Recurrence of Critical Limb Ischemia After Endovascular Intervention in Patients with Diabetic Foot Ulcers

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Objective: To establish the rate of clinical recurrence of critical limb ischemia (CLI) in diabetic patients with ischemic foot ulcers (DFUs) treated by percutaneous transluminal angioplasty (PTA).

Approach: The study group was composed of 304 patients with ischemic DFUs treated by PTA. We evaluated the rate of clinical recurrence of CLI requiring a second PTA (repeated PTA [rePTA]), the factors related to CLI relapse, and the outcomes of rePTA patients. The follow-up was 12.5 ± 6.6 months.

Results: Seventy-four of 304 patients (24.3%) needed rePTA. The mean time to rePTA was 3.5 ± 0.64 months. rePTA group in comparison with no rePTA group had lower rate of healing (28.5% vs. 71.9% $p=0.0001$), higher rate of ulcer recurrence (20% vs. 10.3% $p=0.03$), major amputation (24.3% vs. 4.3% $p=0.0005$), and death (33.3% vs. 7.9% $p=0.002$). Glycated hemoglobin, type A1C (HbA1c; 2.2 [1.9–2.7] $p=0.02$) and dialysis (1.5 [1.4–3.6] $p=0.006$) were independently associated to clinical recurrence of CLI after PTA.

Innovation: To identify the outcomes of patients with clinical recurrence of CLI and the clinical factors involved to reduce the rate of restenosis after endovascular treatment and improve the rate of limb salvage.

Conclusions: Clinical recurrence of CLI is associated with a high rate of nonhealing ulcer recurrence, major amputation, and death. Dialysis and impaired glycemic control were independent predictors of CLI relapse after endovascular treatment.

Keywords: diabetes, diabetic foot ulcers, critical limb ischemia, revascularization, limb salvage

INTRODUCTION

PERIPHERAL ARTERIAL DISEASE (PAD) is a severe complication of diabetes and can be found approximately in 50% of subjects with diabetic foot ulcers (DFUs).^{1–3} PAD is a strong risk factor for major amputation,^{4,5} and peripheral revascularization, surgical, or endovascular is the only therapeutic option. The role of percutaneous transluminal angioplasty (PTA) in di-

abetic patients with critical PAD, especially infrapopliteal disease, is well recognized.^{6–14} Several studies have documented good results in terms of feasibility, technical efficacy, reduced number of complications, and limb salvage rate. Furthermore, PTA can also be performed in patients who cannot be candidates for open surgery due to the presence of several comorbidities.^{7,8,15,16}

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CLINICAL PROBLEM ADDRESSED

Despite the great results obtained through endovascular revascularization in the last years, the current problem is the frequent restenosis after PTA, requiring a second approach. In fact, in comparison to by-pass, PTA is characterized by higher rate of restenosis.^{17–20} Although angioplasty can be easily repeated in case of restenosis or reocclusion,^{21–23} the early and frequent recurrence of critical limb ischemia (CLI) influences the clinicians approach and affects the outcomes of patients with ischemic DFUs. In our limb salvage protocol, all patients affected by DFUs and CLI are treated by revascularization, usually by endovascular approach. After hospitalization, they undergo a close follow-up until the ulcer has healed. In case of recurrence of CLI in the affected limb, the patients are considered for a new revascularization repeated PTA (rePTA). The aim of our study was to establish the rate of rePTA in diabetic patients with DFUs and CLI. Then, we evaluated the outcomes of rePTA patients and the specific factors related to the relapse of CLI in these subjects.

MATERIALS AND METHODS

The study group composed of 304 subjects with DFUs and CLI, who were followed up in our diabetic foot unit. All patients underwent a limb salvage protocol: surgical debridement of infected tissues or gangrene, antibiotic therapy in case of infection, offloading of affected foot, and revascularization. All peripheral revascularizations have been performed through endovascular approach.²⁴

An informed verbal consent was obtained from subjects involved in this study.

PTA procedure

Percutaneous angioplasty was performed in the presence of significant arterial stenosis (>50% of lumen) and/or obstruction. In selected patients, self-expandable stents were inserted in 5- to 8-mm diameter vessels. Stents were not placed below the popliteal arteries as the risk of thrombosis was very high in such low-flow vessels. In selected patients, the subintimal approach was used to create a new lumen between intimal and medial layers.

