Endovascular Treatment of Lower Extremity Ischemia in Chronic Renal Failure Patients on Dialysis: Early and Intermediate Term Results

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ABSTRACT: **Background:** Peripheral arterial occlusive disease is common in patients with chronic renal failure requiring dialysis. Despite the increasing use of endovascular revascularization for lower extremity ischemia, the success rates of treating lower extremity ischemia in this challenging population remain obscure.

Objectives: To assess the results of endovascular revascularization for lower extremity ischemia in dialysis patients.

Methods: We conducted a retrospective review of all dialysis patients who underwent endovascular treatment for critical limb ischemia (CLI) in our institution between 2007 and 2011. Data collected included comorbidities, clinical presentation, anatomic distribution of vascular lesions, amputation and survival rates.

Results: We identified 50 limbs (41 patients). Indications included gangrene in 22%, non-healing wounds in 45%, rest pain in 31%, and debilitating claudication in 4%. Mean follow-up was 12 months (1–51 months). Nineteen patients required amputations. Freedom from amputation at 5 years was 40%. Factors associated with amputation included non-healing wounds or gangrene (68% and 36% respectively) and diabetes ($P < 0.05$). The survival rate was 80% after 5 years.

Conclusions: Despite improvement in endovascular techniques for lower extremity revascularization, the incidence of limb salvage among dialysis patients remains poor, resulting in a high rate of major amputations.

IMAJ 2013; 15: 734–738

KEY WORDS: peripheral arterial disease (PAD), critical limb ischemia (CLI), end-stage renal disease (ESRD), dialysis, endovascular revascularization

Peripheral arterial disease is common in patients with chronic renal failure. Critical limb ischemia, defined clinically as ischemic rest pain, non-healing ulcers or gangrene, represents an extreme manifestation of PAD. Approximately 5% of end-stage renal disease patients develop CLI, which is more prevalent in dialysis patients compared to non-dialysis kidney failure patients [1,2].

Patients with ESRD experience a higher rate of limb loss than patients with normal renal function [3,4]. Estimated rates of major lower extremity amputations in the dialysis population has been estimated to be 4.3% after 1 year and 13% among dialysis patients with diabetes [5,6]. Several factors may contribute to this poor outcome. Dialysis patients typically develop diffuse heavily calcified atherosclerotic lesions, frequently involving tibial arteries and small vessels of the pedal branches. A large percentage of dialysis patients suffer from diabetes, in itself a risk factor for atherosclerosis. They commonly have increased susceptibility to lower extremity life-threatening infections, an additional factor that may contribute to a poor outcome.

In addition, dialysis patients who undergo reconstructive surgery for CLI experience higher perioperative mortality rates, reduced rates of graft patency and poor limb salvage rates compared to non-dialysis patients [2,7]. Indeed, ESRD has been shown to be an independent risk factor for major amputations following surgery, and the presence of renal insufficiency an independent predictor for higher mortality in CLI patients undergoing revascularization [3,8]. It is because of these poor prognostic factors that some authors have advocated that revascularization not be attempted for dialysis patients with forefoot and deep heel defects or extensive infection and that primary amputation be considered for these patients [7,9-11].

The endovascular approach to PAD is gaining widespread use in the management of lower extremity ischemia. These percutaneous interventions were found to reduce periprocedural morbidity and mortality. They can be performed under local anesthesia with minimal blood loss and fluid shifts, frequently in an elective setting and with reduced operative time compared to open surgery. Intuitively, it would seem particularly attractive in high risk populations such as dialysis patients, who frequently are prohibited from

PAD = peripheral arterial disease

CLI = critical limb ischemia
ESRD = end-stage renal disease

undergoing open surgical procedures. Despite the above, it is somewhat surprising that the success rates of treating CLI in this challenging population remain obscure and data regarding patency of treated vessels and limb salvage rates are scarce. This lack of information may partly be due to the fact that dialysis patients are commonly excluded from large randomized trials due to their predicted poor outcome [3]. Since the use of endovascular interventions for CLI in the diabetic patient is increasing, there is a high likelihood of repeat interventions to maintain patency of treated vessels, and vein bypasses continue to be the gold standard for treatment of CLI with predictable results [12]. We present the experience of a single tertiary referral center in the treatment of dialysis patients with CLI or debilitating intermittent claudication who underwent endovascular therapy.

