

Full Length Research Paper

Comparison of effects of iloprost and pentoxifylline on walking capacity and skin oxygenation in diabetic patients with peripheral artery disease

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Diabetes is in close relation with peripheral artery disease (PAD) and there are conflicting results regarding efficacy of iloprost in PAD. The aim of this study was to investigate the efficacy of iloprost in improving walking capacity and increasing oxygenation to diseased tissues in PAD patients with diabetes, compared to pentoxifylline. Data of 80 patients were recorded contemporaneously. Patients were divided into two groups (Group 1: Users of iloprost and pentoxifylline; Group 2: Users of only pentoxifylline). O₂ saturations in diseased limbs were significantly improved at three-months follow-up in both groups (both $p < 0.001$). The difference between groups was in favor of Group 1 ($p = 0.012$). Maximum walking capacity was also increased significantly in both groups (both $p < 0.001$). However, the improvements in walking distance were at similar extent ($p = 0.226$). In comparison with pentoxifylline, iloprost has no superior effect on walking capacity of diabetic patients with intermittent claudication. However, iloprost improves oxygenation of tissues better than pentoxifylline, therefore iloprost may be preferred especially in diabetic patients with critical limb ischemia as an adjunctive therapy followed by pentoxifylline or cilostazol. Usage of iloprost may contribute to the recovery of diabetic ulcers and also, it may postpone occurrence of diabetic ulcers.

Key words: Diabetes mellitus, iloprost, pentoxifylline, walking capacity, oxygen saturation.

INTRODUCTION

About 27% of people over the age of 55 years have peripheral arterial disease (PAD) and intermittent claudication (IC) is a common presentation of lower-limb PAD with a prevalence of 1 to 7% in men, 50 to 75 years old (Fowkes et al., 1991). IC demonstrate significant impairment not only in walking capacity and physical activity, but also in social functioning, emotional and mental health (Pell, 1995). People with diabetes are 2 to 4 times more likely to have PAD compared with the general population (Hiatt, 2001). Around 15% of people with diabetes develops PAD after 10 years of the disease which rises to 45% after 20 years (Health Care Industry, 2003).

The goals of treatment for patients with claudication are to relieve their exertional symptoms, increase walking capacity and globally improve their quality of life. For this purpose, pharmacologic therapy, supervised exercise training, interventional radiology and surgery have all been used. Many agents, including vasodilators have been tried for the relief of symptoms; although their effectiveness is still subject to debate. There are currently two medications for the relief of claudication, pentoxifylline and cilostazol (Reilly and Mohler, 2001). Iloprost is a synthetic analogue of prostacyclin, with a 10-fold higher half-life than the native compound. It has been suggested to improve the symptoms of patients with severe chronic limb ischemia, possibly by their vasodilating and antiplatelet actions (Arosio et al., 2001). However there are conflicting results regarding its efficacy in PAD (Creager et al., 2008; Lievre et al., 2000; Mohler et al., 2003).

The aim of this study was to investigate the efficacy of

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Table 1. Demographic characteristics of patients in two study groups.

Parameter	Group 1 (no = 38)	Group 2 (no = 42)	P value
Age (years)	61.84 ± 3.66	62.60 ± 3.04	0.318*
Male	31 (81.58%)	33 (78.57%)	0.739**
Current smoking	12 (31.58%)	16 (38.10%)	0.544**
Dyslipidemia	28 (73.68%)	26 (61.90%)	0.264**
Hypertension	27 (71.05%)	33 (78.57%)	0.441**
Ischemic heart disease	11 (28.95%)	9 (21.43%)	0.441**
Baseline ABI	0.70 ± 0.08	0.68 ± 0.07	0.274*
Maximum walking distance (m)	289.74 ± 61.80	277.38 ± 43.34	0.300*
Oxygen saturation (%)	84.53 ± 3.55	84.71 ± 2.85	0.794*

*, Student's t test; **, Fisher's exact test.

iloprost in improving walking capacity and increasing oxygenation to diseased tissues in PAD patients with diabetes and to compare its efficacy with pentoxifylline.

