

Original Article

Contribution of prostaglandin E1 treatment in patients with critical limb ischemia

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Abstract: Background and aims: Peripheral arterial disease (PAD) in advanced stages has severe disabling complications. Major amputations (MA) and high mortality rates are common in patients with critical limb ischemia (CLI). Revascularization (interventional angioplasty or vascular surgery) appears to be possible in the large majority of cases if these patients are referred to a specialist earlier. Patients with CLI and lacking options for revascularization have worse prognosis. The purpose of this retrospective study was to investigate the impact of including prostaglandins in the treatment of patients with CLI lacking the possibility of revascularization. Method: This retrospective study cohort includes 67 patients (34 male and 33 female), mean age 71 ± 10.7 years treated for CLI not suitable for revascularization. Prostaglandin E1 (alprostadil) was applied by intravenous perfusion with doses of 40 μg twice a day for 2 weeks. Results: 23 patients (34.3%) underwent amputation and 17 patients (40.3%) died during the total follow-up period (01/2009-07/2014). Mortality rate was higher in patients who have undergone an amputation, in diabetics and in patients without statin medication. Conclusion: Patients with CLI lacking options for revascularization have despite treatment with prostanoids (alprostadil) a poor prognosis, with high amputation rate and increased mortality. Statin medication was a protective factor for survival.

Keywords: Peripheral arterial disease, critical limb ischemia, prostaglandin treatment, major amputations, prognosis

Introduction

Peripheral arterial disease (PAD) is a severe illness with life-threatening complications. Critical limb ischemia (CLI), as the most advanced stage of PAD, is characterized by the presence of rest pain or ulceration or gangrene on the leg, or toes. Foot ulcers involve dramatic restrictions in the quality of life and also lead to enormous socio-economical loss, due to high amputation rate. Revascularization (endovascular, open surgery, or hybrid) is the priority treatment option in CLI. However, there are many patients in whom revascularization is not possible, or advisable, so further therapeutic approaches must be considered, in order to avoid major complications. This includes methods aiming for the improvement of limb perfusion such as

prostaglandin treatment. The aim of our retrospective study was to evaluate the benefit of addition Prostaglandin E1 intravenous to their treatment, in patients with critical limb ischemia, from the prognostic point of view.

Materials and methods

Subjects

We retrospectively analysed 67 hospitalized patients with critical limb ischemia not suitable for revascularization. Analysed patients were admitted to the 2nd Department of Internal Medicine in the years 2009-2013 and the final follow-up was dated on 1st of July 2014. Critical limb ischemia was defined as persistently recurring rest pain, which requires analgesic therapy,

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Table 1. Clinical and biochemical characteristics of the cohort

Variables	Study group (n = 67)
Age (years)	71.2 ± 10.7
Gender - male, n (%)	34 (50.74%)
Weight (kg)	79.8 ± 21.1
Height (cm)	168.0 [161.0-175.0] ⁺
BMI (kg/m ²)	27.06 [23.05-30.60] ⁺
Serum creatinine (µmol/L)	82.0 [72.1-103.4] ⁺
Serum Urea (mmol/L)	7.26 [5.56-8.66] ⁺
Total cholesterol (mmol/L)	4.8 ± 1.5
LDL (mmol/L)	2.9 ± 1.12
HDL (mmol/L)	1.2 [0.99-1.46] ⁺
TAG (mmol/L)	1.3 [0.90-1.81] ⁺
Diabetes mellitus - n (%)	37 (55.2%)
Statin therapy - n (%)	42 (62.7%)
ABI on right lower limb	0.64 [0.38-0.96] ⁺
ABI on left lower limb	0.57 [0.38-0.91] ⁺
Medial calcinosis (ABI ≥1.4)	6 (8.96%)
Angiography - n (%)	60 (89.55%)
Amputation - n (%)	23 (34.3%)
Death - n (%)	27 (40.3%)

BMI - body mass index, LDL - low density lipoprotein cholesterol, HDL - high density lipoprotein cholesterol, TAG - total triglycerides, ABI - ankle-brachial index, n - number. Results are shown as mean ± standard deviation (SD) or median [interquartile range]⁺.

lasting longer than 2 weeks, with systolic pressure in the region of the ankle < 50 mmHg or on the thumb < 30 mmHg, or presence of ulceration or gangrene on the leg or toes with transcutaneous oxygen tension $TcPO_2$ < 10 mmHg in afflicted region. 13 patients had rest pain (Fontaine stage III, Rutherford stage 4) and 54 had ischemic ulcers or frank gangrene (Fontaine stage IV, Rutherford stage 5 or 6). Ankle/brachial pressure index (ABI) was determined using BOSO ABI-system 100 equipment, Germany in the whole study group. Patients were afterwards treated with infusion of Prostaglandin E1 (alprostadil) 40 µg twice a day in 250 ml 0.9% saline solution into the cubital vein over 120 minutes for 2 weeks during hospitalization. Measurement of blood pressure, pulse frequency and electrocardiogram were performed before and after every prostaglandin treatment.