Before and after PTA, the patients were treated by dual antiplatelet therapy (Cardioaspirin 100 mg plus Clopidogrel 75 mg or Ticlopidine 250 mg $\times$ 2 in case of intolerance to Cardioaspirin or Clopidogrel) at least for 1 month and after only by Cardioaspirin or Clopidogrel long life. All cardiovascular risk factors (smoke, hypertension, dyslipidemia, and hyperglycemia) were checked and treated if required. According to our protocol, after hospitalization, the patients have been regularly followed

up in our Diabetic Foot Unit until ulcer healing. Recurrence of CLI was considered in case of non-healing (absence of granulation tissue, absence of epithelialization signs, and reduction of ulcer size less than 50% after at least 4 weeks of standard of care), recurrence of pain, and ulcer relapse in association with transcutaneous oxygen pressure (TcPO₂) <30 mmHg and/or positive duplex scanning. If clinical signs of ischemia were supported by instrumental evaluation, the patients were considered for another angiographic evaluation and treated by a new PTA (rePTA) if required.

We evaluated the rate of patients who needed rePTA, the mean time to rePTA, the predictive factors related to the recurrence of CLI and the outcomes according to rePTA or not expressed as healing, major amputation, and death. Healing was considered in case of complete epithelialization of previous ulcers. Amputation above the ankle was considered major amputation. Amputation free-survival after PTA for rePTA and no rePTA groups was reported by Kaplan–Meier analysis.

Statistical analysis

Statistical analysis was performed by SAS (JMP12; SAS Institute, Cary, NC) for personal computer. Data are expressed as means $\pm$ SEM. Comparison between groups was reported by a χ^2 -test (frequency data) or ANOVA (continuous data). Univariate logistic analysis was performed for all potential predictor variables according to the detected outcome. All predictors identified by univariate analysis were evaluated simultaneously in a multivariable regression. $p < 0.5$ was considered as statistically significant.

RESULTS

Table 1 reports the baseline characteristics of the whole population, rePTA group, and no rePTA groups. Three hundred four patients were treated by PTA. In 57 (18.7%) cases a stent was applied in iliac-femoral district; 52 (17.1%) patients were treated by subintimal approach. Fourteen (4.6%) patients had minor PTA technical complications. In 4/304 (1.3%) cases, there was a distal embolization; in 4/304 (1.3%), an arterial dissection; and in 6/304 (2%), a retroperitoneal bleeding (hematoma). Three of four patients with distal embolization needed major amputation due to severity of foot ischemia and untreatable pain. The follow-up was 12.5 ± 6.6 months.

Restenosis after PTA

Seventy-four of 304 patients (24.3%) needed rePTA after the first treatment. The mean time to rePTA was 3.5 ± 0.64 months. In 70/74 (94.2%)

Table 1. Baseline characteristics of the whole population, rePTA group, and no rePTA group

	General	rePTA	No rePTA	p
Sex (male)	72%	68.5%	73.5%	0.64
Age (years)	68.3 ± 10.9	67.1 ± 10.1	68.7 ± 11.5	0.49
Diabetes (type 2)	91.1%	88.2%	91.7%	0.55
Diabetes duration (years)	21 ± 1.6	20.3 ± 2	21.4 ± 1.2	0.63
HbA1c (mmol/mol)	61.4 ± 22.8	67.6 ± 23.2	58.6 ± 21.6	0.05
Smoke	9%	9.3%	10%	0.91
Hypertension	79.5%	75.8%	80%	0.61
Dyslipidemia	64%	71.7%	62.5%	0.23
Dialysis	31.4%	54%	24.5%	0.001
IHD	68%	78.8%	63.1%	0.09
Heart failure	38.4%	45.5%	35.5%	0.31
Anemia	75%	91.2%	68.8%	0.005
Ulcer size (>5 cm ²)	68.6%	73.5%	65.6%	0.39
Infection	70.5%	70.6%	69.4%	0.89
Osteomyelitis	68.8%	82.3%	63.4%	0.14
Heel Ulcer	25.7%	38.2%	19.3%	0.03

HbA1c, glycated hemoglobin, type A1C; IHD, ischemic heart disease; PTA, percutaneous transluminal angioplasty; rePTA, repeated PTA.

cases, there was a restenosis of vessels treated at the first approach; in 4/74 (5.8%) cases, there was a restenosis and a progression of PAD too (stenosis or occlusion of new vessel not affected at the first PTA). Superficial femoral artery (SFA) was treated for a second time in 40/243 (16.4%) of cases, popliteal artery in 18/98 (18.3%), tibial-peroneal trunk in 8/93 (8.6%), anterior tibial artery in 23/182 (12.6%), peroneal artery in 8/98 (7.8%), and posterior tibial artery in 20/148 (13.5%).

Table 2 reports the arterial pattern disease of the whole population and separately of rePTA group and no rePTA group. At baseline, rePTA had more vessels affected, a higher involvement of peroneal, pedal, and plantar arteries than no rePTA group. Furthermore, rePTA group had lower increase of TcPO₂ after endovascular intervention than no rePTA group.