PATIENTS AND METHODS

In this prospective study, details of all PAD patients with diabetes who were treated in our hospital due to complaint of intermittent claudication between September 2007 and April 2011 have been recorded contemporaneously. The study consisted of 80 patients. Male and female patients over 40 years of age suffering from intermittent claudication due to PAD of the lower limbs for longer duration than 6 months with stable claudication for at least 3 months prior to entry were included in this study. PAD was diagnosed by arteriography or Doppler scan. All patients were required to have a rest ankle-brachial index (ABI) of ≤ 0.90 in the symptomatic leg. Patients were excluded from the study in cases of critical limb ischemia (rest pain, ulcer or gangrene), nonatherosclerotic PAD, acute myocardial infarction or stroke within the last 6 months, performed coronary artery interventions or surgical limb arterial bypass within the last three months, cardiac failure (NYHA Class > II), unstable angina, angina pectoris (Canadian classification > II), hyperkinetic ventricular arrhythmias, severe hypertension (sitting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg) or hypotension (systolic blood pressure < 90 mmHg), morbid obesity (body mass index ≥ 40 kg/m²) and other diseases that affected walking. Exclusion was also mandated for patients who had hemorrhagic diathesis, concomitant clinical conditions in which iloprost might increase the risk of bleeding (that is active peptic ulcer, trauma, cerebral haemorrhage), thrombocytopenia (< 80.000 /mm³) or thrombocytosis (> 500.000 /mm³), severe hepatic failure (alanine transaminase and aspartate transaminase > 3 times the upper normal limit on two separate tests), renal failure requiring dialysis treatment, currently participating in a supervised exercise regimen. Patients using aspirin, clopidogrel or ticlopidine were not excluded from the study. Patients were given appropriate dietary recommendations and were counseled to stop smoking.

The same pneumatic cuff (8 to 12 cm wide) was placed bilaterally on the upper arms (brachial pressure) and at the ankle just above the medial malleoli. The ultrasound transducer was located distal to the cuff on the brachial, the posterior tibial and dorsalis pedis arteries to measure bilateral brachial and the ankle pressures. The ABI was calculated by dividing ankle pressure by the highest brachial systolic pressure. Functional oxygen saturation was determined by pulse oximetry (SpO₂) on each toe with the finger

sensor probe at room temperature (25°C) and repeated after three months of therapy (in Group 1, once more on seventh day). Maximal walking distances were measured before therapy. Subsequent exercise measures and ABI calculations were then performed after three months of therapy. Any exercise training method was not carried out in patients throughout this period. Patients were studied in two groups; patients without previous medication to whom iloprost and pentoxifylline were administered, constituted the first group. The second group comprised the patients without previous medication to whom only pentoxifylline was administered. Iloprost was administered daily as a daily 6-h intravenous infusion for 7 days. Initial intravenous infusion rate corresponded to 0.5 ng/kg/min. At 30-min intervals, infusion rate was increased up to 2.0 by 0.5 ng/kg/min, if patient tolerated.

All patients were discharged to home on oral aspirin 150 mg tablet/day and pentoxifylline 1200 mg tablet/day for a period of 12 weeks.

Statistical analysis

Statistical analyses were carried out by using the statistical packages for SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Mean and standard deviation (SD) were calculated for continuous variables. The Shapiro-Wilk test was used to assess the normality of the continuous data. The means of independent groups were analyzed by Student's t test. Fisher exact test was used to analyze the categorical variables. Student's t test and nonparametric test were used to assess the similarity of demographic data in different groups (Table 1). The repeated measures (O₂ saturations and maximum walking distance at different times) in each group was analysed by one-way ANOVA (Figures 1 and 2). Differences between groups at the end of three months were studied by 'general linear model' for 'repeated measures' (Figure 3). A 2 (group) × 2 (time) mixed-model repeated-measures analysis of variance was performed to compare between-method differences. Two tailed p values were considered statistically significant at p<0.05.

RESULTS

Baseline demographic characteristics of two groups of patients were similar (Table 1). The mean age in all treatment groups was 62.24 ± 3.35 years. Of the 80 patients, 64 (80%) were male and 16 (20%) were female.

