 2399 patients showed a significant increase in MWD. Patients receiving 50 mg of cilostazol daily reported an improvement in MWD by 44%, those receiving 100 mg daily, by 50%, and controls, by 21%. Significant changes in PFWD were observed in 5 studies. Two studies in which pentoxifylline was used did not show any changes in comparison with the placebo group. After 24 weeks of cilostazol treatment, an increase in plasma HDL cholesterol levels by 12.8% ($P = 0.0001$) and a decrease in triglyceride levels by 15.8% ($P = 0.0001$) were observed.[2]

Regensteiner et al.[12] conducted 6 randomized studies comparing the quality of life between patients using cilostazol and those using placebo. In both groups, a significant improvement in the quality of life was seen, although it was greater in the cilostazol group. The author showed that the improvement in MWD and PFWD in patients using cilostazol is well reflected in the quality of life questionnaires, namely, the Short Form (36) Health Survey and Walking Impairment Questionnaire.[13,14]

In a study comparing cilostazol with pentoxifylline, Dawson et al.[15] showed no beneficial effects of cilostazol after it was switched to pentoxifylline. In a randomized trial on the effect of cilostazol on the parameters of blood coagulation and fibrinolysis, Hobbs et al.[16] did not confirm any changes in patients with intermittent claudication. Randomized trials on the effect of cilostazol on the ankle–brachial index did not show its superiority over placebo (0.64 ±0.02 vs 0.68 ±0.02).[17] Studies on the effect of cilostazol on MWD and PFWD showed that patients receiving 50 mg of cilostazol twice daily had a 1.5-fold increase in MWD and PFWD and doubled their walking distance. On the other hand, patients receiving 100 mg of cilostazol twice daily doubled their MWD and PFWD and tripled their walking distance.[18,19]

Rendell et al.[20] compared the effects of cilostazol in patients with atherosclerosis with concomitant diabetes type 2 and patients without diabetes. They did not observe any significant intergroup differences in the results of cilostazol treatment. It was observed that diabetic patients with more severe claudication symptoms respond better to cilostazol therapy as shown by prolonged claudication distance.

Warner et al.[21] analyzed 6 studies available in MEDLINE (1946–2012) and Cochrane CENTRAL (1996–2012) regarding patients after peripheral vascular interventions of the femoral and popliteal arteries. Two types of therapy were used after surgery: antiplatelet drugs vs antiplatelet drugs + cilostazol. Patients receiving antiplatelet drugs with cilostazol showed a significant decrease in the rate of restenosis and amputations as well as an improvement in revascularization.

Safety and adverse events of the drug The most common adverse effect of cilostazol is headache, which resulted in the discontinuation of treatment in 1.3% of the patients when administered at a dose of 50 mg twice daily and in 3.7% of the patients when used at a dose of 100 mg twice daily, while in the placebo group, headache occurred in 0.3% of the patients. Less common adverse effects include myocardial infarction, stroke, exacerbation of preexisting cardiac arrhythmias; however, their prevalence is similar to that observed in the placebo group (0.72% vs 0.87%).[22]

Conclusions Cilostazol (100-mg tablets twice daily) significantly increases claudication distance in patients with peripheral arterial disease. Diabetes patients with more severe symptoms of claudication achieved better results than patients with longer claudication distance. Patients after surgical revascularization who received an antiplatelet drug in combination with cilostazol had a significant decrease in the rates of restenosis and amputations as well as an improvement in revascularization. Cilostazol was also shown to improve the healing process of ischemic wounds. The drug is well tolerated, and the number of adverse effects is low. However, it is contraindicated in patients with some cardiovascular diseases including acute cardiac infarction up to 6 months following the onset, cardiac arrhytmias, and circulatory insufficiency.

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