Statistical analysis

Data were analysed with GraphPad Prism 5 software for Windows. The Kolmogorov-Smirnov

test was used to verify the normal distribution of parameters in the cohort. Results were reported as the mean ± standard deviation or median and interquartile ranges. Overall mortality was assessed using the Kaplan-Meier curves.

Results

We retrospectively analysed 67 patients with critical limb ischemia (34 males and 33 females). Mean age of patients was 71.24 ± 10.73 years. 5 patients did not complete the whole treatment, due to adverse effects (mainly hypotension) of the prostaglandins therapy in 3 patients and 2 patients died during the time of hospitalization. Basic characteristics of patients are shown in **Table 1**. Mean ABI was on the right limb 0.64 [0.38-0.96] and on the left limb 0.57 [0.38-0.91]. Medial calcinosis defined as ABI ≥ 1.4 was present in 6 patients (8.96%). 17 patients (25.37%) underwent minor amputation, 6 patients (8.96%) had high amputation of the lower limb and 27 patients (40.30%) died until the final follow-up (**Table 1**). Mortality was higher in patients with lower limb amputation (**Figure 1**) and in diabetic patients (**Figure 2**). We observed lower mortality in patients with CLI and statin therapy (**Figure 3**).

Discussion

Impaired endothelial function is considered to be an important contributor factor in the development of atherosclerosis and its complications. The injured endothelium is unable to protect the vascular wall, against vasospasm and local thrombosis, because of the reduced bioavailability of nitric oxide and prostacyclin, which are powerful vasodilating and anti-platelet agents [1]. Several studies showed that patients with symptomatic PAD have increased risk of death, several cardiovascular events and loss of the limbs, especially in those with CLI. This poor outcome might be associated with the fact that PAD and CLI are often underdiagnosed and undertreated diseases. Long-term outcomes, such as death and amputation rates, are highly increased in patients with Fontaine IV stage (explain, please) [2]. Average incidence of CLI in Europe, is estimated to be around 450 cases per one million inhabitants. The relative risk of major limb amputation is 50% in patients that do not undergo revascularization and 26% in individuals that underwent revascularization, while the relative risk

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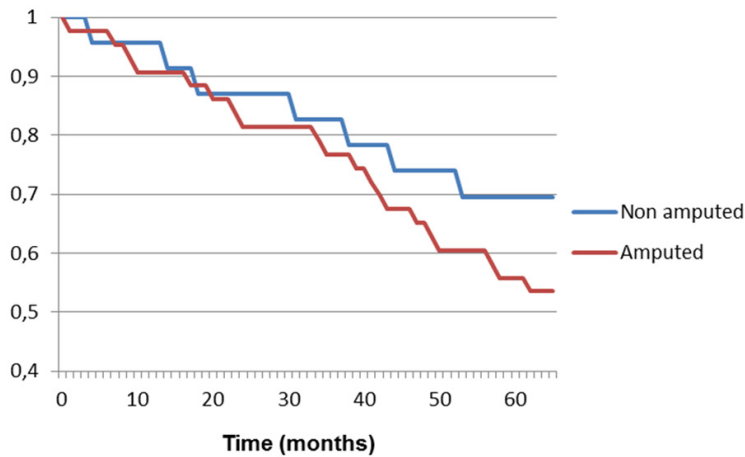


Figure 1. Mortality curves according to the presence of lower limb amputation ($P < 0.01$).

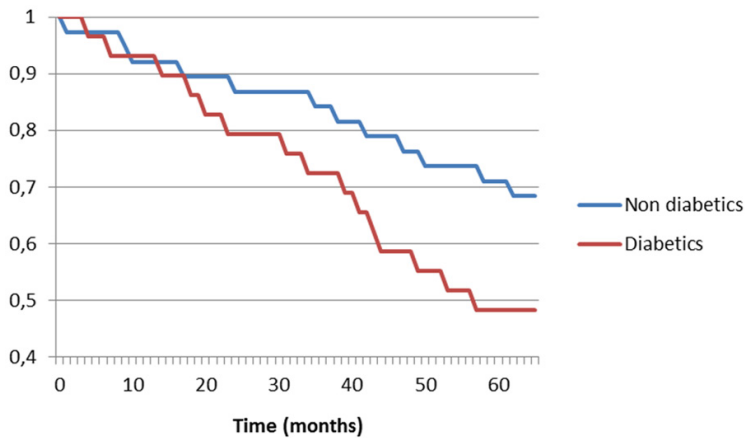


Figure 2. Mortality curves according to the presence of diabetes mellitus ($P < 0.001$).

