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Clinical and circulatory effects of Iloprost either administered for 1 week or 4 weeks in patients with peripheral obstructive arterial disease at Leriche-Fontaine stage III

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Abstract. – ***Background*: Iloprost therapy for severe peripheral obstructive arterial disease (POAD) has demonstrated to be effective in reducing the need for amputation. However the feasibility of a 28-day infusion regimen in less severe stages of the disease is poor due to the lenght in hospital stay.**

A randomized, controlled, parallel-group pilot study was carried out with the aim to evaluate clinical and circulatory effects of Iloprost, a stable prostacyclin analogue, administered with two different infusion schedules to patients with POAD at Leriche Fontaine stage III.

***Methods:* Twenty patients 16 males and 4 females, mean age 66 ± 6 years) with objective signs of POAD, rest pain for at least two weeks and posterior tibial artery pressure > 50 mmHg, were randomized to either Iloprost i.v. infusion up to 2 ng/Kg/min for 6/h/day for 28 days (Group A) or to Iloprost i.v. infusion up to 1.5 ng/Kg/min for 16/h/day for 7 days (Group B). At baseline (before starting first infusion) after 7 days (for group B only, end of therapy) and after 28 days (end of therapy for Group A, end of study for Group B) the following parameters were evaluated: walking distance, rest pain and analgesic consumption, plethysmographyc parameters (first flow, peak flow and peak flow time) and laser Doppler parameters (rest flow, post ischemic flow).**

***Results:* After 28 days, both Iloprost infusion schedules increased walking capacity (maximum walking distance/pain free walking distance +119/+84% +199/+85% respectively, for Group A and B respectively) reduced ischemic pain (- 45% and - 48% respectively for Group A and B) and analgesic consumption and improved plethysmographyc and laser Doppler parameters. Tolerability seemed to be better in Group B, suggesting that the lower dose and the shorter duration of the therapy period might result in reduced incidence of headache thus, in principle, increasing patient acceptability.**

***Conclusions:* The results of this pilot study, if confirmed by larger trials, could have important positive implications in terms of costs, patient comfort and management.**

Key Words:

Iloprost, Arterial disease, Walking distance, Short infusion.

Introduction

Iloprost is a synthetic prostacyclin analogue characterized by improved selectivity for platelets, reduced vasodilatory effects and increased stability in comparison with natural prostacyclin[1].

Its main pharmacological effects include inhibition of platelet aggregation, blockade of leukocyte migration and activation, tissue protection, vasodilation and profibrinolytic effects[2-8]. Many clinical studies have been demonstrated that Iloprost, infused for 6 hours/day for 28 days up to 2 ng/Kg/min, in patients with severe Peripheral Obstructive Arterial Disease (POAD) significantly increases the number of patients alive with viable limbs in comparison with placebo by reducing the need for amputation as well as rest pain, analgesic consumption and by increasing the rate of ulcer healing[9-14].

However, some issues remain outstanding: firstly the clinical benefits of Iloprost seem to last for several months after the infusion peri-

od has been completed, secondly the prolonged (28 days) period of therapy is a potential limitation due to excessive lenght in hospital stay, mainly for patients with some residual walking capacity.

The former issue has been addressed by some authors which have been demonstrated that Iloprost effects are particularly evident on microcirculation where significant increase in number and diameter of arterioles and venules is observed at very low doses (about 0.5 ng/Kg/min). This effect has been found to correlate with long-term improved nutritional blood flow and clinical responses[5,15,16]. The latter could be evaluated by comparing different schedules of infusion to verify whether a more intensive but shorter cycle of infusion could result in similar benefits compared with the currently used therapy. Actually the clinical effects of Iloprost are already significant after the first 2 weeks of infusion[12,14] and there are no clinical evidences that the more prolonged the infusion the more prolonged are clinical benefits.

Would a shorter cycle of therapy have clinical effects comparable with the currently used 28 days therapy this could result in easier patient management and reduction in hospital stay.

