

Evaluation of angiosome-targeted infrapopliteal endovascular revascularization in critical diabetic limb ischemia

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ABSTRACT

Objective To evaluate the rates of wound healing and limb preservation following angiosome-targeted infrapopliteal endovascular revascularization in the treatment of diabetic limb ischemia.

Methods We performed a retrospective analysis of data gathered from 102 infrapopliteal angioplasty cases (60 males and 42 females; mean age, 72 ± 11 years) with Fontaine IV ischemia (ankle-brachial index, ABI: 0.16 ± 0.06). Forty-seven angioplasties were performed based on the angiosome concept (direct revascularization, DR), while 55 did not incorporate the angiosome concept (indirect revascularization, IR). The curative effects of angioplasty were assessed by postoperative determinations of ABI performed every 3 months during clinical follow-up visits conducted to assess healing of the ischemic wound. Amputation and death events were recorded throughout the study.

Results All 102 patients were successfully revascularized without complications, and during a mean follow-up period of 18 ± 11 months, the mean postoperative ABI improved to 0.84 ± 0.10 . The postoperative 6 and 12 month healing rates in the DR group were 85.1% and 93.5%, respectively, while the limb-salvage rates were 100% and 93.5%, respectively. The postoperative 6 and 12 month healing rates in the IR group were 60% and 76.4%, respectively, while the limb-salvage rates were 90.1%, and 85.5%, respectively.

Conclusion Angiosome-based Infrapopliteal angioplasty was associated with better wound healing and higher rates of limb salvage in cases of critical diabetic foot ischemia. Revascularization should be provided to patients who have undergone indirect perfusion of the ischemic angiosome, as acceptable rates of limb salvage are obtained.

Keywords: angiosome, infrapopliteal, angioplasty, foot, critical ischemia.

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Informed consent: Written informed consent was obtained from each patient or his/her immediate family.

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INTRODUCTION

Patients with critical limb ischemia (CLI) receive revascularization to prevent limb loss or major amputation (MA), improve their quality of life, and prolong survival. MA is associated with increased mortality in CLI patients, and although a multidisciplinary approach to treating CLI is recommended in the TransAtlantic InterSociety Consensus (TASC) II guidelines to help avoid MA, no current pharmacologic therapy can ensure limb salvage without revascularization (1). Additionally, increasing evidence supports the clinical relevance of the angiosome concept when performing bypass surgery or an endovascular treatment (EVT) to permit limb salvage in CLI patients (2,3). When using either revascularization modality, establishing a sufficient direct blood flow to the ulcer based on the angiosome concept greatly improves the likelihood of limb salvage.

The “angiosome concept” was first introduced in 1987 by Taylor and Palmer (4), and divides the human body into three-dimensional vascular areas supplied by specific source arteries and drained by specific veins. Taylor and Pan (5) defined five distinct angiosomes in the lower leg area that were fed by the medial sural artery, lateral sural artery, posterior tibial artery, peroneal artery, and anterior tibial artery, respectively. Six distinct angiosomes arising from the posterior tibial artery, anterior tibial artery, and peroneal artery have been identified in the foot and ankle region. The posterior tibial artery separates into three different branches: a calcaneal branch that supplies the medial ankle and plantar heel, a medial planter branch that feeds the medial planter instep, and a lateral planter branch that supplies the lateral forefoot, plantar midfoot, and entire plantar forefoot. The anterior tibial artery extends to the dorsum of the foot as the dorsalis pedis. The peroneal artery supplies the lateral ankle and plantar heel via the calcaneal branch and the anterior ankle via an anterior branch.

It is currently unknown whether use of the angiosome concept can improve the outcomes of infrapopliteal angioplasty. To investigate whether angiosome-based infrapopliteal angioplasty might provide clinical benefits, we compared clinical outcome data obtained from one group of patients who underwent direct revascularization (DR) with those obtained from a second group of patients who underwent indirect revascularization (IR).

MATERIALS AND METHODS

General information

We retrospectively analyzed data from 102 patients who were diagnosed as diabetes with CLI (Fontaine IV ischemia) and had successfully completed infrapopliteal endovascular revascularization surgery at our hospital (First Affiliated Hospital of Dalian Medical University, China) between January 2011 and May 2013.

Forty-seven of the 102 patients had undergone direct revascularization (DR), which was defined as recanalization of branches of wound-feeding arteries on the patient’s foot. For example, if the wound was located on the dorsum of the foot, DR of the anterior tibial artery was performed; if the wound was on the plantar of the foot, DR of the posterior tibial artery was performed. Fifty-five patients had undergone indirect revascularization (IR), which was defined as recanalization of non-wound-feeding branches of arteries. For example, if the wound was located on the dorsum of foot, branches of the infrapopliteal artery except for the anterior tibial artery were revascularized; if the wound was on the plantar of the foot, branches of the infrapopliteal artery except for the posterior tibial artery were revascularized. The protocol for this study was reviewed and approved by the Ethics Commission of First Affiliated Hospital of Dalian Medical University.