PATIENTS AND METHODS

We performed a retrospective study of all the dialysis patients suffering from CLI or debilitating intermittent claudication who underwent endovascular treatment in our institution between the years 2007 and 2011. Patients were identified by reviewing the electronic charts of all patients undergoing dialysis at our institution during the above period, including all radiographic imaging performed on those patients. Patients were included in the study if they had undergone a therapeutic peripheral arterial intervention for lower extremity ischemia. Only those who underwent endovascular revascularization were included. Patients undergoing diagnostic angiograms with or without open surgery or treated for acute limb ischemia were excluded from the study. The institutional review board at Sheba Medical Center approved this study and waived requirements for informed consent for this retrospective analysis.

The data obtained included patients' demographics, comorbidities, and clinical presentation. Preoperative angiograms were individually reviewed. Anatomic distribution and severity of the vascular lesions was documented and classified based on the Trans-Atlantic Inter-Society Consensus (TASCII) classification. The modality of treatment, i.e., percutaneous balloon angioplasty vs. primary stenting, was recorded.

The technical success of endovascular revascularization was defined as the ability to cross and treat the diseased segments encountered during the angiogram. Patients were followed at 3, 6, 9 and 12 months within the first year, and every 6 months thereafter, by clinical assessment, ankle brachial indices and pulse volume recordings. Re-intervention, amputation and survival rates were documented. Factors associated with risk of amputation were calculated using chi-square analysis. Survival analysis was performed using the Kaplan-Meier method. A major amputation was defined as below the knee or above the knee.

PROCEDURES

A computed tomography angiogram was performed before the procedure, if there was no contraindication. Iliac lesions were commonly treated via a retrograde approach through the ipsilateral common femoral artery. For the treatment of infra-inguinal disease, an antegrade approach was selected and performed through the ipsilateral common femoral artery, provided that the proximal superficial femoral artery was patent. Otherwise, a contralateral approach was used. All iliac lesions were treated with primary stenting. SFA lesions were treated primarily with percutaneous balloon angioplasty and selective stenting if necessary (residual stenosis > 30% or flow-limiting dissection). Infra-popliteal disease was treated exclusively with percutaneous balloon angioplasty. All diseased segments were treated if they were accessible. Following the endovascular revascularization, all patients received antiplatelet therapy (aspirin, life-long, and clopidogrel for 3 months). In selected cases anticoagulation was added.

RESULTS

During the study period 1234 lower extremity endovascular interventions were performed for CLI in our institution. Among these, 50 limbs (4%) in 41 dialysis patients (39 hemodialysis, 2 peritoneal dialysis) were treated. Mean age was 68 years (range 50–86) and 70% were male. Indications for interventions included: gangrene 22%, non-healing wounds 45%, rest pain 31%, and debilitating intermittent claudication in 4%. Patients' demographics and comorbidities are detailed in Table 1. The majority of aorto-iliac lesions were classified as TASCII A and B (94%). The entire spectrum of TASCII lesions (A, B, C, and D) was encountered in the SFA-popliteal region [Figure 1]. All patients suffered from tibial disease. Two or more anatomic levels of disease were present in 45

SFA = superficial femoral artery
TASCII = Trans-Atlantic Inter-Society Consensus

Table 1. Demographics and comorbidities

	Number (%)
Age (yr) (range)	68 (50–86)
Male:Female	29:12
Coronary artery disease	32 (78%)
Hypertension	36 (87%)
Diabetes	34 (82%)
Hyperlipidemia	33 (80%)
Chronic obstructive lung disease	6 (14%)
Current smoker	6 (14%)
Past smoker	6 (14%)