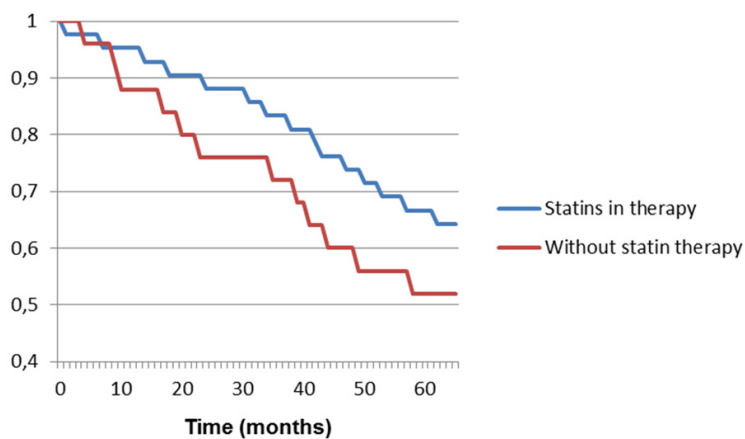


Figure 3. Mortality curves according to the statin medication ($P < 0.01$).

for death is 50% and 18% respectively. Although amputation is associated with a poor prognosis, 1/3 of amputated patients die within 1 year, 1/3 achieves partial autonomy and only 1/3 of patients obtain complete autonomy [3]. In our project we observed higher rate of amputations (34.3%) which is in accordance with other studies with CLI [4].

PAD and CLI are connected with multiple systemic alterations including heart, brain, and kidney associated diseases. Advanced systemic alterations in CLI patients, such as diabetes mellitus and heart failure, are related with an increased mortality. We proved that diabetes mellitus was strongly associated with higher mortality rate, which was shown as well in previous study with 28,517 patients with CLI [5, 6].

Low ABI is an independent predictor factor of cardiovascular risk, 10-years cardiovascular mortality is 4.2 times higher in men and 3.5 times in women, with low ABI [7]. According to Framingham Risk Score (FRS) a low ABI is associated with higher 10-years total mortality, cardiovascular mortality and higher rate of major coronary events [8]. Medial calcinosis is connected with an increased cardiovascular and global mortality, as well [9]. Risk for serious cardiovascular events is in patients with medial calcinosis, the same as in patients with PAD and $ABI \leq 0.7$ [10, 11].

Treatment of CLI with prostaglandins is not a new option. The impact of prostaglandins in the treatment of PAD, is still controversial. Short-term studies in subjects with CLI had not shown

clear results, there was no ulcer healing, or pain reduction, in a great part of these studies. Although, the majority of long-term studies in patients with CLI, demonstrated a clear reduction of pain and ulcer size, some of these studies indicate a reduced major amputation in study groups. Prostaglandins treatment improves the claudication, the walking capacity and the quality of life [12]. A meta-analysis of the administration of prostaglandin E1, for patients with PAD stages III or IV (Fontaine) not eligible for arterial reconstruction, has shown that it does not have significant beneficial effects over placebo on ulcer healing and pain relief, but also increases the survival rate after 6-months of follow-up [13].

We observed lower mortality rate in the subgroup with statin treatment, which was a protective factor in CLI patients in this cohort. The benefits of statins for morbidity and mortality have been already shown by various studies, not only in patients with ischemic heart disease, but also in patients with PAD. Statins treatment is associated with lower mortality rate, cardiac and cerebrovascular events, as well as with increased amputation-free survival in CLI patients [14].

Conclusions

Patients with PAD and CLI have poor outcomes, regarding amputations and mortality rate. Our results showed that therapeutic strategies using prostaglandin treatment in patients with CLI without options for revascularization, might reduce amputation its rate, but do not affect the overall mortality in these patients. Patients with a history of diabetes mellitus, amputation of lower limb and without statin treatment have higher mortality rate. We have confirmed that statin therapy seems to be a protective factor for patients with CLI.

Disclosure of conflict of interest

None.

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