Preparation for operation

Following admission, each patient was monitored for blood glucose levels, and the amount of insulin was adjusted to maintain a glucose level of 7–10 mmol/L. Each patient received aspirin (100 mg/d), clopidogrel (75 mg/d), and cilostazol (100 mg/d) as antiplatelet therapy for at least 3 days, and prostaglandin E1 (20 µg/d) was administered to improve microcirculation. Patients with chronic kidney disease were examined by a non-contrast agent magnetic resonance angiography (NCMRA) to assess damage to the critical limb artery prior to surgery.

Angioplasty in the DR group

Twenty-six patients with a wound on the dorsal foot underwent anterior tibial artery recanalization based on the angiosome concept, and 18 of those patients successfully completed the operation. Among 8

patients with a wound on the thumb of the foot, the posterior tibial artery was recanalized in 5 patients, while both the anterior and posterior tibial arteries were recanalized in the remaining 3 patients. Twenty-one patients with a wound on the foot plantar region successfully completed recanalization of the posterior tibial artery.

All patients were treated by infrapopliteal angioplasty performed via antegrade puncture of the femoral artery. A Reekross18 2.0 mm/120 mm balloon (Bard Ltd; Covington GA, USA) and a V18 guidewire (BSC Ltd; Boston, MA, USA) were inserted into the target vessel using a 5F sheath tube (Terumo Ltd, Japan) and a blood vessel roadmap. When the Reekross18 balloon catheter became positioned at the entrance of the normal vessel in the patient's foot, a Transend 300 guidewire was inserted and replaced the V18 guidewire. Next, Amphirion Deep balloons (2.0 mm/120 mm and 2.5 mm/120 mm, respectively) (Medtronic Ltd, Italy) were inserted into the target vessel, and used to expand the vessel from its distal to proximal end. A Reekross18 balloon catheter and V18 guidewire were used for recanalization in patients whose vessels had to be recanalized using subintimal technology. A Reekross18 balloon catheter was inserted into the distal end of the vascular lumen, and a Transend300 guidewire was again used to replace the V18 guidewire. Next, the Amphirion Deep balloons (2.0 mm/120 mm and 2.5 mm/120 mm) were placed into the target vessel, and used to expand it from its distal to proximal end. An Amphirion Deep 2.0 mm/120 mm balloon and a PT guidewire (BSC Ltd, USA) were used to retrogradely recanalize the target vessel via the deep or shallow plantar arch in patients who required recanalization of the pedal proximal loop.

Angioplasty in the IR group

Rather than using the angiosome concept to guide recanalization of the target vessel, angioplasty in the IR group was performed based on the severity of the vascular occlusion, and at least one branch of the infrapopliteal artery was recanalized in each patient. Among the 55 patients in this group, canalization was performed on the anterior tibial artery in 3 patients, the posterior tibial artery in 9 patients, and the peroneal artery in 20 patients. Simultaneous canalization was performed on the anterior tibial and peroneal arteries in 10 patients, and the posterior tibial and peroneal

arteries in 13 patients. The quality of angioplasty preformed in the IR group was the same as that in the DR group.

Postoperative management

Beginning on postoperative day 1, each patient received 1500 mL of physiological saline via intravenous drip to protect liver function. Patients with creatinine levels $> 106 \mu\text{mol/L}$ received small doses of dopamine (2 g/kg/min) via intravenous drip within 24 hours prior to and after the operation, respectively. Patients with an ejection fraction (EF) $< 40\%$ either before or after rehydration therapy received daily intravenous furosemide (20 mg). All patients received antiplatelet therapy before the operation, and anticoagulation therapy (low molecular weight heparin, 5000 IU, q12 h, IH) within 72 h after the operation. Clopidogrel was stopped on postoperative day 90, while aspirin (100 mg/d) and cilostazol (100 mg/d) were continued. All patients in both groups were transferred to the chronic wound healing center in our hospital 4 days after their operation.

Observation of curative effect

An ankle brachial index (ABI) value was calculated immediately after each operation to assess the effect of recanalization. Following surgery, all patients were requested to schedule a follow-up visit in the out-patient department to assess the condition of their wound. Adverse events including MA and death were recorded every 3 months after the operation.