Figure 1. Anatomic distribution and TASCII classification of vascular lesions

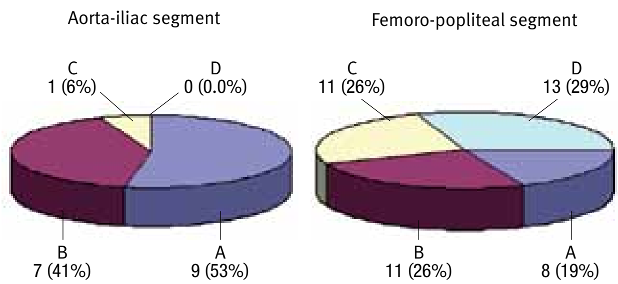

Figure 2. Findings on follow-up: **[A]** Freedom from amputation following treatment, **[B]** Survival rates following treatment

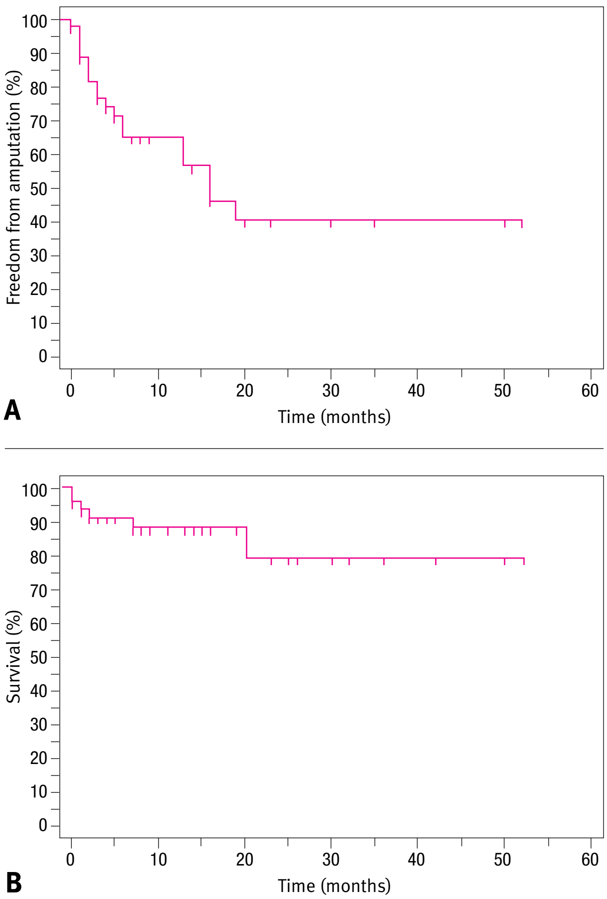

Table 2. Factors associated with amputation

	No. of limbs	No. of amputations (%)
Presenting symptom		
Claudication	2	0 (0)
Rest pain	15	2 (13)
Non-healing wounds	22	13 (68)*
Gangrene	11	4 (36)*
Gender		
Male	29	16 (55)
Female	12	3 (25)
Diabetics		
Yes	34	15 (44)*
No	7	0 (0) *
Smoking		
Yes	11	4 (36)
No	30	12 (40)
Coronary artery disease		
Yes	32	12 (37)
No	9	3 (33)
All lesions treated		
Yes	21	10 (50)
No	29	(31)

* $P < 0.05$

limbs (90%) and involved either a combination of aorto-iliac or SFA popliteal disease combined with tibial disease.

Technical success was achieved in all 17 iliac lesions (100%). Of the 43 SFA lesions identified, 31 (72%) were successfully treated. Only 21 of the 50 below-the-knee/tibial arteries (42%) could be treated due to inability to recananlize the diseased vessels.

Mean follow-up was 12 months (1–51 months). During this period 6 patients (14%) required re-interventions. Nineteen patients required major amputations. Estimated freedom from amputation was 65% at 1 year and 40% at 5 years [Figure 2A]. Average time to amputation was 6 months. Factors associated with a higher rate of amputation included presenting symptoms of non-healing wounds or gangrene (68% and 36%, respectively), and the presence of diabetes ($P < 0.05$) [Table 2]. Treatment of all levels of disease encountered during the procedure was not associated with an improved rate of limb salvage. Six deaths occurred, resulting in an estimated survival rate of 80% after 5 years [Figure 2B]. Four patients died from sepsis and two from coronary ischemic events.

