Clinical Outcomes of Transmetatarsal Amputation in Patients with Diabetic Foot Ulcers Treated without Revascularization

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ABSTRACT

Introduction: Most studies on outcomes of transmetatarsal amputation (TMA) have been for patients who underwent revascularization. This study was performed to evaluate the outcomes of TMA in diabetic patients without revascularization.

Methods: One hundred two diabetic patients who were not candidates for revascularization underwent TMA and received a multidisciplinary treatment. These patients were followed up for a mean period of 38 months to observe the outcomes, including wound healing, above-the-ankle amputation and death. The associations between variables and the outcomes were analyzed by Cox regression analysis.

Results: By the end of the follow-up, 97 patients with full data were analyzed. Sixty-three (64.9%) patients had wounds healed completely after a median interval of 8 months, 16 (16.5%) patients underwent above-the-ankle amputation, and 26 (26.8%) died. Cox regression analysis showed that patients with higher ABI (RR = 3.097, 95% CI: 1.587–6.043) and serum albumin (RR = 2.755, 95% CI: 1.335–5.687) exhibited a higher probability of wound healing.

Conclusions: Diabetic patients who were not candidates for revascularization who underwent TMA could achieve a satisfactory wound healing rate with a multidisciplinary treatment. ABI and serum albumin were significant predictors of wound healing.

Keywords: Diabetic foot; Outcome; Revascularization; Transmetatarsal amputation

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INTRODUCTION

Diabetic foot is a complicated syndrome that is comorbid with several diabetic complications, such as peripheral arterial disease (PAD) and peripheral neuropathy. It was reported that 10% of diabetic patients will develop this syndrome at least once during their lifetime [1]. Patients with diabetic foot ulcers (DFUs) may undergo minor or major amputation, which will have a considerable impact on patients' life

expectation, quality of life and economic burden. Among minor amputations, transmetatarsal amputation (TMA) appears to be the most convincing in terms of limb salvage rates and in maintaining foot and ankle biomechanics for DFU patients with forefoot necrosis and infection. Under current clinical practice, vascular intervention, anti-infection treatment, surgical operation and postoperative wound care have been performed. However, the reported TMA wound healing rates from multiple series were not good (range, approximately 40–70%) [2–8].

Around half of patients with DFU have coexisting PAD [9, 10], which is considered the most significant limiting factor for healing of ischemic DFU [11]. Therefore, many researchers had implemented revascularization before the definitive surgical procedure or before final wound closure in DFU patients who needed partial foot amputation to improve ischemia. However, the postoperative limb salvage rates or healing rates in DFU subjects receiving revascularization were still low [3, 4, 6, 12]. DFU patients who have indications for TMA always have forefoot gangrene resulting from severe atherosclerotic lesions below the tibial arteries, microangiopathy, infection and severe comorbid conditions. Revascularization for these patients is, therefore, considered inappropriate or has limited effects after operation [13–15].

Up to now, few published outcomes of DFU patients without revascularization existed. Therefore, we recruited DFU patients who were not candidates for revascularization who had undergone TMA to observe the outcomes.

METHODS

Patient Selection

From July 2012 to December 2016, 148 type 2 diabetic patients underwent TMA in our diabetic foot unit. All the patients had forefoot gangrene with more than one toe involved and 30 of them had undergone toectomy but failed to heal. One hundred two patients who were not candidates for revascularization because of severe comorbidity, nonambulatory status,

inadequate outflow vessels, patients' refusal or other conditions not accepted by vascular surgeons were selected.

As this was a follow-up observational study, and there was no intervention during the procedure, it was not registered. All procedures performed were in accordance with the ethical standards of the institutional review board of Ruijin Hospital affiliated with the Shanghai Jiao Tong University School of Medicine and the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from each enrolled patient.

Recorded Demographic, Clinical Variables and Assessed Comorbidities

All the enrolled patients were evaluated within 24 h after being admitted to identify medical conditions, which included: duration, therapy of diabetes, duration of foot ulcer, a past history of hypertension, coronary heart disease, stroke or other chronic diseases. A careful overall physical examination was finished and recorded by an experienced physician. The clinical laboratory variables included glycated hemoglobin (HbA1c) level on admission, serum albumin, hemoglobin, serum creatinine, serum lipids, leukocyte count and 24-h micro-albuminuria quantification. The eGFR value was calculated using the MDRD equation for Chinese adults [16].

