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ARTICLE

Endovascular therapy and free flap transfer in chronic limb-threatening ischemia

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ABSTRACT

Although revascularization has evolved, treating foot gangrene with chronic limb-threatening ischemia remains challenging. There have been many reports on bypass surgery and free flap transfer. Meanwhile, few studies have reported on endovascular therapy and free flap transfer, with high flap survival rates and high wound complication rates. Wound complications are a serious problem that can lead to limb amputation, but previous studies have failed to identify risk factors for wound complications. In this study, we evaluated the results of endovascular therapy and free flap transfer for chronic limb-threatening ischemia and analyzed risk factors for wound complications. A total of 31 legs from 28 patients who underwent endovascular therapy and free flap transfer for lower limb salvage between August 2016 and April 2020 were retrospectively reviewed. The primary endpoints were flap survival and limb salvage rates and wound complication rates. In addition, we performed a statistical analysis of risk factors for wound complications. The flap survival rate was 100%, with partial necrosis in 6% of the patients. The limb salvage rate was 100%. The wound complication rate was 45%. The multivariate analysis showed end-stage renal failure on dialysis as a significant risk factor for wound complications (odds ratio = 133, 95% confidence interval = 2.74–6430, $p = 0.014$). Endovascular therapy and free flap transfer in chronic limb-threatening ischemia achieved high flap survival rate and limb salvage, but had a high incidence of wound complications. We identified end-stage renal failure on dialysis was a significant risk factor for wound complications.

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Free flap transfer; endovascular therapy; chronic limb-threatening ischemia; risk factors; wound complications

Introduction

Limb salvage in patients with severe foot gangrene and chronic limb-threatening ischemia remains challenging because it requires multidisciplinary treatment. Free flap transfer is preferred for extensive wounds in weight-bearing or exposed bone areas. Revascularization is also indicated for chronic limb-threatening ischemia.

In the past, bypass surgery was the preferred method for revascularization in chronic limb-threatening ischemia. In recent years, with the development of equipment and techniques, endovascular therapy is now performed in many institutions, as in 'endovascular treatment first' [1]. Although numerous studies have reported the success of bypass surgery and free flap transfer [2–4], few have focused on endovascular therapy and free flap transfer. The latter studies have reported higher flap survival rates but also higher rates of wound complications [5–8]. Wound complications in patients with chronic limb-threatening ischemia are a serious problem with risk of limb amputation. Nonetheless, the risk factors for wound complications remain unclear. This study aimed to investigate the results of endovascular therapy and free flap transfer and analyze the risk factors for wound complications. By identifying the risk factors, we hope to reduce wound complications for patients with these risk factors.

Patients and methods

This retrospective study evaluated 31 legs of 28 patients who underwent endovascular therapy and free flap transfer for lower limb salvage between August 2016 and April 2020. Endovascular therapy and free flap transfer are indicated for patients who were ambulatory before surgery or had a strong desire for limb salvage. All lesions were extensive tissue defects in weight-bearing areas or stumps after ray or foot amputation that could not be treated with simple wound closure or skin grafting. Patients who underwent endovascular therapy of only above-knee arteries were excluded.

This study was approved by the Institutional Review Board of Saitama Medical University Hospital (Approval no. 21029.01). Owing to its retrospective design, written informed consent was not required, and information about opting out was available on the website of Saitama Medical University Hospital. This study followed the guidelines of the Declaration of Helsinki.

Demographic and clinical data, including age; sex; comorbidities (diabetes, end-stage renal failure on dialysis, ischemic heart disease, and cerebrovascular accident); American Society of Anesthesiologists (ASA) status; Wound, Ischemia, and foot Infection (WIfI) classification; global limb anatomical staging system (GLASS) stage; C-reactive protein (CRP); albumin (ALB); hemoglobin (Hb); defect location; flap type; flap size; flap survival; recipient artery and vein; anastomosis method; wound and medical complications; months of follow-up; and limb salvage rate were investigated.