DISCUSSION

Patients with ESRD on dialysis who develop CLI are at significant risk for limb loss. The use of endovascular modalities in the treatment of CLI is gaining popularity, but there are limited data regarding the short and mid-term results in this subgroup of patients.

The technical success of endovascular revascularization in our series was 100% for iliac lesions, 72% for SFA lesions and 42% for tibial lesions. This rate is relatively high compared to other reported series. Comparison between different series is difficult since the definitions of technical success vary. While some report success as the ability to cross and treat all lesions, other reports do not specify if in fact all levels of disease were treated [3,13]. Overall, it appears that the technical success rate is high (86–97%) despite the pattern of heavily calcified occluded arteries that characterize chronic dialysis patients. This high success rate can be attributed to technical improvements in dedicated endovascular devices and experience obtained throughout the last years with infra-inguinal and infra-geniculate endovascular procedures.

Our limb salvage rate following percutaneous intervention was 65% at 1 year and 40% at 5 years. The outcome following endovascular revascularization in dialysis patients varies between different reported series. A recently published retrospective analysis of 123 limbs in 111 patients who were treated by endovascular revascularization for CLI reported an overall amputation rate of 25%. However, in the subgroup of dialysis patients the amputation rate reached 46% [14]. Graziani et al. [11] treated 107 dialysis patients presenting 132 ischemic limbs. At 24 and 48 months limb salvage rates were 84% and 62%, respectively. Factors associated with poor outcome included the presence of diabetes, a higher number of treated lesions, and distal disease. Brosi and co-authors [15] reported their experience with below-the-knee percutaneous balloon angioplasty in 29 dialysis patients. After 12 months follow-up limb salvage was achieved in 73% of their patients. The authors concluded that amputations were most probably related to the severity of the pedal arteries with involvement of the pedal arch. The latter was observed in 58% of the patients. Albers et al. [9] published a meta-analysis of 1314 procedures performed on 1272 lower limbs. Of these patients, 964 were dialysis dependent, 58 had renal transplant and 5 had renal insufficiency. Pooled estimates of limb salvage at 12 and 24 months were 78% and 74%, respectively.

There are several explanations for our low limb salvage rate. Most of our patients presented with clinically advanced disease. Approximately two-thirds suffered from non-healing wounds or gangrene (Rutherford classification 5 or 6). Those patients had an increased risk of amputation compared to patients who presented with rest pain or debilitating claudication (Rutherford classification 3 or 4). This finding correlates well with other reports [8,13]. Abou-Zamzam and colleagues [8] studied the factors leading to major amputation and found that huge tissue loss was an independent predictor of treatment by primary amputation as compared to revascularization. In addition, all our patients suffered from extensive tibial disease, and only 42% of them could be treated. It is conceivable that timing the intervention for revascularization at an earlier stage, prior to the development of irreversible tissue loss, may yield a more favorable outcome. In our study, the percentage of patients with ulcers who eventually required amputations was higher than those with gangrene. We assume that the presence of an open wound, more than gangrene, predisposes the patients (who are mostly diabetics) to severe limb-threatening infections, thus resulting in a higher amputation rate.

Our experience revealed that the presence of diabetes was a significant risk factor for amputation following treatment. In fact all patients who required major amputations suffered from diabetes, and 44% of the diabetics required amputations. This is not surprising, as diabetics typically develop severe tibial, small vessel and microvascular disease involving the plantar vessels. Thus, the presence of microvascular disease and frequent failure to recanalize tibial vessels might have contributed to increase the rate of amputation, despite successful treatment of lesions located at more proximal levels. Interestingly, the ability to treat all levels of diseased arteries was not associated with an improved rate of limb salvage. This may be due to the presence of microvascular disease that may not be significantly ameliorated by the treatment of macrovascular disease.

