

The effectiveness of Autologous Peripheral Blood Mono-Nuclear Cells implant in subjects with diabetes with no-option chronic limb-threatening ischemia

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INTRODUCTION

Implantation of autologous peripheral blood mononuclear cells (PBMNCs) is an innovative therapeutic approach in the treatment of patients with no-option Chronic Limb-Threatening Ischemia (CLTI).

PBMNCs have been shown to have a strong angiogenesis capacity together with the ability to immuno-modulate chronic wound tissue through polarization of macrophages from the M1 inflammatory to the M2 regenerative phenotype (1-2)

This approach consists in the inoculation in the perilesional area and along the vascular axis of the affected lower limb of a concentrate of mononuclear cells taken from peripheral blood by using a selective filtration separation system. The angiogenic effect is mainly linked to a paracrine release effect by monocytes of angiogenic cytokines (in particular VEGF and bFGF) and growth factors (3).

AIM OF THE STUDY

The main objective of this study is to evaluate PBMNCs effectiveness in diabetic patients with no option CLTI.

METHODS

We performed a retrospective, observational study recruiting consecutive subjects treated from October 2018 to October 2021 with PBMNCs at our Diabetes Center because of diabetic foot ischemic lesions complicated by Wifl Stage 4 no-option CLTI. Patients were considered no option if deemed not revascularizable by conventional angioplasty or distal bypass after at least one endovascular intervention attempt performed by a senior experienced operator thus defining a condition of very high major amputation risk. Patients that required primary major amputation were excluded. PBMNCs were produced in the operatory room by selective filtration point of care system (Athena MonoCells Solution Kit, Italy) and immediately implanted, after appropriate surgical debridement of the wound bed, by multiple perilesional and intramuscular injections for a maximum of three times for each patient at intervals of 30-45 days from each other. The occurrence of major amputations and the number of healed patients were the primary study outcomes. As a secondary outcome we calculated mean TcPO₂ value at 1-3 weeks after the last PBMNCs injection. A t-test for paired data was used to compare pre and post operative TcPO₂ mean values.

RESULTS

Overall, 59 patients (mean age 71.9±10.7 years, disease duration 26.5±13.4 years, mean HbA1c levels 63.1±15.3 mmol/mol, 81.4% males) were studied. Baseline characteristics are listed in Table 1.

Among all, 32% (n=19) had only one PBMNCs injection, 15.3% (n=9) had two injections and 52.5% (n=31) had three injections. After excluding losses to follow-up (n=11, 18%), healing and major amputations were recorded in 54.1% (n=26) and 25 % (n=12) of the cases, respectively. Remaining patients (n=10, 17%) were, at the end of follow up, still ulcerated but did not undergo any major amputation. No procedure-related adverse effects were recorded.

While pre-operative TcPO₂ values were available for all included patients, it was possible to retrieve post-operative TcPO₂ data only for 27.1% (n=16) of patients. The mean post-operative TcPO₂ value on this group was significantly increased compared to pre-operative readings (mean increase in TcPO₂ 27.1 mmHg, CI_{95%} 13.7-40.5, p=0.002).

Table 1- Inclusion criteria

Age above 18 years old
Being affected by Diabetes Mellitus
Accessing diabetic foot referral centre for ischemic lesions
Being diagnosed with No-Option CLTI (see text for definition on No-Option)
Not in need of primary major amputation

