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ORIGINAL ARTICLE

Tibial cortex transverse transport facilitating healing in patients with recalcitrant non-diabetic leg ulcers

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SUMMARY

Objective: The treatment of recalcitrant not-diabetic leg ulcers remains challenging. Distraction osteogenesis is accompanying by angiogenesis and neovascularization in the surrounding tissues. We previously applied tibial cortex transverse transport (TTT) to patients with recalcitrant diabetic foot ulcers and found neovascularization and increased perfusion in the foot and consequently enhanced healing and limb salvage and reduced recurrence. However, the effects of TTT on recalcitrant non-diabetic leg ulcer remains largely unknown.

Methods: Consecutive patients (n = 85) with recalcitrant non-diabetic leg ulcers (University of Texas Grade 2-B to 3-D, ie, wound penetrating to the tendon, capsule, bone, or joint with infection and/or ischemia) were recruited and divided into TTT (n = 42) and control (n = 43) groups based on the treatment they received. There were 36 (85.7%) arterial ulcers, 4 (9.5%) venous ulcers and 2 (4.8%) mixed ulcers in the TTT group and 32 (74.4%) arterial ulcers, 7 (16.7%) venous ulcers and 4 (9.3%) mixed ulcers in the control group ($p > 0.05$). The two groups were matched on demographic and clinical characteristics. Patients in the TTT group underwent tibial corticotomy followed by 4 weeks of distraction medially then laterally, while those in the control group received conventional surgeries (debridements, revascularization, reconstruction with flaps, or skin grafts or equivalents). Ulcer healing and healing time, limb salvage, recurrence, and patient death were evaluated at a 1-year follow-up. Changes in leg small vessels were assessed in the TTT group using computed tomography angiography (CTA).

Results: TTT group had higher healing rates at 1-year follow-up than the control group (78.6% [33/42] vs. 58.1% [25/43], OR 2.64 [95% CI 1.10 to 6.85], p = 0.04). The healing time of the TTT group was shorter than the control group (4.5 vs. 6.1 months, mean difference −1.60 [95% CI -2.93 to −0.26], p = 0.02). There were no significant differences in rates of major amputation, reulceration, or mortality between the groups ($p > 0.05$). TTT group displayed more small vessels 4 weeks postoperatively at the wound area, the foot, and the calf of the ipsilateral side in CTA. All patients in the TTT group achieved good union at the osteotomy site and had no skin or soft tissue necrosis or infection around the incision area.

Conclusion: The findings showed that TTT facilitated the healing of recalcitrant non-diabetic leg ulcers and reduced the healing time compared with conventional surgeries. They suggest that TTT is an effective procedure to treat recalcitrant non-diabetic foot ulcers compared with standard surgical therapy. The procedure of TTT is relatively simple. Randomized controlled trials are required to confirm these findings.

The translational potential of this article: TTT can be used as an effective treatment for recalcitrant non-diabetic leg ulcers in patients. The mechanism may be associated with the neovascularization in the ulcerated foot induced by TTT and consequently increased perfusion. Together with previous findings from recalcitrant diabetic leg ulcers, the findings suggest TTT as an effective procedure to treat recalcitrant chronic leg ulcers.

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Introduction

Chronic leg ulcer is an open skin lesion of the leg or foot persisting for more than four weeks and showing no tendency to heal after three or more months of appropriate treatment [1,2]. The most common causes of chronic leg ulcers are peripheral venous or arterial disease and neuropathy and diabetes [3]. Based on diabetic status, chronic leg ulcers can be classified into diabetic or non-diabetic ones. In contract to diabetic foot ulcers, non-diabetic leg ulcer occurs in patients with higher ages and lower body mass index [4,5]. The incidence of non-diabetic chronic leg ulcers ranges from 1.9% to 15% and is rising because of an increased prevalence of obesity, hyperlipidemia, hypertension, and smoking [1,6,7]. Non-diabetic chronic leg ulcer is frequently complicated by infection, gangrene, and amputation, and is associated with prolonged disability, important socioeconomic impact, and significant psychosocial morbidity.