The diagnosis of comorbidities was based on a clear history record or through the following methods. PAD was diagnosed if lower limb artery occlusions were spotted by Doppler ultrasound and/or ankle-brachial pressure index (ABI) < 0.9 with an automatic arteriosclerosis detector (Omron, BP-203RPEIII, Japan) [17]. Degree of severity of PAD was subdivided according to measured ABI and classified as mild (ABI, 0.7–0.9), moderate (ABI, 0.41–0.69) or severe (ABI, ≤ 0.4). Diabetic peripheral neuropathy (DPN) was diagnosed by a combination of neuropathic symptoms and signs with abnormal result of the 10-g monofilament test or vibration test using a 128-Hz tuning fork [17]. The diagnosis of heart failure was made according to European Society of Cardiology categories [18].

Treatment

All the foot care and treatments were performed by the same treatment team according to the guidelines for diabetic foot management [19, 20]. TMA surgery was performed by an experienced orthopedic surgeon. All the patients received improved medical treatment, wound care plans, medical nutrition therapy and rehabilitation exercise.

Antibiotic therapy was immediately administered according to the guidelines [20]. The antibiotic therapy was adjusted as soon as the results of the susceptibility tests were available, but not altered if infection was well controlled. Vasodilators were used, mostly assisted by Chinese patent medicines with the role of accelerating blood circulation to improve patient's ischemic symptoms and help antibiotic transport to the wound, and cardiotonic drugs were used in patients with heart failure when appropriate. We paid attention to the improvement of nutritional status and major organ functions, with relaxed glucose control (maintain HbA1c 7.5–8.5%).

Following TMA, the patient was kept in bed with the stump elevated. The dressing was changed every 1–4 days until the stump was out of danger of ischemia and sepsis. Negative pressure wound therapy was done if needed. Rehabilitation through double-leg empty pedal bicycle movement 3000–5000 times per day was confirmed in our study.

Outcomes and Follow-Up

The primary end point of the study was wound healing after TMA. The foot was considered healed when complete re-epithelialization of the surgical wound had occurred. The healing times were calculated, considering the interval between the day of TMA and the day of complete re-epithelialization. A midfoot amputation or an above-the-ankle amputation was proposed and performed in patients in whom the lesion was extended, for stump infarction or for severe infection after TMA. An above-the-ankle amputation was considered a major amputation.

One hundred two patients were followed up at clinic after discharge, generally twice a month for the first 3 months, then every month for the second 3 months and every 3 months after half a year until March 2017 or until death (adjusting the follow-up time when necessary). For patients receiving therapy elsewhere, the follow-up was done by telephoning.

Statistical Analysis

Quantitative variables were described by the mean $\pm$ SD or median (range). Discontinuous variables were expressed using frequency. Kaplan-Meier survival analysis and the log-rank test were performed to analyze variables that affected end points (wound healing, above-the-ankle-amputation and death). Variables of $p < 0.5$ were included in the Cox regression analysis model to analyze the independent influencing factors of end points. All the statistical analyses were performed using the IBM SPSS statistical system (version 23.0). $p < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

By the end of this study, the mean follow-up period was 38 months, ranging from 1 to 87 months. Five patients were lost, and there were 97 patients with full follow-up data; the demographic and clinical characteristics of the study patients are listed in Table 1. The study patients had a long duration of diabetes, accompanied by poor glycemic control and malnutrition, a high prevalence of comorbidities and organ dysfunction.

Primary Wound Healing

Of the 97 patients, 63 (64.9%) had healed completely after a median interval of 8 months (range 1–24 months). The accumulated healing rates at 6 months, 12 months and 3 years were 52.6%, 59.8% and 64.9%, respectively. Patients with serum albumin < 30 g/l and with an ABI <

Table 1 Demographic data, risk factors and comorbidities of the study patients

Variable	Value
Age (years)	66.5 ± 9.9
Male, n (%)	62 (63.9)
Insulin treatment, n (%)	88 (90.7)
Diabetes duration (years)	13.1 ± 7.4
DFU duration (days)	46 (5, 1080)
Hospital stay (days)	30.0 ± 19.8
BMI (kg/m^2)	22.6 ± 2.7
ABI	0.7 ± 0.2
HbA1c (%)	9.7 ± 2.5
24-h urine protein (g/24 h)	1.3 ± 2.0
PAD, n (%)	89 (91.8)
DPN, n (%)	93 (95.9)
Current smoker, n (%)	44 (45.4)
Hypertension, n (%)	64 (66.0)
History of coronary heart disease, n (%)	45 (46.4)
Stroke, n (%)	34 (35.1)
Heart failure, n (%)	36 (37.1)
Left ventricular ejection fraction (%)	60.4 ± 7.5
eGFR < 90 ml/min per 1.73 m^2, n (%)	35 (36.1%)
History of DFU, n (%)	37 (38.1)
Leukocyte count, × 10^9/l	11.6 ± 5.4
Hemoglobin (g/l)	103.4 ± 17.6
Serum albumin (g/l)	30.8 ± 4.5
Total cholesterol (mmol/l)	3.7 ± 1.1
Triglycerides (mmol/l)	1.3 ± 1.0
High-density lipoprotein cholesterol (mmol/l)	0.8 ± 0.3
Low-density lipoprotein cholesterol (mmol/l)	2.3 ± 0.9