Outcomes

rePTA patients had a lower rate of healing (28.5% vs. 71.9%) $p=0.0001$, higher rate of ulcer recurrence (20% vs. 10.3%) $p=0.03$, major amputation (24.3% vs. 4.3%) $p=0.0005$, and death (33.3% vs. 7.9%) $p=0.002$ in comparison with no rePTA group (Fig. 1).

Time to amputation for rePTA and no rePTA group was, respectively, 2 ± 0.7 and 4.6 ± 1.7 months ($p=0.03$).

Time to ulcer recurrence for rePTA and no rePTA group was, respectively, 6.7 ± 2 and 10.9 ± 1.7 months ($p=0.13$).

At multivariate analysis of independent variables found at the univariate analysis, impaired glycemic control (glycated hemoglobin, type A1C [HbA1c]) (2.2 [1.9–2.7] $p=0.02$) and dialysis (1.5 [1.4–3.6] $p=0.006$) were independent predictors of clinical recurrence of CLI.

Table 2. Arterial pattern disease of the whole population, rePTA group, and no rePTA group

	General (n = 304)	rePTA (n = 74)	No rePTA (n = 230)	p
Vessels affected	4.4 ± 1.5	5.1 ± 1.6	4.2 ± 1.4	0.001
Vessels treated at first PTA	2.6 ± 1.2	2.4 ± 1	2.6 ± 1.2	0.5
Iliac	12/304 (3.9%)	8/74 (10.8%)	4/230 (1.7%)	0.09
CFA	2/304 (0.6%)	0/74 (0%)	2/230 (0.8%)	0.43
Profunda	10/304 (3.2%)	0/74 (0%)	5/230 (2.1%)	0.09
SFA	243/304 (79.9%)	60/74 (81.1%)	183/230 (79.5%)	0.91
Popliteal	106/304 (34.8%)	25/74 (33.8%)	81/230 (35.2%)	0.76
TTP	101/304 (33.2%)	32/74 (43.2%)	69/230 (22.7%)	0.09
ATA	262/304 (86.2%)	67/74 (90.5%)	195/230 (84.8%)	0.4
Peroneal artery	170/304 (55.9%)	53/74 (71.6%)	117/230 (50.8%)	0.02
PTA	248/304 (81.5%)	65/74 (87.8%)	183/230 (79.5%)	0.29
Pedal artery	100/304 (32.9%)	34/74 (45.9%)	66/230 (28.7%)	0.03
Plantar Arteries	107/304 (35.2%)	37/74 (50%)	70/230 (30.4%)	0.04
Subintimal approach	52/304 (17.1%)	14/74 (18.9%)	38/230 (16.7%)	0.7
Stent	57/304 (18.7%)	13/74 (17.5%)	44/230 (19.1%)	0.8
TcPO ₂ 1 (mmHg)	42.7 ± 13.5	32.5 ± 11.3	45.4 ± 12.8	0.0001

ATA, anterior tibial artery; CFA, common femoral artery; SFA, superficial femoral artery; TcPO₂, transcutaneous oxygen pressure; TTP, tibioperoneal trunk.

Figure 1. Outcomes in rePTA and no rePTA group. PTA, percutaneous transluminal angioplasty; rePTA, repeated PTA.

DISCUSSION

To our knowledge, there are few studies assessing the risk of clinical restenosis and the factors related to CLI relapse in diabetic patients with CLI with foot tissue loss. Faglia *et al.* described the extensive use of peripheral angioplasty and the risk of clinical recurrence of ischemia after PTA in diabetic patients with ischemic foot ulcer, even though specific risk factors related to restenosis were not described.^{8,13}

The authors reported a low risk of restenosis in diabetic patients with ischemic foot ulcers treated by PTA: 7.3% after 4 months in a first study⁸ and 6.4% per year in a second one.¹³ In a similar group of patients treated by PTA, our group reported 9.6% of clinical ischemia recurrence in ~20 months of follow-up.⁷

Our data confirm that PTA is characterized by a certain risk of restenosis. We found that ~24% of patients had rePTA because of the recurrence of CLI. In all cases, the reintervention was due to the restenosis of treated vessels. Probably the morphological rate of restenosis is higher than clinical CLI relapse. However, from our clinical point of view, when ulcer heals and pain disappears, the possible restenosis of treated vessels is not relevant.

We found a higher rate of clinical CLI relapse than data reported by Faglia (6.4 and 7.3%) and Uccioli (9.6%); however, our cohort of subjects was characterized by several comorbidities, mainly dialysis. In fact, in our study, the rate of dialyzed patients is higher than in similar studies (31.4% vs. 3.7%, 6.0% and 12.8%).^{7,8,13} In addition, dialysis resulted in an independent risk factor for clinical recurrence of CLI in the above mentioned patients. In our opinion, this element could justify the high rate of restenosis found in our population.