Statistical analysis

The correlations between wound complications and risk factors were analyzed. The following risk factors were assessed: end-stage

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renal failure on dialysis, ASA status, GLASS stage, CRP, ALB, Hb, and flap size. $p < 0.05$ was considered significant in the univariate analysis. The continuous variables (CRP, ALB, Hb, and flap size) were analyzed by a t-test or the Mann–Whitney U test. Categorical variables (end-stage renal failure on dialysis, ASA status [3 or 2], and GLASS stage [4 or <3]) were subjected to a univariate analysis with Fisher's exact test. The multivariate logistic regression analysis was conducted using the variables with $p < 0.10$ in the univariate analysis, and $p < 0.05$ was considered significant in the multivariate analysis. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [9].

Treatment procedure

Wound management/blood flow estimation

First, the patient was assessed for gangrene infection. Simultaneously, ankle hemodynamic index and ultrasonography were performed to evaluate blood flow in the lower extremities. If the patient presented with a severely infected wound, debridement was performed first. By contrast, if the gangrene was not severely infected, endovascular therapy was performed first.

Bacterial culture tests were performed on admission, and antibiotics were promptly administered according to sensitivity. After the severe infection was resolved, negative-pressure wound therapy was performed in the wound bed preparation.

Endovascular therapy

All patients underwent angiography and endovascular therapy within 10 days before free flap transfer. If it took a long time from the initial endovascular therapy to the reconstructive surgery, a second angiography and, if necessary, simultaneous endovascular therapy were performed. After endovascular therapy, the patient took anticoagulants.

Free flap transfer

After wound infection was controlled and recipient artery patency was confirmed using angiography and ultrasonography, free flap transfer was performed. As the flap was harvested from the back, the surgical posture was the lateral position. We divided into two teams, one to expose the recipient vessel with the debridement and the other to elevate the flap. The flap was chosen after considering the size and thickness of the defect and the required pedicle length. In vascular anastomosis, we first performed venous anastomosis without clipping the recipient artery, clipped it, and then performed an arterial anastomosis to shorten the ischemic time in the foot.

Postoperative care

All patients were treated with prostaglandin E1 after free flap transfer. At the first postoperative month, patients with unhealed wounds underwent angiography and endovascular therapy if necessary, followed by additional surgical treatment. After the wounds had healed, all patients received custom-made orthotics.

Results

Demographic data

This study evaluated 21 male patients and 7 female patients. The mean age was 68 (range, 44–82) years. Table 1 displays the demographic and preoperative characteristics of the patients. A brief description of typical cases is shown in Figure 1.

Table 1. Demographic data of the 28 patients.

	n (%)
Mean age, years (range)	68 (44–82)
Male	21 (75)
Diabetes mellitus	26 (93)
End-stage renal failure on dialysis	13 (46)
Ischemic heart disease	14 (50)
Cerebrovascular accident	7 (25)
Ambulatory before treatment	26 (93)

Preoperative evaluation

The ASA score, WIfI classification, and GLASS stage before debridement and revascularization are shown in Table 2. ASA scores of 2 and 3 were reported in 19 and 12 cases, respectively. The WIfI classification is a risk stratification based on wound, ischemia, and foot infection. All patients had a WIfI classification of 4. The GLASS stage evaluates anatomic patterns in patients with chronic limb-threatening ischemia and was defined by grading the femoral–popliteal and infrapopliteal segments separately (0–4) and then integrating them into three GLASS stages (I–III) for the limb. GLASS stages of I, II, and III were reported in 7, 9, and 15 cases, respectively.

Operative procedure

Table 3 shows the defect locations, flap type, flap size, recipient artery, and recipient vein. The most common defect was the stump following amputation. There were seven stumps after ray amputation, seven after transmetatarsal amputation, eight after midfoot amputation, and nine at the sole or heel. The scapular flap was most commonly used for reconstruction ($n = 15$), followed by the latissimus dorsi musculocutaneous flap ($n = 7$). The thin circumflex scapular artery perforator flap was used in 5 cases and the parascapular flap in 4 cases.