The therapies of non-diabetic chronic leg ulcers include wound care, debridements, negative pressure therapy, flap reconstruction, split-thickness skin grafting, and revascularization (autogenous venous bypass or endophlebectomy, valve repair, valve transposition, or transplantation) [1,7,8]. They have no definitive effects and are associated with frequent complications such as flap loss and arterial reocclusion. Therefore, the treatment of non-diabetic chronic leg ulcers is still challenging.

Previously, based on the distraction osteogenesis/angiogenesis or Ilizarov's law of stress-tension [9,10], we developed the technique of tibia transverse distraction which involves corticotomy at proximal tibia followed by medial-then-lateral distraction [11,12]. We applied it to the treatment of severe and recalcitrant diabetic foot ulcers and attained outstanding clinical results (significant higher rates of ulcer healing and limb salvage and lower recurrence rate) [11]. Furthermore, the effect is attributable to the bone transport mediated-increase in angiogenesis and neovascularization and consequent perfusion in the foot [11]. We have coined the term tibia transverse transport (TTT) for this technique [12]. Given that non-diabetic chronic leg ulcer shares some important common pathogenesis (such as ischemia and infection) with diabetic foot ulcer, we speculated that TTT may have effects on the treatment of non-diabetic chronic leg ulcer. However, no studies have reported the effect of TTT on patients with non-diabetic chronic leg ulcers. Thus, we aimed to evaluate the effect of TTT on healing, limb salvage, and recurrence of non-diabetic leg ulcers compared with conventional treatments (debridements, revascularization, negative pressure wound therapy, local or free flaps, or skin graft or equivalent). Venous ulcer was defined as an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension [7].

Material and methods

Study design and setting

Consecutive patients with non-diabetic chronic leg ulcers or recurrent ulcers were recruited from our hospital between January 2018 and June 2019. The patients were divided into the TTT (recruited from the Department of Bone and Joint Surgery and received TTT) or the control group (recruited from the Department of Vascular Surgery and not received TTT) according to whether they received TTT. Inclusion criteria included over 18 years of age, with a non-healing or recurrent ulcer for at least 3 months. Previous non-surgical treatments included wound care, wearing braces, compression, infection, and blood glucose control. Previous surgical procedures included debridements [13–15], revascularization [7,16], skin equivalents or grafting, and local or free flap transplantation [17]. Exclusion criteria included diabetic foot ulcers, ulcers on the tibial incision area, ulcers caused by tumors, history of cerebral infarction or myocardial infarction, or heart failure, cancer within the last 3 months; and use of cortical steroids, immunosuppressive drugs, and/or chemotherapy treatment. If the patient had a stenosis ≥80% of the arterial lumen of anterior or posterior arteries or peroneal artery but could be treated by revascularization procedure for treatment, then they were also suitable for TTT. The study was approved by the institutional review board at the First Affiliated Hospital of Guangxi Medical University. All participants provided informed consent before entering the study.

Description of patients

A total of 85 patients (42 in the TTT group and 43 in the control group, separately) were eligible for recruitment (Table 1). Based on the etiology of the patients' ulcer, there were 36 (85.7%) arterial ulcers (arterial ischemia cause [8]), 4 (9.5%) venous ulcers (venous cause [7]), and 2 (4.8%) mixed ulcers (arterial ischemia plus venous cause) in the TTT group and 32 (74.4%) arterial ulcers, 7 (16.7%) venous ulcers, and 4 (9.3%) mixed ulcers in the control group ($p > 0.05$). All the leg ulcers were in Grade 2-B to 3-D (wound penetrating to the tendon, capsule, bone, or joint with infection and/or ischemia) of the University of Texas wound classification system [18]. All patients underwent debridements in both groups. Most patients in the control group received revascularization ($p < 0.001$) as anticipated, while there were no differences in local or free flap ($p = 0.48$) or negative pressure wound therapy ($p = 0.48$) between the groups. There were no differences in factors associated with ulcer healing such as age, sex, smoking status, ulcer duration, or ulcer size between the groups ($p > 0.05$).

Clinical and imaging evaluation

The location and duration of the leg ulcers were recorded. The severity of the ulcer was evaluated using the University of Texas wound classification system [18]. If an infection was suspected or confirmed, a culture of wound secretions was performed to identify the causative

Table 1
Patient descriptive characteristics.