Definitions of related study parameters

Technical success was defined as performing percutaneous transluminal angioplasty (PTA) for an infrapopliteal (ATA, ATP or PA) occlusive arterial lesion; after which, the residual stenosis was $\leq 50\%$. Ulcer healing was defined as complete epithelialization of the tissue defect achieved by either secondary intent or after any additional local ulcer surgery. MA was defined as an amputation proximal to the ankle level.

Statistical analysis

All data were analyzed using PASW Statistics for Windows, Version 18.0. Chicago, IL: SPSS Inc. Differences between groups were analyzed using the

Chi-square test, and *P*-values < 0.05 were considered statistically significant.

RESULTS

Among the 102 patients in this study, 57 were male, 45 were female, and the mean age was 72 ± 11 years. Following hospital admission, each patient received a general examination which included calculation of an ABI value, laboratory tests for liver and kidney function, echocardiography (including left ventricular ejection fraction: LVEF), cervical vascular ultrasound, assays of enzymes, an electrocardiogram (ECG), and either computed tomography angiography (CTA) or NCMRA of the abdominal aorta and critical limb artery.

Ninety-one patients (89.2%) had a >10 year history of diabetes, 33 patients (32.3%) had chronic kidney dysfunction (CKD), 95 patients (93.1%) had 2–3 lesions in branches of the infrapopliteal artery, and 53 patients (52%) showed occlusion of the deep or shallow plantar arch. Furthermore, 60 (58.9%) of the 102 patients, had a wound on the dorsal portion of the foot and 42 (41.1%) had a wound in the foot plantar tissue. Clinically related risk factors of the patients and characteristics of the wounds are shown in Tables 1 and 2.

The target vessels in all 102 patients were successfully recanalized without complications (perforation, rupture or thrombosis, etc.) and the mean patient follow-up duration was 18 ± 11 months. During the 6–12 month postoperative period, one patient in the DR group and two patients in the IR group died after experiencing a cardiovascular event. During the follow-up period, 40 patients in the DR group showed good wound healing at six months after their operation, 4 patients showed good healing by the 12th postoperative month, and 2 patients underwent critical limb amputation due to insufficient healing at 12 months after their operation. In the DR group, the rates of postoperative healing at 6 and 12 months were 85.1% (40/47) and 93.5% (44/46), respectively, and the limb-salvage rates were 100% (47/47) and 93.5% (44/46), respectively. In the IR group, 33 patients showed good healing by the 6th postoperative month and 8 patients displayed good healing by the 12th postoperative month. However, five patients in the IR group had undergone critical limb amputation by six months after surgery and ten had been amputated by 12 months after surgery. The postoperative healing

Table 1 Clinical characteristics of the patients and their related risk factors.

Risk factors	DR group (n = 47)	IR group (n = 55)	<i>P</i> -value
Age > 70 yrs	39 (83%)	43 (78.2%)	0.545
History of DM > 10 yrs	44 (93.6%)	47 (85.5%)	0.187
Coronary artery disease	35 (74.5%)	40 (72.7%)	0.834
Hypertension	36 (76.6%)	43 (78.2%)	0.849
CKD	4 (8.5%)	6 (10.9%)	0.686
End-stage renal disease (hemodialysis)	10 (21.3%)	13 (23.6%)	0.696
Hyperlipidemia	41(87.2%)	49 (89.1%)	0.773

Table 2 Clinical characteristics of the wounds.

Features	DR group (n = 47)	IR group (n = 55)	<i>P</i> -value
2-3 injured branches of infrapopliteal artery	44 (93.6%)	51 (92.7%)	0.860
Length of lesion > 10 cm	41 (87.2%)	52 (94.5%)	0.197
Occlusion of deep or shallow plantar arch	26 (55.3%)	27 (49.1%)	0.532
Defect in dorsal tissue of the foot	26 (55.3%)	34 (61.8%)	0.508
Defect in plantar tissue of the foot	21 (44.7%)	21 (38.2%)	0.508

Table 3 Healing rates in the two groups during follow up.

Group	6 months	12 months
DR group (n = 47)	85.1% (40/47)	93.5% (44/46)
IR group (n = 55)	60% (33/55)	77.4% (41/53)
<i>P</i> -value	0.005	0.01

Table 4 Limb-salvage rate in the two groups during follow up.

Grouping	6 months	12 months
DR group (n = 47)	100% (47/47)	93.5% (44/46)
IR group (n = 55)	90.1% (50/55)	84.9% (45/53)
<i>P</i> -value	0.035	0.078

rates in the IR group at 6 and 12 months after surgery were 60% (33/55) and 76.4% (42/55), respectively, and the limb-salvage rates were 90.1% (50/55) and 85.5% (47/55), respectively. The postoperative healing and limb salvage rates in the two groups of patients are shown in Tables 3 and 4.

