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The prostacyclin analogue Iloprost as an early predictor of successful revascularization in diabetic patients affected by critical limb ischemia and foot ulcers

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ABSTRACT

Purpose: The aim of this study is to evaluate the role of Iloprost as an early predictor of successful revascularization in patients affected by ischemic diabetic foot ulcers (DFUs).
Methods: Consecutive patients with ischemic DFUs with persistent low TcPO2 (<30mmHg) one day after a technical successful Percutaneous Transluminal Angioplasty (PTA) have been included.
All patients underwent Iloprost infusion and TcPO2 has been recorded at days 3, 14 and 30.
According to the TcPO2 reported at day 3, patients were divided into two groups: group A (patients with TcPO2 ≥30mmHg) and group B (patients with TcPO2 <30mmHg). Baseline TcPO2 values at days 3, 14 and 30 after Iloprost infusion and needing of re-intervention (re-PTA) have been evaluated.
Results: Twenty-five patients have been included, 12/25 (48%) in Group A and 13/25 (52%) in Group B.
There were no significant differences at the baseline and one day after PTA between the two groups while TcPO2 values recorded in Group A at days 3, 14 and 30 after Iloprost infusion were significant higher in comparison to the Group B ($\chi = 0.005$).
The rate of re-PTA were respectively 33,3% (Group A) and 53,8% (Group B) ($p = 0.03$).
Conclusions: Iloprost may be an early predictor of successful revascularization in patients affected by critical limb ischemia (CLI) and DFUs.

1. Introduction

Peripheral arterial disease (PAD) is an independent risk factor for ulceration and lower limb amputation in diabetic patients [1]. CLI is the most severe form of PAD. According to the Trans-Atlantic Inter-Society Consensus (TASC), CLI is defined as the presence of chronic ischemic rest pain and/or ulcers and/or gangrene attributable to objectively proven peripheral arterial occlusive disease: Transcutaneous Oximetry (TcPO2) <30mmHg, toe pressure <50mmHg, ankle pressure 50-70mmHg in patients with ischemic ulcers or 30-50mmHg in patients with ischemic rest pain [2]. CLI has a severe prognosis both in terms of lower limb amputation and death.

Both open and endovascular revascularization are first line therapies to treat PAD in diabetic patients. Nowadays, the use of PTA in diabetic patients is increasing. The effectiveness, feasibility and low operative risk of PTA justify its widespread use in diabetic patients affected by multiple co-morbidities [3–11].

The effectiveness of lower limb revascularization is often evaluated by TcPO2 [12–17]. TcPo2 is a non-invasive tool used to evaluate peripheral perfusion. It is useful to define the appropriate treatment [18,19], to predict the outcome after lower limb revascularization [12–15] and to determine the major amputation level [20,21].

It has been showed that TcPO2 values increase slowly also in case of effective revascularization; 2–3 weeks are often required to achieve the optimal TcPO2 values needing for wound healing [14].

For this reason, physicians are often not able to know the real effectiveness of revascularization the first weeks after PTA.

Iloprost is a synthetic prostacyclin analogue with a vasodilator effect. Its pharmacological properties have been documented in preclinical and clinical studies. [22–24]. Its use has been described as complementary therapy to the revascularization reducing arterial restenosis, increasing the run-off and reducing the risk of contrast-induced nephropathy [25,26].

Due to its vasodilator effects, Iloprost might early reveal a successful PTA by inducing a faster increase of TcPO2 values.

The purpose of the current study is to evaluate the usefulness of Iloprost as an early predictor of successful revascularization in diabetic patients affected by CLI and foot ulcers which show TcPO2 values <30mmHg immediately after a technically effective PTA.

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2. Material and methods

We included diabetic patients affected by CLI and foot ulcers which had a technically successful PTA without a corresponding increase of TcPO2 values the day after the revascularization (TcPO2<30mmHg). Verbal informed consent was obtained from all subjects involved in the study.

The patients underwent Iloprost infusion (0.5-2 ng/kg/min for 6 h) for three consecutive days after PTA.

TcPO2 was recorded at days three, 14 and 30 after the Iloprost treatment.

According to the TcPO2 values recorded at day three, patients were divided into two groups: group A including patients with TcPO2 ≥/>30mmHg and group B including patients with TcPO2 <30mmHg.