Figure 1: Selective filtration of PBMNCs and injection

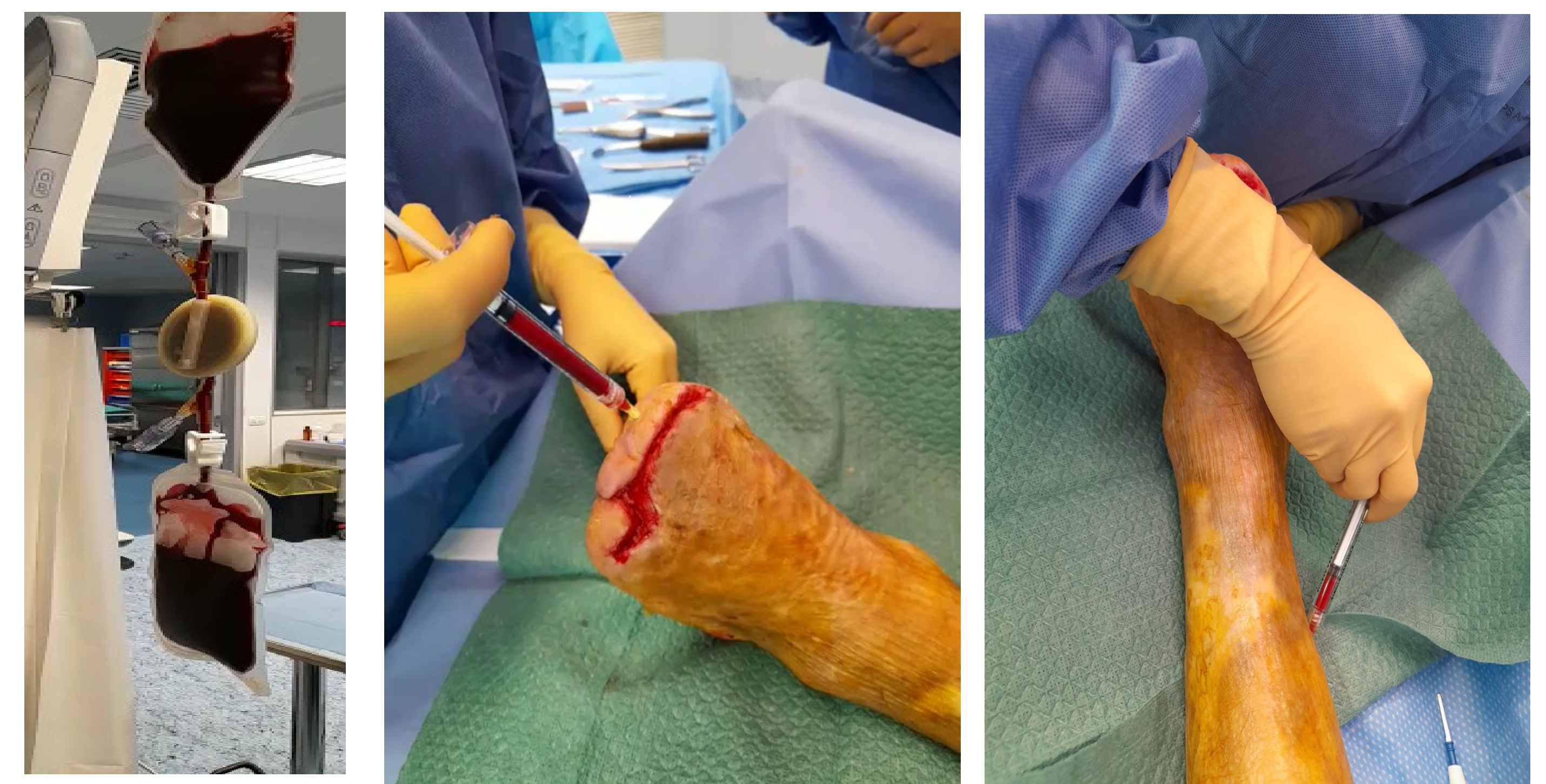


Table 3. Baseline clinical characteristics of the study sample (n=59)

Continuous variables expressed as mean ± Standard Deviation, Proportions expressed as percentage
Unit of Measure in brackets

Age (years)	71.9 ± 10.7
Diabetes duration (years)	26.5±13.4
HbA1c levels (mmol/mol)	63.1±15.3
Male sex (%)	81.4
Type 1 Diabetes (%)	11.9
Type 2 Diabetes (%)	88.1
Dialysis (%)	8.5
Ischemic Heart Disease (%)	54.1
Diabetic Retinopathy (%)	58.0
Diabetic Peripheral Neuropathy (%)	59.2
Rheumatologic Disease (%)	5.1
History of contralateral limb amputations (%)	33.9
History of ipsilateral limb amputations (%)	40.7
Current smoker (%)	18.6
Past smoker (%)	18.6
Creatinine (mg/dl)	1.6 ±1.4
Baseline dorsal foot TcPO ₂ (mmHg)	25.4
Main lesion located on forefoot (%)	62.7
Main lesion located on midfoot (%)	15.3
Main lesion located on hindfoot (%)	16.9
Main lesion located on leg (%)	5.1

CONCLUSIONS

The use of PBMNCs appears to be an effective and safe therapeutic option to prevent major amputation and promote healing in no-option CLTI patients.

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