SFA and popliteal artery showed a higher rate of restenosis than infrapopliteal vessels, and the mean time to rePTA was ~3.5 months; therefore, the first months after revascularization should be considered the critical period for restenosis. rePTA patients showed a high risk of nonhealing, major amputation, and death, as this group was made up of subjects with more comorbidities that could influence the worst outcomes than no rePTA patients. However, already in other studies, a high risk of major amputation in patients with restenosis after revascularization has been reported.²⁵ Furthermore, rePTA patients showed a high risk of ulcer recurrence than no rePTA patients.

We found that dialysis and high glycemic levels significantly increased the risk of rePTA. Dialysis is a well-recognized risk factor for PAD, and dialyzed patients have high risk of nonhealing, major amputation, and death.^{26–29} In our recent study, we already reported that dialyzed diabetic patients had a higher rate of rePTA when compared with the nondialyzed.³⁰ Therefore, we can confirm that dialysis is a strong and specific risk factor of CLI relapse in diabetic patients with DFUs.

In relationship to glycemic levels, the association between glycemic control and outcomes has been extensively studied mainly for coronary artery procedure (balloon angioplasty).^{31–35} Both preprocedural HbA1c and fasting blood glucose have been evaluated with mixed results.^{32,34} In fact, some studies highlighted the role of hyperglycemia as risk factor for restenosis after percutaneous coronary intervention, while the role of HbA1c and insulin resistance is less clear.³⁶ The neointimal proliferation, after both balloon angioplasty and stenting, seems to contribute to the high rate of restenosis in diabetic patients.³⁷ To our knowledge, only one study described the risk of restenosis in relationship to glycemic levels after lower limbs angioplasty. Singh *et al.* reported that high blood glucose levels (>144 mg/dL) during infrapopliteal balloon angioplasty was associated with a significant reduction of primary patency and increased risk of major amputation in patients with CLI and tissue loss.³⁸ Our data show that impaired glycemic control expressed by elevated values of HbA1c is an independent risk factor for clinical recurrence of CLI in diabetic patients with DFUs treated by PTA. Although the data are still poor and the biological determinants of restenosis among patients with diabetes are not completely known, we retain that an adequate glycemic control during and after the angioplasty procedure could reduce the risk of neointimal proliferation, endothelial inflammation, and restenosis. Nevertheless,

it is already reported that HbA1c is a predictive factor for major amputation.⁷

Peripheral angioplasty is extensively used in our reality, and we have already reported in other studies the effectiveness of PTA in terms of limb salvage for ischemic DFUs.^{7,30} Furthermore, this procedure can be proposed with a low risk for fragile patients with several comorbidities. However, a significant risk of restenosis and clinical recurrence of CLI should be considered, mainly in dialyzed patients. The first months after the revascularization seem to be at high risk for restenosis and a great effort should be addressed to achieve wound healing in this first period. Furthermore, close postprocedural surveillance to optimize the durability of endovascular procedures by combining appropriate pharmacotherapy and periodic assessment of vessel patency is required. Nowadays, industrial efforts are directed to create new technical tools (low-profile balloons, drug-eluting balloons, medicated and nonmedicated stents) to ensure the long-term patency of the treated vessels.^{39–43} Finally, close clinical surveillance should be addressed to cardiometabolic risk factors and medical therapy after revascularization. Hypertension and dyslipidemia need to be treated, and dual antiplatelet therapy at least for 1 month after PTA is mandatory. Medical management with dual antiplatelet therapy and statin is recommended after vascular procedure, not only to reduce the risk of CLI recurrence but also to improve survival.⁴⁴

Innovation

It is well known about the high rate of restenosis after PTA in diabetic patients with CLI and ischemic DFUs. This study is the first one that reports the correlation between clinical recurrence of CLI after endovascular revascularization and outcomes; furthermore, the clinical factors that independently influence the recurrence of CLI have

KEY FINDINGS

- PTA can be performed with a low risk of technical complications (4.6%).
- Approximately 24% of patients had a clinical recurrence of CLI after PTA in a mean follow-up of ~12 months.
- Patients with recurrence of CLI reported higher rate of nonhealing, ulcer recurrence, major amputation, and death than patients who did not show CLI recurrence.
- HbA1c and dialysis influence independently the recurrence of CLI after PTA.

been identified. Close monitoring of renal parameters and glycemic levels may reduce the rate of restenosis after PTA.

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Abbreviations and Acronyms

CLI = critical limb ischemia
 DFUs = diabetic foot ulcers
 HbA1c = glycated hemoglobin, type A1C
 PAD = peripheral arterial disease
 PTA = percutaneous transluminal angioplasty
 rePTA = repeated PTA
 SFA = superficial femoral artery
 TcPO₂ = transcutaneous oxygen pressure