2.1. Revascularization procedure

All revascularization procedures were performed by endovascular technique. Angioplasty was performed in case of significant arterial stenosis (>50%) and/or obstruction. After a local anesthesia and a bolus injection of sodium heparin in the artery (usually 5000 IU), a preliminary angiographic study was performed. Guidewires were inserted to cross arterial obstruction followed by a balloon catheter to allow the required dilation. In selected patients self-expandable stents were applied. In some cases sub-intimal approach was adopted. Hydration regimen was provided by NaCl 0,9% for 12 h before and after the endovascular procedures. The amount of administered fluid depends on the cardiac functional capacity (on average 1 ml/kg/h). All patients were treated by aspirin (100 mg/die) and clopidogrel (75 mg/die) before the procedure and for one month after. Afterwards clopidogrel was discontinued. Long-term aspirin (100 mg) was recommended. In case of intolerance to aspirin or clopidogrel, ticlopidine was administered.

2.2. Transcutaneous oxygen tension measurement

TcPO2 was measured by an electrochemical transducer (Periflux 5000-PF 5040, Perimed, Jarfalla, Stockholm, Sweden). Testing was performed at the ambient room temperature with the patient resting in the supine position. The measuring side was cleaned using chlorhexidine solution. The transducer was placed on the dorsum of the foot in the first intermetatarsal space. Care was taken to avoid placement on bone or edema area. The transducer was fixed to the skin with an adhesive ring and the contact liquid was put inside the ring. Stable TcPO2 readings were achieved in 20 min.

2.3. Iloprost infusion

Iloprost was administered after dilution as an intravenous infusion over 6 h daily via a peripheral vein or a central venous catheter through an infusion pump. The blood pressure and heart rate were continuously monitored and measured at the beginning of the infusion and after every dose increase. The dose was adjusted according to individual tolerability within the range of 0.5 to 2.0 ng/kg body weight/min. The treatment was started at the infusion rate of 0.5 ng/kg/min for 30 min. Then, it was increased every 30 min of 0.5 ng/kg/min up to 2.0 ng/kg/min.

In case of headache, nausea or hypotension the infusion rate was reduced until the tolerated dose. In case of severe side effects, the infusion was interrupted. On the second day the infusion rate started from the highest tolerated dose achieved the first day of treatment.

2.4. Outcomes

The need of re-PTA has been considered as outcome. Re-PTA was considered in case of new revascularization due to non-healing and/or restenosis of treated vessels at the first PTA.

2.5. Statistical analysis

Statistical analysis was performed using SAS (release 8; SAS Institute, Cary, NC) for personal computers. Data are expressed as means ± standard deviation (SD). Comparisons between group characteristics was done with ANOVA (continuous data).

3. Results

Twenty-five patients were included. Twelve patients (48%) were included in Group A and thirteen patients (52%) in Group B.

The baseline characteristics of whole population, group A and B are reported in Table 1. The majority of patients were aged (mean age >65 years), male (84%) and had type 2 diabetes (96%) with a disease duration of ≈20 years. High blood pressure was recorded in 96% of patients. A history of coronary artery disease and cerebral ischemic attack was present respectively in 36% and 20% of patients. 12% of patients reported end stage renal disease (ESRD) requiring hemodialysis.

The rate of re-PTA was 44%, respectively 33,3% for group A and 53,8% for group B ($p = 0.03$).

There were not significant differences between the two groups concerning the treated vessels (Table 2).

TcPO2 values were recorded at the baseline, one day after PTA and at three, 15 and 30 days after Iloprost infusion. There were no significant differences at the baseline and one day after PTA between the two groups, while the values recorded in Group A at days three,14 and 30 after Iloprost infusion were significantly higher than values recorded in group B ($\chi = 0.005$) (Fig. 1).

Furthermore, in group A TcPO2 values were stably >30mmHg from day three to day 30 after Iloprost infusion while in the group B the TcPO2 values were <30mmHg at each evaluation.

4. Discussion

TcPO2 is often used as an instrumental follow up after lower limb revascularization. Some authors reported TcPO2 >30mmHg as cut off for adequate blood flow restoration after lower limb revascularization and wound healing [14–17].

Nevertheless, TcPO2 value may increase slowly also after technically successful lower limbs PTA [14,27]. These data suggest that the complete restoring of the microcirculation needs some weeks after revascularization.

Table 1
Baseline characteristics of the whole population, Group A (responders to Iloprost treatment) and Group B (no responders to Iloprost treatment).