ABI ankle-brachial pressure index, *DPN* diabetic peripheral neuropathy, *PAD* peripheral artery disease

0.7 (especially ≤ 0.4) had lower wound healing rates (Table 2). Variables with $p < 0.5$ in log-rank test were age, duration of diabetes, history of hypertension, stroke, heart failure, BMI, serum albumin, hemoglobin, HbA1c, ABI, DPN and leukocyte count. Including the above variables in Cox regression analysis showed that patients with higher ABI (RR = 3.097, 95% CI: 1.587–6.043, $p = 0.001$) and serum albumin (RR = 2.755, 95% CI: 1.335–5.687, $p = 0.006$) exhibited a higher probability of wound healing (Table 3).

Fifty-five patients (61.8%) had healed with an ABI < 0.9. When performing analysis in patients with PAD ($n = 89$), variables with $p < 0.5$ in log-rank test were age, duration of diabetes, duration of DFU, stroke, heart failure, BMI, serum albumin, HbA1c, ABI, DPN, eGFR, hemoglobin and leukocyte count. Including the above variables in Cox regression analysis showed that ABI (RR = 2.232, 95% CI: 1.053–5.229, $p = 0.045$) and serum albumin (RR = 3.475, 95% CI: 1.618–7.463, $p = 0.001$) remained significant factors affecting wound healing, and heart failure was another important factor (RR = 2.289, 95% CI: 1.128–4.645, $p = 0.022$) (Table 3).

Table 2 Wound healing rates of patients at different variable levels

Variable	Number	Wound healing rate (%)
Serum albumin		
< 30 g/l	43	58.1
≥ 30 g/l	54	70.4
ABI		
≤ 0.4	9	11.1
0.41–0.69	31	35.5
0.7–0.9	49	87.8
0.91–1.3	8	100

Table 3 Cox regression analysis of association between variables and wound healing

Patients	Variable	p	RR	RR 95% CI
Total	Serum albumin	0.006	2.755	(1.335, 5.687)
	ABI	0.001	3.097	(1.587, 6.043)
With PAD	Serum albumin	0.001	3.475	(1.618, 7.463)
	ABI	0.045	2.232	(1.053, 5.229)
	Heart failure	0.022	2.289	(1.128, 4.645)

Above-the-Ankle Amputation

Sixteen (16.5%) patients underwent above-the-ankle amputation, and the median interval was 13 months after TMA (range 1–26 months). The cause of higher level amputation was expanded infection, critical ischemia, adipose tissue liquefaction or stump infarction. All patients who received above-the-ankle amputation had an ABI < 0.90; among them, eight had an ABI ≤ 0.4, and seven had an ABI 0.41–0.69. No independent factors affecting above-the-ankle amputation were found.

Death

Of the 97 patients, 26 (26.8%) died, including 13 patients from cardiac accident (9 from heart failure and 4 from myocardial infarction), 4 from renal failure, 3 from cerebrovascular accident, 2 from malignant tumor, 2 from pulmonary infection and secondary multiple organ failure, 1 from severe infection of foot ulcer and 1 unknown because of sudden death. Two patients had died from heart failure within 30 days postoperatively and 24 patients during the follow-up period at a median of 20 months (range 1–45 months). The accumulated mortality rates at 6 months, 12 months and 3 years were 5.2%, 10.3% and 24.7%, respectively. No independent factors affecting death were found.

DISCUSSION

Our study showed that the TMA patients treated without revascularization had deteriorated medical condition, mainly manifested in long durations of diabetes and foot ulcer, severe comorbidities and widespread malnutrition. However, we achieved a higher 3-year accumulated healing rate (64.9% in total; 61.8% in patients with PAD) and a lower 3-year accumulated mortality rate (24.7%) after a comprehensive treatment and postoperative care. This study provided a reference for the treatment of TMA patients who were not feasible for revascularization.