Parameters	TTT (n = 42)	Control (n = 43)	p value
Age (years)	63.5	63.1	0.88
Male sex, n (%)	33 (78.6)	33 (76.8)	0.84
Duration of ulcers (months)	6.4	4.9	0.44
Ulcer area (cm^2)	16.2	11.0	0.21
University of Texas wound classification system, n (%)			
2-B	6 (14.3)	9 (20.9)	0.42
2-C	6 (14.3)	7 (16.7)	0.80
2-D	12 (28.6)	11 (25.6)	0.76
3-B	1 (2.4)	2 (4.7)	0.98
3-C	1 (2.4)	1 (2.3)	0.48
3-D	16 (38.1)	13 (30.2)	0.44
Site of ulcer, n (%)			
Foot	35 (83.3)	30 (69.8)	0.14
Leg	7 (16.7)	13 (30.2)	
Etiology, n (%)			
Arterial	36 (85.7)	32 (74.4)	0.19
Venous	4 (9.5)	7 (16.7)	0.55
Mixed	2 (4.8)	4 (9.3)	0.69
Stroke, n (%)	1 (2.4)	0 (0.0)	0.99
Hypertension, n (%)	16 (38.1)	12 (27.9)	0.32
Coronary heart disease, n (%)	4 (9.5)	4 (9.3)	0.74
Current smoker, n (%)	15 (35.7)	24 (55.8)	0.06
Prior treatment, n (%)			
Debridements	39 (92.9)	40 (93.0)	0.98
Negative-pressure wound therapy	0 (0.0)	0 (0.0)	—
Revascularization	10 (23.8)	11 (25.6)	0.85
Skin graft or equivalent	2 (4.8)	0 (0.0)	0.46
Local or free flap	1 (2.4)	1 (2.3)	0.48
Current treatment, n (%)			
Debridements	42 (100.0)	43 (100.0)	—
Negative-pressure wound therapy	1 (2.4)	1 (2.3)	0.48
Revascularization	0 (0.0)	39 (90.7)	<0.001
Skin graft or equivalent	0 (0.0)	0 (0.0)	—
Local or free flap	0 (0.0)	1 (2.3)	0.48

Data are presented as the mean ± SD or n (%); TTT = tibial cortex transverse transport organism and its antibiotic sensitivity. For open, infected wounds, a bone probe test was performed and x-rays of the ulcer site were taken to detect osteomyelitis [19]. Peripheral arterial disease of the lower extremities was defined as the absence of palpable dorsal and posterior tibial arteries and/or an ankle brachial index <0.9 [20]. Vascular status of the lower extremities is assessed by color ultrasound Doppler and computed tomography angiography (CTA) [11]. If there was evidence of obstruction and occlusion caused by atherosclerosis, the patient was referred to a vascular surgeon for further evaluation and revascularization if indicated.

Surgical techniques

TTT was performed according to the surgical protocol and a monolateral external fixator assembly was used as previously reported [11,12] (Fig. 1). Briefly, a curve skin incision 3 cm in length, 2 cm medal to tibial crest, and 3 cm distal to the tibial tuberosity was made, followed by retraction of the subcutaneous soft tissues. The periosteum was exposed and preserved. Then a rectangle corticotomy 5 cm in height and 1.5 cm in width was created by drilling multiple holes along the rectangle on the anteromedial cortex of the proximal tibia. After pre-drilling, two 3-mm nails were screwed into the osteotomies cortex for bone transport, and another two 4-mm nails were screwed into the tibia bilaterally for stabilization of the external frame. Then the modular components were assembled to form a stable construct for bone transport.

After the assembly of the external fixator, aggressive debridements was performed according to international guidelines [13–15]. The size of the leg ulcers was assessed by measuring the maximum length and maximum width by an observer (GL) who was unaware of the treatment (TTT or conventional surgeries). The wounds in the TTT group were left open without the use of skin grafts or flap grafts. In the control group, all the patients underwent early and aggressive debridements [13–15].