N. patients	Total = 25	Group A = 12	Group B = 13	*p*-Value
Males (%)	84	83.3	84.6	0.93
Age (years)	69 ± 9.23	67.66 ± 8.6	70.2 ± 9.9	0.49
Type 2 DM (%)	96	91.7	100	0.21
DM duration (years)	23.64 ± 14.68	26.7 ± 17	20.7 ± 12	0.32
A1c (%)	7.57 ± 1.52	7.64 ± 1.7	7.5 ± 1.3	0.83
Smokers (%)	24	33.3	15.38	0.3
Dialysis yes (%)	12	8.3	15.4	0.6
Stroke (%)	20	8.3	30.8	0.1
Hypertension (%)	96	100	92.3	0.2
Ischemic heart disease (%)	36	33.3	46.1	0.5
LDL cholesterol (mg/dl)	100.12 ± 36.19	103.7 ± 40.7	96.7 ± 32.8	0.6
Infection (yes %)	88	83.3	92.3	0.48
Texas WC stage: C (%)	8	8.33	7.69	0.9
Texas WC stage: C + D (%)	92	91.67	92.31	0.9
Texas WC grade: 1 (%)	20	8.33	30.77	0.2
Texas WC grade 2 (%)	4	8.33	–	0.2
Texas WC grade: 3 (%)	76	83.33	69.23	0.2
Ulcer area > 5 cm^2 (%)	60	75	46.1	0.1

DM: diabetes mellitus; A1C: glycated hemoglobin; LDL: low density lipoprotein; WC: wound classification.

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Table 2
Description of vessels treated by peripheral angioplasty.

Artery underwent to angioplasty	Total	%	Group A	Group B	*p*-Value
Iliac tract	4	8.3	2	2	ns
Profunda femoral artery	0	0	0	0	ns
Superficial femoral artery	14	29.1	8	6	ns
Popliteal artery	8	16.6	3	5	ns
Anterior tibial artery/pedis artery	9	18.7	6	3	ns
Posterior tibial artery/plantar arch	7	14.6	3	4	ns
Peroneal artery	6	12.5	3	3	ns

ns: not statistically significant.

Furthermore, in order to ensure an adequate foot perfusion according to TcPO2 values, in some cases, elective surgery may be delayed by 2–3 weeks after revascularization.

The reflow injury due to the restoration of blood flow to previously ischemic organs and tissues could be a hypothesis to explain the late increase of TCPO2 value. The reflow injury has been described after revascularization procedures in case of acute ischemia. It is due to the release of pro-inflammatory cytokines and oxygen radicals, up-regulation of endothelial and leukocyte adhesion molecules and activated interactions between leukocytes and endothelial lining [28–30].

The same effect might explain the microcirculation alterations and the endothelium-dependent vasodilatation.

Several studies showed the role of Iloprost in reducing the reflow injury [31].

Iloprost interferes with several mechanism involved in this specific inflammatory response. It reduces the release of free radicals and cytokines, interferes with platelet activation and blood clotting and reduces the expression of intracellular adhesion molecules. [22,32–34]

In line with the published literature, the current study confirms that TcPO2 values usually increase slowly despite a technically effective endovascular revascularization.

However, Iloprost infusion in patients with low TcPO2 values after revascularization allowed to identify two groups, one with an early increase of TcPO2 values and another without.

Our study highlights the usefulness of Iloprost as an early predictor of successful revascularization in diabetic patients affected by CLI and foot ulcers. In fact, patients showing an increase of TcPO2 after Iloprost therapy needed less re-PTA than patients showing persistent low TcPO2.

Therefore, in some cases the use of Iloprost may be recommended to know immediately the effectiveness of revascularization and to plan the timing of surgical approach.

In fact, an optimal response to Iloprost showed by the fast increase of TcPO2 allows an early surgical approach and a reconstructive step. Otherwise, a failed increase of TcPO2 after Iloprost infusion (as occurred in 50% of patients) is usually related to a persistence of foot ischemia requiring a new revascularization.

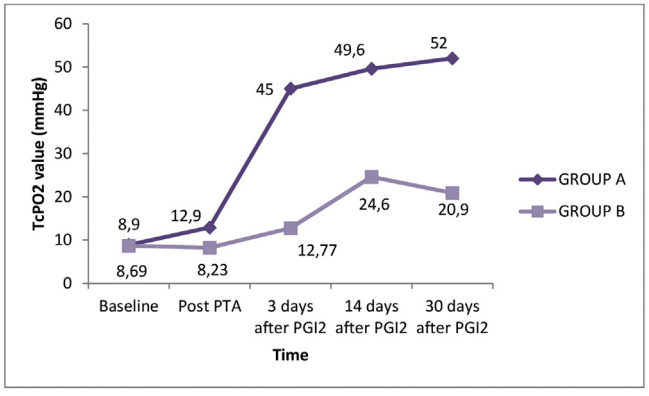

Fig. 1. TcPO2 values recorded before and one day after PTA and at 3, 14 and 30 days after the prostacyclin analogue Iloprost, according to Group A and Group B ($\chi = 0.005$). PTA: percutaneous transluminal angioplasty PGI2: prostacyclin analogue.

5. Conclusions

The use of Iloprost in patients with persistent low TcPO2 values after a technically successful revascularization may help clinicians to identify the need of a new revascularization or to plan an early surgical approach.

Conflicts of interest

None.

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