In contrast, the following were previously reported results on TMA in which most subjects received revascularization [3, 4, 6, 12]. Patients' baseline characteristics were as follows: average age ranging from 55 to 64 years old, cardiovascular-related factors including smoking 18–56% [3, 4, 12], hyperlipidemia 17.6–51% [3, 4], hypertension 63–76% [4, 12] and cardiac disease 37–51% [4, 12] and other indicators [12], BMI 27.6 kg/m^2, heart failure 32% and renal insufficiency 21%. Outcomes included healing rate 43–62% [3, 6, 12], limb salvage rate 68% [4] and survival rate 67–82% and 35–69% at 1 and 3 years, respectively [3, 6, 12]. It is enough to observe that our research patients' medical conditions were not better than those of these patients regardless of age, cardiovascular-related factors and other comorbidities. However, we achieved healing and survival rates comparable to the above studies. Maybe this favorable outcome is partially owing to medicine and rehabilitation (double-leg empty pedal bicycle movement is similar to intensive walking exercise) to improve lower extremity circulation during the entire study [15, 21], paying attention to the improvement of nutritional status [22, 23] and organ functions as well as proper HbA1c level [24].

In the above studies [3, 4, 6, 12], some patients had undergone revascularization, either endovascular or surgical, before amputation was performed. Study outcomes were based on patients who had and had not undergone revascularization. Some came to the conclusion

that the need for revascularization was not associated with limb loss [4]. It is currently unclear how to identify those patients with PAD and DFU who are most likely to benefit from revascularization. Furthermore, there is debate about the selection of the correct revascularization technique [25]. We also learned that some studies on foot ulcers treated without revascularization while focusing on wound and comorbidity management yielded encouraging results. Marston et al. [26] reported 52% of limb ulcers in which 70.4% were diabetic and healed within 1 year of follow-up, and Elgzyri et al. [27] reported 50% of studied DFU patients healed either primarily (76%) or with a minor amputation (24%) of continuous follow-up until healing. It can be concluded from these studies that diabetic patients with ischemic foot ulcers not feasible for revascularization still have a possibility of healing.

PAD has been shown to be the significant predictor of ulcer healing in diabetic patients [11]. Pinzur et al. [28] reported a 92.2% healing rate after TMA with a minimum ABI of 0.5 in diabetic patients and serum albumin of 30 g/l. Pollard et al. [7] reported a palpable pedal pulse was a clinically significant predictor of healing after TMA. Marston et al. [26] reported ABI was independently associated with amputation at 1 year; 32% of limbs with an ABI < 0.5 and 43% of limbs with an ABI < 0.4 required amputation compared with 15% of limbs with an ABI 0.5–0.7. In the current study, ABI was closely associated with wound healing. The healing rate in patients with an ABI 0.7–0.9 was 87.8% and ABI 0.41–0.69 was 35.5%, but ABI ≤ 0.4 only 11.1%; 16 patients received above-the-ankle amputation, and half of them had an ABI ≤ 0.40. This suggested that patients with severe lower limb ischemia might be not feasible candidates for TMA. Instead, further amputation based on angiography might be performed.

The presence of DFU has to be recognized as a sign of multi-organ disease [29, 30], and a multidisciplinary treatment is the best way to improve the outcome [31, 32]. For TMA, receiving revascularization or not, the following methods should be considered as top priorities to facilitate the success of partial foot amputation procedures: teamwork that includes comprehensive medication therapy, wound care, rehabilitation exercise, and improving nutritional status and organ function.

There were several limitations to the study. First, it was a single-center observation, inevitably including selection bias. Second, although the principles of treatment are the same, comparison with other studies is difficult owing to differences in design, patient selection, definitions, follow-up time, specific treatment details and other confounding factors. Third, very few studies have been conducted on diabetic patients with the same question, and the sample size of our study was not large. We expect a TMA cohort of a bigger sample investigating this issue to be reported in the future.

CONCLUSIONS

Diabetic patients who were not candidates for revascularization who underwent TMA could achieve good wound healing rates with improved medical treatment, wound care plans, medical nutrition therapy and rehabilitation exercise. This study indicates that PAD and patients' medical condition are crucial in the wound healing of TMA.

ACKNOWLEDGEMENTS

Xiang collected data. Shanshan Zhang analyzed the data and drafted the manuscript.

Disclosures. Shanshan Zhang, Shumin Wang, Lei Xu, Yang He, Jiali Xiang and Zhengyi Tang have nothing to disclose.

Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the institutional review board of Ruijin Hospital affiliated with the Shanghai Jiao Tong University School of Medicine and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients included in the study.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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