Aftercare and cortex transport

The patient's postoperative care and the tribal cortex transport were carried out as previously described [11]. Briefly, the patient underwent daily nail care and open dressing changes, and postoperative x-rays were taken one day postoperatively to confirm the position of the osteotomy and screws (Fig. 2). After a 2-day latency, tibial cortex transport was initiated at a rate of 0.25 mm every 6 h, and then the patient was discharged and instructed to continue the tibial cortex transport at home, ie, medially for 14 days, followed by lateral translation for 14 days (Fig. 1). To confirm the cortex transport, x-rays were taken 2 and 4 weeks after transport initiation (Fig. 2). Because of the good stability of the external fixator, early local weight bearing with crutches (two days after the operation) was possible. After 4 weeks of cortex transport, the external fixator was removed in the outpatient department, and CTA was performed again. Four weeks after the removal of the external frame, x-rays were taken to confirm that the cortex had returned to its original position (Fig. 2), and then full weight-bearing walking was allowed. Daily wound care and decompression were the same for both groups.

Follow-up

Patients were followed up for evaluation and dressing changes weekly in the outpatient department for the first 12 weeks postoperatively. Follow-up was then performed monthly intervals until the 1-year follow-up was completed. The ulcer status (healing, healing time, major amputation, or recurrence) was evaluated and recorded.

Outcomes

The primary outcomes include the rate of ulcer healing, limb salvage, recurrence, and patient death at 1 year and ulcer healing time. Ulcer healing was defined as complete epithelialization without any drainage of a previous foot ulcer site and after a further 2 weeks of complete closure [21]. A recurrent ulcer was defined as a new leg ulcer in a patient who had a history of leg ulceration irrespective of location and time since previous leg ulcers. The secondary outcome is changes in the lower-limb small arteries in the TTT group evaluated by CT angiography. The numbers and kinds of complications were recorded for both groups.

Statistical analysis

The patient's demographic and clinical data were compared between groups using a t-test for normally distributed variables. For categorical data, the chi-square test or Fisher's exact test (if the expected count was less than 5 for any contingency cell) was used and Mann–Whitney U tests for nonparametric variables. Categorical measures were presented by numbers and percentages and as the mean ± SD for continuous variables. Statistical significance was set at an alpha level <0.05. SPSS version 20.0 (IBM Corp, Chicago, IL, USA) was used for all statistical analyses.

Results

Two (4.7%) and 1 (2.3%) patients in the TTT and control group, separately, died during the 1-year follow-up (Table 2). TTT group had higher ulcer healing rate at 1-year follow-up than the control group (78.6% [33/42] vs. 58.1% [25/43], OR 2.64 [95% CI 1.10 to 6.85], p = 0.04). The healing time of the TTT group was shorter than the control group (4.5 vs. 6.1 months, mean difference −1.60 [95% CI -2.93 to −0.26], p = 0.02).There were no significant differences in rates of major amputation (p = 0.12), ulcer recurrence (p = 0.48) or death (p = 0.98) between the groups. The TTT group displayed more small vessels 4 weeks postoperatively at the wound area, the foot, and the calf of the ipsilateral side in CTA (Fig. 5). All patients in the TTT group achieved good union at the osteotomy site without osteomyelitis and wound healing at the incision area without skin or soft tissue necrosis or infections (Figs. 2–4).

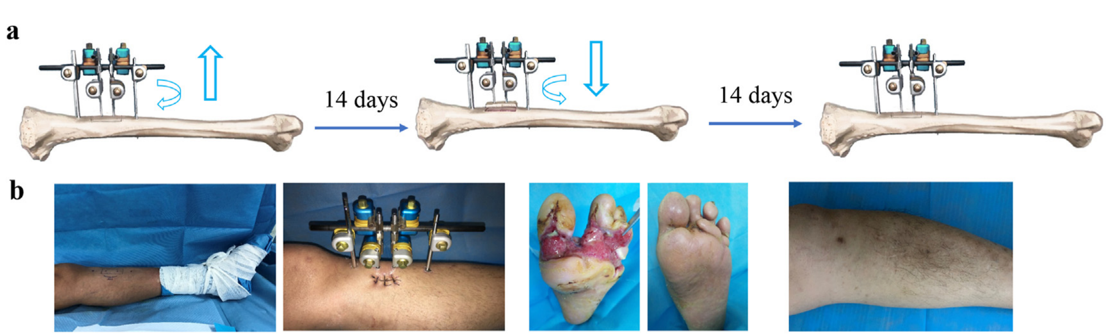

Figure 1. The schematic and procedure of TTT. (a) After corticotomy at the proximal tibia, the cortex was transversely distracted, 14 days medially followed by another 14 days laterally, by an external fixator. (b) TTT was performed followed by debridements. The wound was left open without the use of skin grafts or flaps. Eventually, the ulcer healed as well as the tibial incision.