The mean flap size was 104 (range, 36–198) cm^2. The recipient artery was the anterior tibial artery in 17 cases, posterior tibial artery in 10 cases, and the dorsalis pedis artery in 4 cases. Side-to-end anastomosis of the artery was performed in 26 (84%) cases, and end-to-end anastomosis was performed in 5 (16%) cases. The recipient vein was the concomitant vein in all cases. Eleven cases (35%) underwent a single venous anastomosis, and 20 (65%) underwent a double venous anastomosis. Twenty-three cases (74%) underwent end-to-end anastomosis and 8 (26%) underwent end-to-side anastomosis.

Complications

Wound and medical complications are shown in Table 4. Flaps survived without necrosis in 29 (94%) cases, but partial necrosis occurred in 2 (6%). Venous thrombosis required re-anastomosis of the vein in 1 (3%) case. Wound dehiscence occurred in 7 (23%) cases and wound infection in 5 (16%). Moreover, 14 (45%) cases of wound complications required additional surgical treatment. These patients underwent debridement and re-suturing or skin grafting. As a result, limb salvage was achieved in all the patients. General postoperative complications occurred in 2 (6%) cases, both of whom had pneumonia. No patients died during hospitalization.

Follow-up outcomes

The mean follow-up period was 23 (range, 6–54) months. Recurrence of ipsilateral foot ulceration occurred in 13 (42%)