DISCUSSION

Although infrapopliteal angioplasty has been well-validated as a surgical technique for treating wounds in the feet of diabetic patients (6-9), some wounds do not heal, resulting in the need for amputation or even patient death. We investigated whether performing infrapopliteal angioplasty based on the angiosome concept would benefit wound healing in patients with critical diabetic foot ischemia and reduce the need for limb amputation.

Nearly 15% of individuals with diabetes will develop a foot ulceration (ie, diabetic foot) during their lifetime, and ~24% of such patients undergo amputation (1). However, if these patients receive early and proper monitoring of their foot ulcers, and the ulcers receive appropriate treatment, 85% of such amputations can be avoided (5,10,11). Infrapopliteal angioplasty is increasingly used in the treatment of diabetic foot. While the technical success and subsequent durability of treatment achieved when using angioplasty might seem limited compared with the success and durability achieved with bypass surgery, the limb-salvage rates achieved with the two techniques are equivalent. Multiple studies have reported that patients with an ischemic foot and who undergo knee angioplasty surgery experience restored arterial perfusion, which allows for better wound healing and decreases the need for amputation. A meta-analysis (12) of studies with a total of 2,653 participants showed that use of infrapopliteal artery angioplasty produced one-year and three-year limb-salvage rates of 86.0% \pm 2.7% and 82.4% \pm 2.4%, respectively. However, further studies are needed to determine the appropriate clinical role of infrapopliteal angioplasty.

Improved infrapopliteal angioplasty techniques are currently being developed and evaluated. After Attinger et al. first introduced the angiosome concept in 2006 (10), many investigators began exploring its possible use for achieving revascularization in ischemic feet. The relevant clinical studies indicated that use of the angiosome concept when revascularizing targeted vessels produced better results than those achieved by use of non-target vessel angioplasty, in terms of limb-salvage healing rates (2,3,13-19). Iida et al. (14) conducted a long-term study with a mean follow-up duration of 18 \pm 16 months and reported a postoperative limb-salvage rate of 86% among patients who received endovascular treatment guided by the angiosome concept compared to a 69% salvage rate in a non-guidance group. Similarly, Neville et al. (3) performed a retrospective analysis to investigate whether performing a bypass to the artery directly feeding an ischemic angiosome might impact the rates of wound healing and limb salvage. Those results showed a 91% rate of wound healing in an angiosome-guided group, vs. 62% in a control group. Finally, Alexanderscu and Hubermont (16) performed a parallel review of major recent

publications that discussed the angiosome theory and concluded that application of the angiosome concept in CLI revascularization procedures appeared to have beneficial effects on tissue cicatrization; however, additional comparative and prospective data would be needed to validate such findings. In our study, the postoperative healing rates in the DR and IR groups at 6 months were 85.1% (40/47) and 60% (33/55), respectively, and at 12 months were 93.5% (44/46) and 76.4% (42/55), respectively. The postoperative limb-salvage rates in the DR and IR group at 6 months were 100% (47/47) and 93.5% (44/46), respectively, and at 12 months were 90.1% (50/55) and 85.5% (47/55), respectively. The higher salvage rate in the DR group at 6 months was statistically significant; however, this difference between these groups at 12 months was not significant. These results were similar to those reported by Kabra et al. (18), who also found no significant difference in post-operative limb-salvage rates between DR and IR groups at a 12-month time point (84% vs. 75%). These results suggest that restoring direct infusion of a wound promotes better local wound healing in patients with foot ulcers, and restoring arterial perfusion to the foot can improve limb-salvage rates in patients with lower limb ischemia.

Our study has some limitations that should be mentioned. First, the number of subjects was relatively small, with only 47 angioplasty cases in the DR group and 55 cases in the IR group. Second, the mean duration of follow-up (18 \pm 11 months) was relatively short. Further studies with larger numbers of patients and longer follow-up times are needed to verify the appropriate use of the angiosome concept in angioplasty procedures. Moreover, both the wound healing rates at 12 months and limb-salvage rates at 6 and 12 months in this study were higher compared to those previously reported in the literature. However, these differences might be explained by the conservative type of therapy provided by the therapists in the Wound Repair Division of our hospital. Therefore, we suggest that a systematic therapeutic regimen should be used when treating patients with lower limb ischemia \leq Fontaine class IV.

CONCLUSION

Angiosome-based Infrapopliteal angioplasty may enhance wound healing in patients with critical diabetic foot ischemia and improve the rate of limb

salvage. Revascularization should be provided patients having undergone indirect perfusion of the ischemic angiosome, as acceptable rates of limb salvage are obtained when using this technique.

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