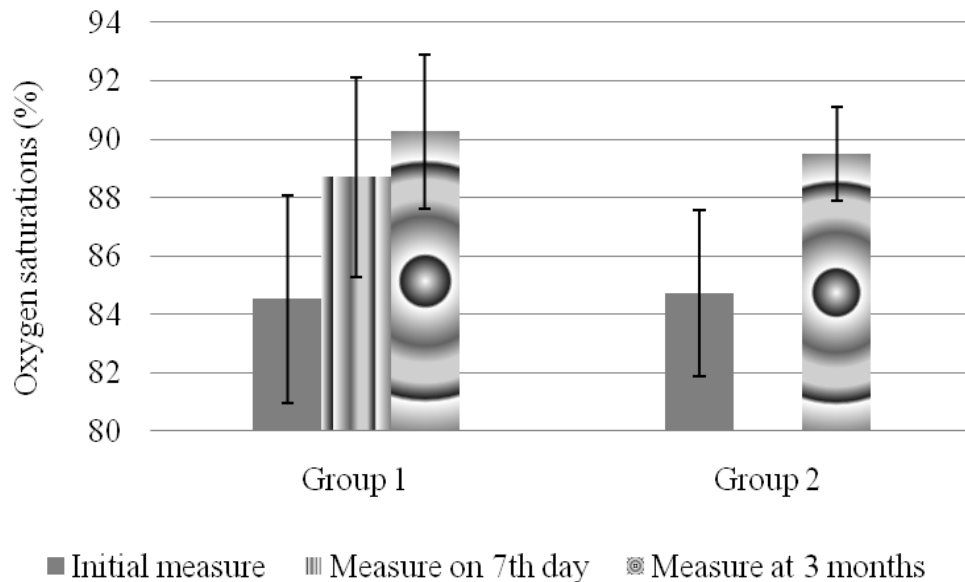


Figure 1. Changes in pulse oximetry derived O₂ saturations of diseased limbs through 3 months expressed as mean ± standard deviation.

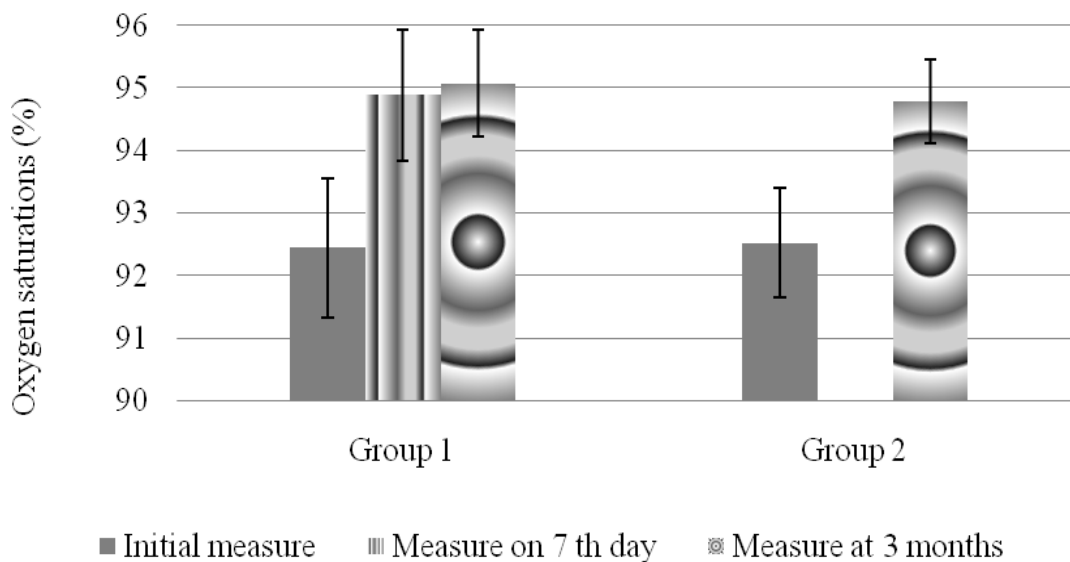


Figure 2. Changes in pulse oximetry derived O₂ saturations of healthy limbs through 3 months, expressed as mean ± standard deviation.

There were 38 patients in Group 1 and 42 patients in Group 2. The distribution of atherosclerosis risk factors such as smoking, dyslipidemia and hypertension were not different between groups. The duration of treatment did not differ and concomitant therapies during follow-up were very similar for both groups. The most frequent concomitant medications were antihypertensive and antianginal drugs (60%; calcium channel blockers, ACE inhibitors, nitrates, or α- adrenergic receptor-blocking

agents) and lipid-lowering drugs (75%). The ABI remained stable throughout the study and did not differ between groups. Pulse oximetry derived O₂ saturations in diseased limbs were significantly improved immediately on the seventh day following iloprost administration (84.53 ± 3.55 versus 88.71 ± 3.42, p<0.001). This beneficial effect continued through three months (90.26 ± 2.63, p<0.001). Changes in diseased limb O₂ saturation at the three-month follow-up were significant in Group 2, too