In contrast to our low limb salvage rate, our survival rate was higher compared to other reports. Willenberg et al. [3] reported a 32% mortality rate among patients with severe renal insufficiency. Others reported survival rates of 72% at 1 year and 27% at 5 years [9]. The reason for these differences is not clear. It is possible that earlier amputation with removal of the ischemic infected limb might have prevented septic complications, resulting in improved overall survival. However, this assumption cannot be verified from this study and no substantial data exist to support this approach. In general, annual mortality rates among dialysis patients have been historically high. Notably, there has been a steady improvement in overall survival among dialysis patients over the past two decades [16]. In addition, it should be emphasized that there seems to be a large variability in mortality rates depending on the country reporting. For example, crude mortality rates are consistently higher in the United States than in Europe or Japan, and DOPPS (the Dialysis Outcomes and Practice Patterns Study) reported crude 1 year mortality rates during the period 1996 to 2002 as high as 6.6% in Japan, 15.6% in Europe, and 21.7% in the United States [17].

CONCLUSIONS

Despite improvement in endovascular techniques and their increasing utilization for lower extremity revascularization, peripheral revascularization in dialysis patients has not led to high limb salvage rates. Poor outcome may be related to the severity of ischemia on presentation, the cumulative burden of the atherosclerotic disease, and the distal location of the disease.

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Capsule

Cellular immune correlates of protection against symptomatic pandemic influenza

The role of T cells in mediating heterosubtypic protection against natural influenza illness in humans is uncertain. The 2009 H1N1 pandemic (pH1N1) provided a unique natural experiment to determine whether cross-reactive cellular immunity limits symptomatic illness in antibody-naive individuals. Sridhar et al. followed 342 healthy adults through the UK pandemic waves and correlated the responses of pre-existing T cells to the pH1N1 virus and conserved core protein epitopes with clinical outcomes after incident pH1N1 infection. Higher frequencies of pre-existing T cells to conserved CD8 epitopes were found in individuals who developed less severe illness, with total symptom score having the strongest inverse correlation with the frequency of interferon-gamma (IFN-γ)$^+$interleukin-2 (IL-2)$^-$ CD8$^+$ T cells ($r = -0.6$, $P = 0.004$). Within this functional CD8$^+$IFN-γ$^+$IL-2$^-$population, cells with the CD45RA$^+$ chemokine (C-C) receptor 7 (CCR7)$^-$ phenotype inversely correlated with symptom score and had lung-homing and cytotoxic potential. In the absence of cross-reactive neutralizing antibodies, CD8$^+$ T cells specific to conserved viral epitopes correlated with cross-protection against symptomatic influenza. This protective immune correlate could guide universal influenza vaccine development.

Nature Med 2013; 19: 1305

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Capsule

A small molecule AdipoR agonist for type 2 diabetes and short life in obesity

Adiponectin secreted from adipocytes binds to adiponectin receptors AdipoR1 and AdipoR2, and exerts anti-diabetic effects via activation of AMPK and PPAR-α pathways, respectively. Levels of adiponectin in plasma are reduced in obesity, which causes insulin resistance and type 2 diabetes. Thus, orally active small molecules that bind to and activate AdipoR1 and AdipoR2 could ameliorate obesity-related diseases such as type 2 diabetes. Iwabu et al. report the identification of orally active synthetic small molecule AdipoR agonists. One of these compounds, AdipoR agonist (AdipoRon), bound to both AdipoR1 and AdipoR2 in vitro. AdipoRon showed very similar effects to adiponectin in muscle and liver, such as activation of AMPK and PPAR-α pathways, and ameliorated insulin resistance and glucose intolerance in mice fed a high fat diet, which was completely obliterated in AdipoR1 and AdipoR2 double-knockout mice. Moreover, AdipoRon ameliorated diabetes of genetically obese rodent model *db/db* mice, and prolonged the shortened lifespan of *db/db* mice on a high fat diet. Thus, orally active AdipoR agonists such as AdipoRon are a promising therapeutic approach for the treatment of obesity-related diseases such as type 2 diabetes.

Nature 2013; 503: 493

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