Material and Methods

Twenty patients (16 males and 4 females) aged between 55 and 75 years, with POAD at Leriche Fontaine stage III (nocturnal rest pain for at least two weeks and posterior tibial artery pressure > 50 mmHg) gave their consent to participate into the study. Study protocol and procedure were described to the patients and they were explained that they were free to withdraw from the study at any time without giving a reason. The main exclusion criteria were: critical limb ischemia, type I diabetes mellitus, severe arterial hypertension, hypotension (systolic blood pressure <90 mmHg), renal and/or hepatic insufficiency, any impossibility to perform treadmill test, alcohol abuse, poor compliance. The following concomitant treatments were not allowed and had to be withdrawn at the beginning of the run-in period: antiplatelet agents (including aspirin), oral anticoagulants, heparin, vasoactive drugs, haemorrheologics. After check for inclusion and exclusion criteria patients performed a Doppler examination for documentation of site, number and severity of the arterial obstructions and underwent a physical examination, including detailed medical history. Demographics of patient population is described in Iloprost I.

Patients included were randomized to one of the following treatment schedule: *Group A*, Iloprost i.v. infusion starting from 0.5 ng/Kg/min up to a maximum of 2 ng/Kg/min for 6-hour/day for 28 days; *Group B*, Iloprost i.v. infusion starting from 0.5 ng/Kg/min up to a maximum of 1.5 ng/Kg/min, for 16-hour/day for 7 days. Iloprost (Endoprost - Italfarmaco SpA, Milan - Italy) was supplied in sterile vials, each containing 0.100 mg of active principle. Infusions were done using a peristaltic infusion pump after dilution with saline. Infusion rate was up-titrated during the first three days until the maximum dose level or the maximum tolerated dose were reached, as already described[13].

Before starting infusion (T_0), after 7 days (T_7: end of treatment for *Group B* only) and after 28 days (T_{28}: for both *Group A* and *Group B*) the following parameters were evaluated: intensity of rest pain (by score: 0 absent, 1 mild, 2 moderate, 3 intense, 4 unbearable), analgesic consumption, blood pressure and heart rate, ankle/brachial pressure index, first flow, peak flow and time to peak flow (by means of strain gauge plethysmography), rest flow, post-ischemic flow (Laser Doppler), walking distance (treadmill). Patients of both groups were hospitalized for the entire study duration and physical activity was controlled for *Group B* in order to avoid any possible influence at the end of the study measurements.

Blood pressure was measured at the posterior tibial artery of both legs by means of mercury sphygmomanometer using a Doppler probe. Measurements were repeated in the corresponding brachial artery in order to calculate the ankle/brachial pressure index (ABPI). Brachial, systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) were measured on each treatment day, before starting infusion and frequently during infusion. Strain-gauge pletysmography and Laser-Doppler were performed using a mercury plethysmograph (Periquant 3800, Gtman, Eurasburg-Germany) and a Laser Doppler flowmeter (PF3, Perimed,

Table I. Demographic and clinical characteristics of patient population by treatment (*Group A*: 6 hrs/day - 28 days; *Group B*: 16 hrs/day - 7 days).

	Group A (n=10)	Group B (n=10)
Age (years)	66.4 ± 5.2	66.1 ± 6.4
Sex (M/F)	8/2	8/2
Weight (Kg)	73.5 ± 9	76.8 ± 11.7
Height (cm)	164.7 ± 7.5	162.6 ± 6.1
Diabetes mellitus	5	5
- oral antidiabetics	2	3
- insulin	0	0
- diet	5	5
Obesity	2	5
Physical exercise	0	0
Smoke:		
- No	2	2
- Previous smoker	6	4
- Current smoker	2	4
Systolic blood pressure (mmHg)	146.5 ± 11.3	146 ± 17.9
Diastolic blood pressure (mmHg)	81.5 ± 2.4	81 ± 9.9
Heart rate (beats/min.)	67.4 ± 9.9	66.2 ± 3.3

Stockolm - Sweden), in a room kept at constant temperature (21 ± 1 °C). Patients had to rest for at least 20 minutes in supine position before each examination. Exercise test was performed on a treadmill according to a standardized protocol with constant speed (3 Km/h) and slope (0%). The maximum walking distance (MWD) and the pain free walking distance (PWD) were measured. At each visit during the study, adverse reactions were recorded by questioning or examining the patient.

Statistical analysis was done by BMDP/386 dynamic program (release 7.0, 1994). Given the pivotal nature of the trial no specific assumption was made although a conservative statistical approach was considered. From the statistical point of view, the study design implied a different number of measurements between *Group A* and *Group B*: two measurements (basal, 28 days) and three (basal, 7 days and 28 days), respectively. Therefore two analysis were performed: basal vs end of treatment (which was 28 days for *Group A* and 7 days for *Group B*), basal vs end of study which was 28 days for both groups. As far as *Group B* is concerned, the time course of the effect on each parameter was also followed (basal, day 7 and day 28) and has been reported in the tables or figures. ABPI and plethysmographic data are reported for the "worst leg" on the basis of the pre-study ABPI. Continuous variables were analysed using ANOVA for repeated measures. Data are reported as means and standard deviations (SD).