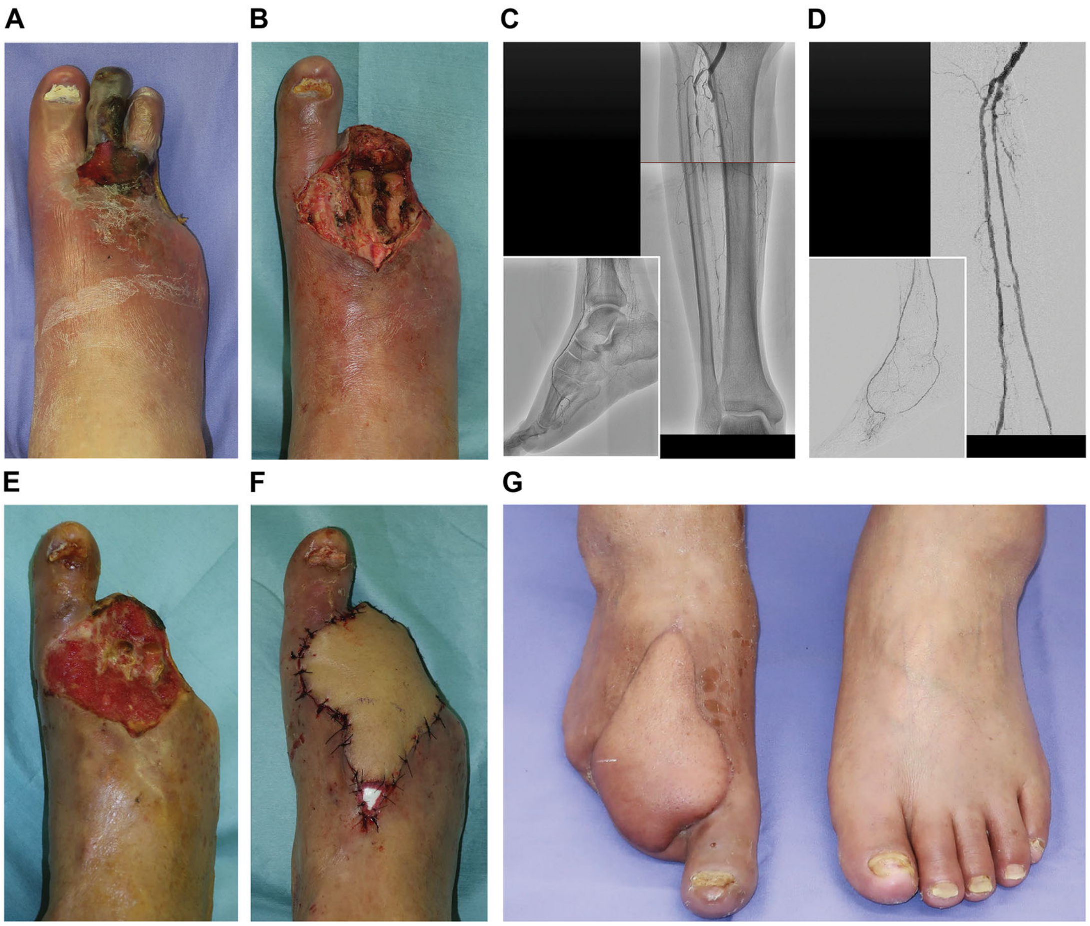

Figure 1. A 73-year-old man with a history of amputations of the fourth and fifth toes, coronary artery bypass grafting, and hypertension and who was receiving dialysis for end-stage renal failure presented with progressive gangrene of the second and third toes (A). Considering the severity of the infection, debridement was performed before endovascular therapy. Amputation at the metacarpophalangeal joint of the second and third toes and debridement of the dorsum of the foot were performed (B). The angiogram showed multisegmental lesions in the below-knee arteries (C). Endovascular therapy was performed on the anterior and posterior tibial arteries (D). As there were 31 days from the initial endovascular therapy to free flap transfer, a second angiography was performed 7 days before free flap transfer, and the plantar artery was occluded and treated. Once the wound infection had resolved (E), reconstruction was performed using an 11×6-cm thin circumflex scapular artery perforator flap (F). The recipient artery was the dorsalis pedis artery and was anastomosed in a side-to-end fashion, and the recipient vein was a concomitant vein and was anastomosed in an end-to-side fashion. A 12-month follow-up showed good contour with ambulation without further wound problems (G).

cases, 10 (32%) required endovascular therapy, and 2 (6%) underwent Syme amputation. Two (6%) cases underwent major amputations on the contralateral side. All patients who were ambulatory before treatment could walk with custom-made orthotics or insoles. Eight (26%) patients died during follow-up.

Risk factor analysis

Results of the univariate and multivariate analyses of risk factors associated with wound complications are shown in Table 5.

In the univariate analysis, end-stage renal failure on dialysis was a significant risk factor (odds ratio (OR) = 15.1, 95% confidence interval (CI) 2.27–147.82, $p = 0.001$). A multivariate logistic regression analysis was performed with end-stage renal failure on dialysis and flap size (had values of $p < 0.10$ in the univariate analysis). The results showed that end-stage renal failure on dialysis was a significant risk factor (OR = 133, 95% CI 2.74–6430, $p = 0.014$).

Discussion

This study investigated the outcomes of endovascular therapy and free flap transfer in patients with foot gangrene who had extensive wounds and chronic limb-threatening ischemia. The results showed high flap survival rate and high incidence of wound complications. Both results were similar to those in previous studies of endovascular therapy and free flap transfer [5–8]. Additionally, we identified end-stage renal failure on dialysis as a risk factor for wound complications.

Previously, bypass surgery was the first choice of revascularization for chronic limb-threatening ischemia. Since the first report by Briggs in 1985, many studies on bypass surgery and free flap transfer have been published [2–4]. Recently, endovascular therapy has evolved with the development of techniques and instrumentation [1], and reconstructive surgeons have begun to perform endovascular therapy and free flap transfer. The first report of endovascular therapy and free flap transfer was reported in 2014, but there are few reports [5–8]. In these studies, flap survival rates have been as high as 93%, and the present study reports comparably favorable results.