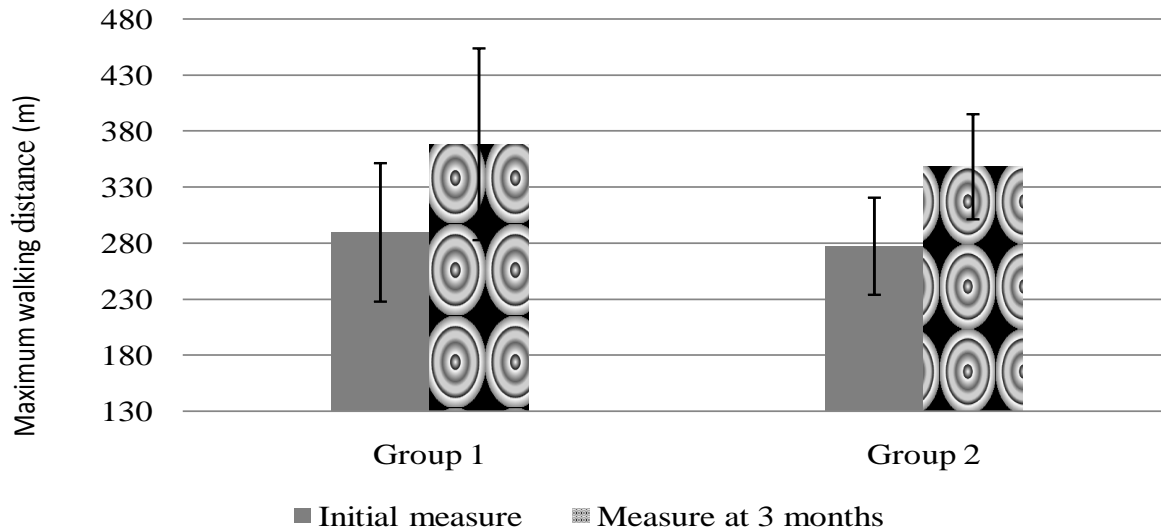


Figure 3. Changes in maximum walking capacities of patients through 3 months expressed as mean ± standard deviation.

(84.71 ± 2.85 versus 89.48 ± 1.61, $p < 0.001$) (Figure 1). O_2 saturations in healthy extremities increased both on the seventh day and at third month following iloprost therapy (92.44 ± 1.12, 94.88 ± 1.05, 95.07 ± 0.86, respectively, $p < 0.001$). Also in Group 2, third month measures of O_2 saturations in healthy extremities were significantly higher than initial measures (92.52 ± 0.87 versus 94.79 ± 0.67, $p < 0.001$) (Figure 2). Maximum walking capacity was increased significantly in Groups 1 and 2 (289.74 ± 61.80 versus 368.42 ± 85.57, $p < 0.001$; 277.38 ± 43.34 versus 348.33 ± 46.90, $p < 0.001$, respectively), however improvements in both groups were at similar extent. Increase in mean walking capacity was 79 m (27.16%) in Group 1, while it was 71 m (25.58%) in Group 2 (Figure 3).

According to the multiple comparison analysis regarding to the differences between groups at the end of three months; difference between improvements of walking capacity in Groups 1 and 2 were not significant ($p = 0.226$). On the other hand, regarding to O_2 saturations, all measures of Group 1 at three months were superior than ones of Group 3 ($p = 0.012$ for diseased limbs and $p = 0.001$ for healthy limbs).

DISCUSSION

Although technical advances have associated with a corresponding increase in revascularizations, 14 to 20% of critical limb ischemia patients have completely nonreconstructable disease or have had failed attempts at reconstruction resulting with a rapidly downward course in terms of both life and limb (Thomas and Nassef, 2006). Within 1 year after the onset of critical limb ischemia, only about half sustain amputation-