Results

All patients completed the study. Demographic and clinical characteristics are reported by treatment in Table I. There were no significant differences between the two groups.

Rest pain and analgesic consumption

Rest pain score (Figure 1) was significantly reduced without significant differences between groups (*Group A*: from 2.20 ± 1.03 to 1.20 ± 1.23, *Group B*: from 2.00 ± 1.05 to 1.10 ± 1.10). Analgesic consumption was concomitantly significantly reduced without differences between groups.

Treadmill exercise test

As shown in Figure 1, both groups increased significantly walking distance in comparison with the baseline values without difference between each other. For *Group B* the increase was of 82.5% ($p < 0.01$ vs baseline) after 7 days and of 119.3% ($p < 0.01$ vs baseline) after 21 days from the stop of the infusion (study day 28th).

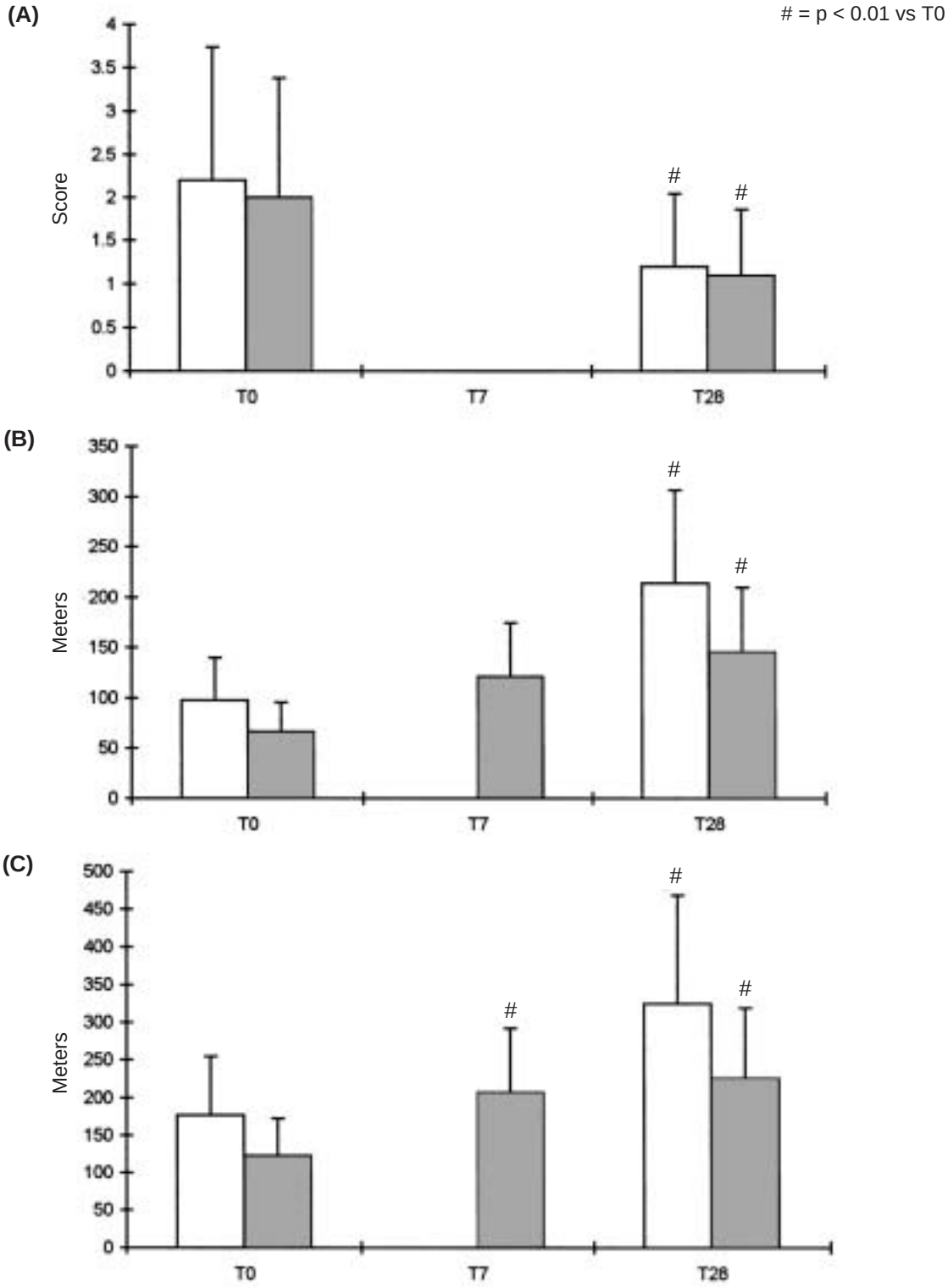

Figure 1. Mean (SD) of rest pain score (*A*), pain free walking distance (*B*) and maximum walking distance (*C*) for Group A (open bars) and Group B (dashed bars).

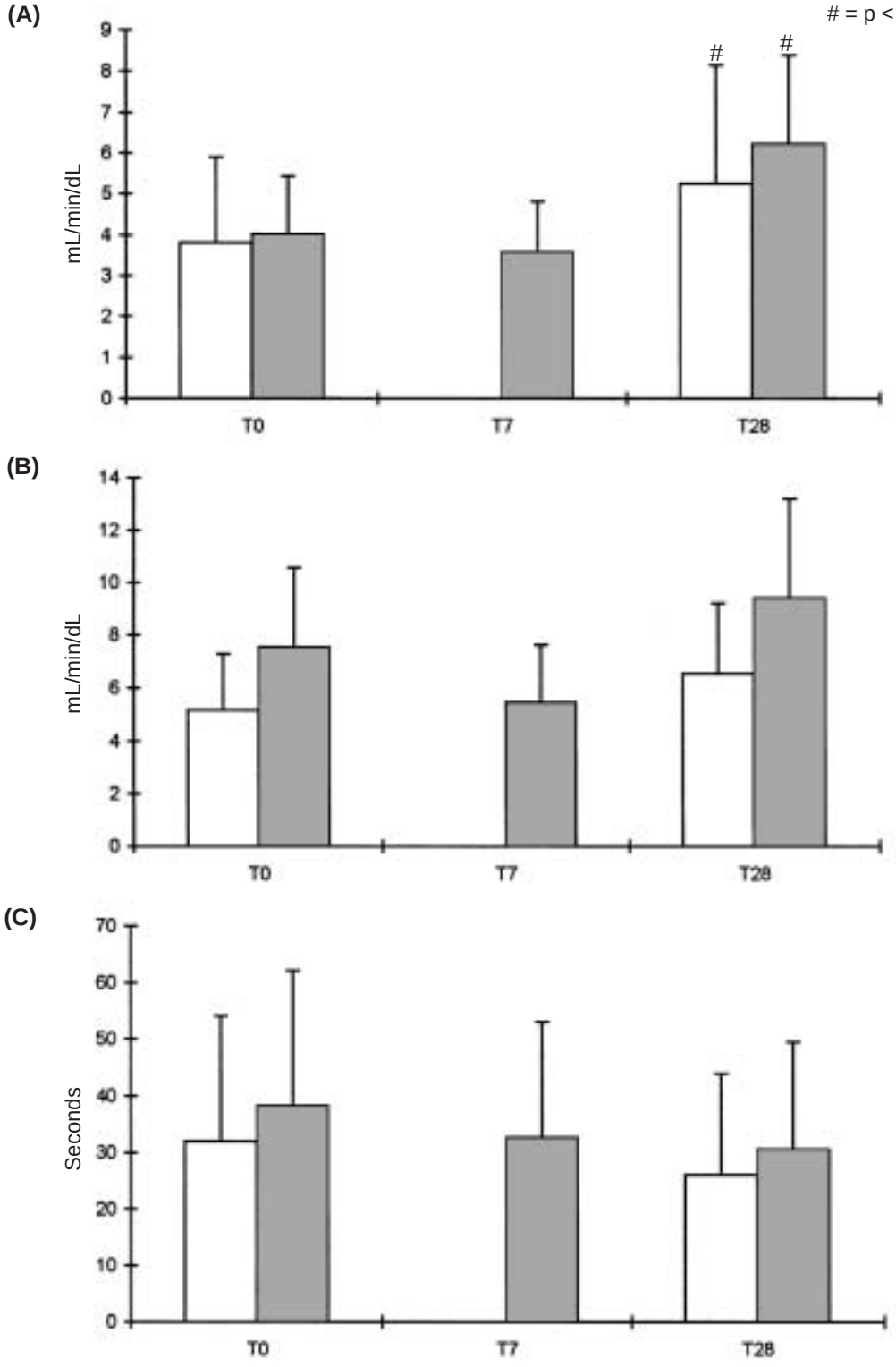

Figure 2. Mean (SD) of first flow (*A*), peak flow (*B*) and peak flow time (*C*), by means of strain-gauge plethysmography, for Group A (open bars) and Group B (dashed bars).