Previous studies of endovascular therapy and free flap transfer have reported wound complication rates of ≥30% [5–8], which was 45% in the present study. Wound complications are intractable problems that can lead to limb amputation, but no studies have identified risk factors for wound complications. When

Table 2. Preoperative evaluation of 31 legs.

	n (%)
ASA	
Score 2	19 (61)
Score 3	12 (39)
WIfI	
Classification 4	31 (100)
W 3	31 (100)
I 0	4 (13)
I 1	21 (68)
I 2	4 (13)
I 3	2 (6)
fI 2	17 (55)
fI 3	14 (45)
GLASS	
Stage I	7 (23)
Stage II	9 (29)
Stage III	15 (48)
FP grade 0	13 (42)
FP grade 1	11 (35)
FP grade 2	3 (10)
FP grade 3	4 (13)
IP grade 1	4 (13)
IP grade 2	4 (13)
IP grade 3	9 (29)
IP grade 4	14 (45)

ASA: American Society of Anesthesiologists; WIfI: Wound, Ischemia, and foot Infection; GLASS: global limb anatomical staging system; FP: femoropopliteal; IP: infrapopliteal.

Table 3. Reconstructive characteristics of 31 legs.

	n (%)
Defect location	
Stump after ray amputation	7 (23)
Stump after transmetatarsal amputation	7 (23)
Stump after midfoot amputation	8 (26)
Sole or heel	9 (29)
Flap type	
Scapular flap	15 (48)
Latissimus dorsi musculocutaneous flap	7 (23)
Thin circumflex scapular artery perforator flap	5 (16)
Parascapular flap	4 (13)
Recipient artery	
Anterior tibial artery	17 (55)
Posterior tibial artery	10 (32)
Dorsalis pedis artery	4 (13)
Recipient vein	
Concomitant vein	31 (100)

Table 4. Wound and medical complications of 31 legs.

	n (%)
Wound complication	
Partial flap necrosis	2 (6)
Venous thrombosis	1 (3)
Wound dehiscence	7 (23)
Wound infection	5 (16)
Medical complication	
Pneumonia	2 (6)

analyzing the risk factors for wound complications, we found the probability of wound complications to be significantly increased in patients with end-stage renal failure on dialysis. In a previous report of free flap transfer in patients with end-stage renal failure on dialysis, wound complications occurred in 40% of patients [10]. In the present study, the incidence of wound complications in patients with end-stage renal failure on dialysis was 71%. These results suggest that the indications for endovascular therapy and free flap transfer should be determined more carefully in patients with end-stage renal failure on dialysis because immunity and wound healing are impaired.

The SPINACH study, a multicenter prospective observational study on Japanese patients with critical limb ischemia, suggested the following as factors favoring bypass surgery: WIfI classification W-3, fI-2/3, history of ipsilateral minor amputation, history of revascularization after critical limb ischemia onset, and bilateral critical limb ischemia. Conversely, diabetes mellitus, renal failure, anemia, history of nonadherence to cardiovascular risk management, and contralateral major amputation were identified as adverse factors for bypass surgery [11]. In the present study, most patients had local factors favoring bypass surgery, such as extensive wounds and severe infections, as reported in the SPINACH study [11]. Simultaneously, these patients had systemic diseases, such as diabetes, end-stage renal failure on dialysis, and anemia, which are considered detrimental factors for bypass surgery. In these conflicting circumstances, we opted for endovascular therapy rather than bypass surgery as emergency revascularization because of the patient's poor general condition and the desirability of a minimally invasive treatment. Previous studies showing similar success rates for endovascular therapy and free flap transfer compared to bypass surgery and free flap transfer [12] supported our deliberations.