free survival, approximately 25% die and 25% require a major amputation (TASC Working Group, 2000a, b). The mortality rate in patients presenting with ischemic gangrene and rest pain is around 40 to 70% after 5 years and 80 to 95% after 10 years (Vane and Corin, 2003). The presence of only IC is a milder state of PAD compared to presence of gangrene or rest pain; however, IC not only impairs life quality, but also it may be a premonitory symptom of advanced PAD. Iloprost, a stable prostacyclin analogue is one of the pharmacologic agent which has been used for the relief of claudication. It induces angiogenesis (Biscetti et al., 2009; Coppolino et al., 2009; Hirsch et al., 2006) through a vascular endothelial growth factor-dependent mechanism as well as vasodilator effect on vessels and inhibitory effect on platelet aggregation (Momsen et al., 2009; Mazzone et al., 2002), leading to beneficial effects especially on the microcirculation (De Donato et al., 2007). Consistently, iloprost appears to reduce the end-point of death and amputation due to PAD (Mohler et al., 2003; Belch et al., 1997). However, studies regarding to improvement of walking capacity have yielded inconsistent results. Iloprost was suggested to be effective in improving walking distance in PAD by many previous series (Lievre et al., 2000; Ceriello et al., 1998; Cozzolino et al., 1999; Disalvo et al., 2006; Goya et al., 2003).

In more recent larger studies, there was improvement in walking distance, but it was insignificant compared to placebo (Creager et al., 2008; Mohler et al., 2003).

Significant placebo effect is a common feature and can be explained partly by exercising itself or habituation to treadmill testing (Mazzone et al., 2002). In addition, iloprost had been suggested to have additional beneficial effects on circulation in diabetic PAD. For example, prostaglandins decreased tumor necrosis factor-induced

vascular cell adhesion molecule-1 (VCAM-1) expression in human vascular endothelial cells in diabetic patients (Matsumoto et al., 2002). Considering that circulating VCAM-1 is predictive of future vascular events, prostaglandins may have a beneficial effect on progression of atherosclerosis in case of diabetes. In another study, treatment with a PGI₂ analogue restored endothelial dysfunction in DM rats, accompanied by the induction of vascular HGF and c-met expression (Hirsch et al., 2006). Our aim was to identify the efficiency of iloprost in improving walking capacity in patients with diabetic PAD. Absence of placebo group was limitation of our study. However, we studied the efficiency of iloprost compared with pentoxifylline whose favorable effect on walking capacity was demonstrated by many reports (Hiatt, 2001; Creager et al., 2008).

In patients without any previous medication, iloprost + pentoxifylline regimen increased maximal walking distance by approximately 27.2% while only pentoxifylline increased by 25.6%. In other words, in case of incipient medical therapy, addition of iloprost to pentoxifylline increased walking capacity a little more, but not statistically significant. Then in long-term period, iloprost does not have any additive effect on exercise performance in diabetic patients with PAD under pentoxifylline therapy. Absence of significant changes in ABI and walking capacity made us think that iloprost does not have superior effect on macrocirculation, sufficiently. Another measure to demonstrate the efficiency of iloprost was O₂ saturation provided by pulse oximetry which has been used to detect peripheral skin perfusion reflecting the level of vascularity and viability of a limb (Colberg et al., 2009; Jawahar et al., 1997; Parameswaran et al., 2005). Contrary to ABI and walking capacity, iloprost improved oxygenation of diseased tissue in all patients, superior to pentoxifylline which showed beneficial effect of iloprost on microcirculation. Furthermore, this beneficial effect began as early as seventh day of therapy. On the other hand, efficiency of iloprost on O₂ saturation was more prominent in healthy limbs than diseased limbs. Probably this was vasodilatory effect which was limited on atherosclerotic arteries.

In a previous study, it was demonstrated that diabetes mellitus often limits improvement of skin perfusion through reductions in the action or release of vasodilatory compounds (Colberg et al., 2009; Singh et al., 2011).

Conclusion

Considering these results and the need for an intravenous infusion, the long-term treatment of iloprost is useless for improvement of walking capacity in diabetic PAD with intermittent claudication. However, iloprost cause immediate improvement in oxygenation of all tissues including diseased ones nourished by arteries

with diabetic atherosclerosis, through microcirculation. This effect is also long lasting effect. Therefore iloprost may be preferred for better oxygenation of tissues in diabetic patients especially with critical limb ischemia because of its fast acting and also long lasting effect on microcirculation as an adjunctive therapy followed by pentoxifylline or cilostazol. Usage of iloprost may contribute to the recovery of diabetic ulcers. In addition, it may postpone occurrence of diabetic ulcers. However, since iloprost effect on diabetic ulcers was not an aim of this study, we cannot conclude any benefit from iloprost, despite significant increase in O₂ saturation of diseased tissues.

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