Ankle/brachial pressure index (ABPI)

Worst leg ABPI did not change significantly at the end of study vs baseline (*Group A:* from 0.47 ± 0.10 to 0.57 ± 0.11, *Group B:* from 0.43 ± 0.07 to 0.49 ± 0.13).

Strain-gauge plethysmography

Changes in plethysmographyc parameters are shown in Figure 2. First flow significantly increased ($p < 0.01$ vs baseline) in both groups after 28 days (end of therapy for *Group A*, end of study for *Group B*). Peak flow showed a trend to increase after 28 days which was not statistically significant. Time to peak flow was slightly although not significantly reduced after 28 days in both groups.

Laser-Doppler

Rest flow did not change during the study. Slight non significant increase of post-ischemic flow was observed for both groups after 28 days (Table II).

Tolerability

Infusions were completed in all patients. The number of patients reporting side effects during the study are listed in Table III. Tolerability seemed to be better in *Group B* as evident from the lower number of patients complaining of adverse reactions, mainly headache.

Discussion

In this pilot study a short regimen of Iloprost infusion (16 hours/day for 7 days) was as effective as standard Iloprost therapy (6 hours/day for 28 days) in reducing rest pain and in improving walking distance in patients with POAD at Leriche-Fontaine stage III. Although the study was not blind it must be pointed out that given the different infusion regimens tested in the study it could have been impossible to realize blind condition. Furthermore, on the one hand the magnitude of the improvements observed is consistent with other data published in literature for patients with similar baseline walking distance[17,18], on the other hand is likely to be far greater than a possible placebo effect (PWD: + 119% and + 119%; MWD +84% and + 85% respectively for Group A and Group B). The effects of the two different infusion schedules of Iloprost were equivalent also on the other evaluated parameters. In fact in both groups first flow significantly increased after 28 days. This finding is consistent with the hypothesis that Iloprost could be able to increase peripheral run-off. In addition, the observed trends to an increase of peak flow with concomitant reduction of time to peak flow, although not statistically significant, might further support the improved peripheral haemodynamics.

Finally, the two infusion shedules have shown similar effects also on microcirculation evaluated by means of laser Doppler. The trend to an increase in post ischemic flow suggests that Iloprost might be able to partially restore the vascular functional reserve without being influenced by the infusion schedule utilized. Overall these findings are consistent with data published by other authors[14,15].

In conclusion, in our patient population, a shorter, intensive Iloprost infusion regimen of 16 hours/day for 7 days at doses no greater than 1.5 ng/Kg/min, was as effective as the

Table II. Mean ± SD of laser-Doppler parameters by treatment. (Group A: 6 hrs/day - 28 days; Group B: 16 hrs/day - 7 days).

	T_0	T_7	T_{28}
Rest flow (pU)			
- Group A (n=10)	2.44 ± 2.02		2.65 ± 2.32
- Group B (n=10)	1.16 ± 0.75	1.76 ± 0.92	1.47 ± 0.65
Post-ischemic flow (pU)			
- Group A (n=10)	4.4 ± 2.7		5.79 ± 4.26
- Group B (n=10)	2.8 ± 2.05	3.57 ± 1.74	4.01 ± 2.91

Table III. Patients reporting side effects during the infusion by treatment. (Group A: 6 hrs/day - 28 days; Group B: 16 hrs/day - 7 days).

	Group A (n=10)	Group B (n=10)
Headache	9	4
Nausea, vomiting	1	2
Phlebitis	1	
Pain, lower limbs	1	

standard regimen of 6 hours/day for 28 days, up to 2 ng/Kg/min, in reducing rest pain, in increasing walking performance and in improving plethysmographyc parameters and, possibly, is better tolerated. Larger studies are needed to confirm this preliminary observation which could have important positive implications in terms of patient comfort and management and cost containment, at least for patients at Leriche-Fontaine stage III.

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