Post-treatment restenosis is a major challenge in endovascular therapy. In a previous study examining angiographic restenosis after infrapopliteal angioplasty, 95% of the patients underwent angiography at 3 months, which indicated a restenosis rate of 73% (40% restenosis and 33% re-occlusion) [13]. In the present study, it often took a long time between the initial endovascular therapy and reconstructive surgery because this surgery was performed after the wound infection was controlled and the general condition improved. In such cases, owing to the possibility of restenosis of the treated artery, angiography was performed again approximately 10 days before the reconstructive surgery, and endovascular therapy was performed if necessary. The reason for keeping a 10-day interval between endovascular therapy and free flap transfer is to ensure that no acute occlusion or intimal dissection has occurred in the treated artery. Previous studies have reported an average interval of 8 days [5] and 17.6 days [6] between endovascular therapy and free flap transfer, which was comparable to the duration reported in the present study. Furthermore, in patients with unhealed wounds, angiography was performed in the first postoperative month, followed by endovascular therapy if necessary, and then additional surgical treatment. In most of these patients, angiography revealed restenosis of the treated artery, which probably contributed to the delayed healing of the wounds. Our protocol mainly focuses on performing timely angiography before and after free flap transfer to treat restenosis of the artery and performing endovascular therapy if necessary.

We harvested a flap from the back because the dermis was thick and durable, and the atherosclerosis of the pedicle artery was mild compared with the limb. The flap was chosen after considering the size and thickness of the defect and the required pedicle length. The most versatile flap is the scapular flap. The parascapular flap is used for larger defects; the latissimus dorsi musculocutaneous flap is used when a long pedicle is required, whereas the thin circumflex scapular artery perforator flap is used when the wound is located on the dorsum or side of the foot. Thus, by selecting a flap according to the defect, we can reconstruct the contour of the foot and fit the orthotic device. Previous reports have used a flap from the thigh such as the vastus lateralis flap, rectus femoris flap, or anterolateral thigh flap [5–8]. However, to preserve the femoral arteries and avoid thigh muscle weakness, we did not use the thigh flaps.

Table 5. Univariate and multivariate analyses of risk factors associated with wound complications.

	Univariate analysis P value	Multivariate analysis Odds ratio (95% CI), P value
End-stage renal failure on dialysis	0.001*	133 (2.74–6430), 0.014[a]
ASA status (≥3)	0.46	
GLASS stage (≥4)	0.29	
CRP	0.71	
ALB	0.48	
Hb	0.12	
Flap size	0.082	1.05 (0.999–1.11), 0.057

[a]Statistically significant.
ASA: American Society of Anesthesiologists; GLASS: global limb anatomical staging system; CRP: C-reactive protein; ALB: albumin; Hb: hemoglobin.

The arterial anastomosis location was determined In consultation with the endovascular physician based on the preoperative angiogram. Although the site of ballooning of the artery should be avoided due to the possibility of intimal damage, most cases were ballooned over a wide area and anastomosis was performed in that area. In most cases, side-to-end arterial anastomosis was performed by creating a hole in the recipient artery. If an artery near the midfoot amputation stump was available, an end-to-end arterial anastomosis was performed because there was no need to preserve the peripheral blood flow beyond the anastomosis. Arterial anastomoses were performed using 8-0 or 7-0 nonabsorbable monofilaments to penetrate calcified lesions, and double needles were used to avoid intimal dissection.

This study was limited by its retrospective nature and small sample size. Although the flap survival rate was high, only patients with a high probability of successful free flap transfer may have been selected. We identified end-stage renal failure on dialysis as a risk factor for wound complications, but end-stage renal failure on dialysis is an irreversible state for which there is no cure and no measures can be taken.

Conclusion

This study demonstrated that endovascular therapy and free flap transfer for foot gangrene with chronic limb-threatening ischemia constitute a reliable treatment option for limb salvage. However, this treatment had a high wound complication rate. End-stage renal failure on dialysis was identified as a significant risk factor for wound complications.

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Author contribution

Conceived and designed the analysis: Shoichi Ishikawa and Shigeru Ichioka; Data collection: Shoichi Ishikawa, Kiyohito Arai, and Takeshi Kurihara; Contributed data/analysis tools: Shoichi Ishikawa, and Tomoya Sato; Performed the analysis: Shoichi Ishikawa and Tomoya Sato; Wrote the paper: Shoichi Ishikawa, and Shigeru Ichioka

Disclosure statement

No potential conflict of interest was reported by the author(s).

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