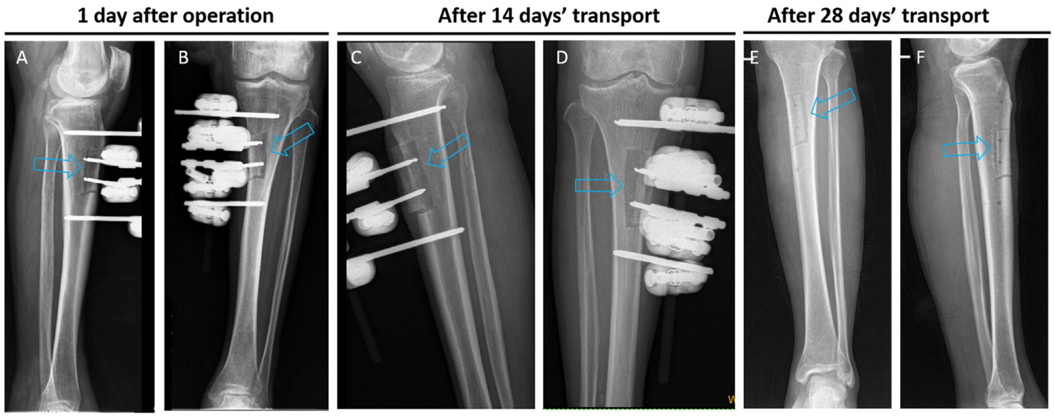

Figure 2. These postoperative radiographs show the procedure of TTT (A–B) The positions of corticotomy and external fixator were confirmed on AP and lateral radiographs 1 day postoperatively (C–D) After 2 weeks of medial distraction, the osteotomies cortex reached the maximum transport, splitting at the tibia (E–F) This was followed by 2 weeks of lateral transport returning the cortex to its original position, after which the external fixator was removed.

Table 2
Outcomes of tibial cortex transverse transport for recalcitrant non-diabetic leg ulcers.

Outcome parameters	TTT (n = 42)	Control (n = 43)	Odds ratio or mean difference (95% CI)	p value
Ulcers healed by 1 year, n (%)	33 (78.6)	25 (58.1)	2.64 (1.10–6.85)	**0.04**
Ulcer healing time (months)	4.5	6.1	−1.60 (−2.93 to −0.26)	**0.02**
Major amputation, n (%)	0	4 (9.3)	1.10 (1.00–1.21)	0.12
Ulcer recurrences, n (%)	0	1 (2.3)	1.02 (0.98–1.07)	0.48
Death, n (%)	2 (4.7)	1 (2.3)	2.05 (0.18–23.48)	0.98

Data are presented as n (%) or the mean ± SD; TTT = tibial cortex transverse transport

Discussion

Distraction osteogenesis stimulates angiogenesis and neovascularization in the bone itself and the surrounding tissues [9,10,12,22,23]. Based on this theory, we previously applied TTT to patients with severe and recalcitrant diabetic foot ulcers, and found neovascularization and sequentially increased perfusion in the ulcerated foot which facilitates ulcer healing and limb salvage and reduces reulceration [11]. However, to our best knowledge, no study has evaluated the effect of TTT on non-diabetic ulcers. In this study, we applied TTT to non-diabetic recalcitrant leg ulcers and found a greater healing rate in a shorter healing time than patients undergoing standard surgical treatment in a 1-year follow-up. These results suggest that TTT is an effective procedure to treat recalcitrant non-diabetic leg ulcers compared with standard surgical therapy.

Treatment of recalcitrant non-diabetic leg ulcers using standard surgical procedures have shown healing rates of 58%–85% after 4-to-7-year follow-up [7,8,17,24]. Additionally, even when the ulcer has healed, there is a 25%–56% recurrence [25–27]. However, we found a healing rate of 78.6% and no cases of recurrence at 1-year follow-up in the TTT group with higher severity of the ulcers (ulcer grade, size, and duration) in the present study. Furthermore, the TTT group had a higher proportion of ulcers healed in a shorter time than the control group although most patients in the control group underwent revascularization which is believed to enhance large vessel perfusion and contribute to ulcer healing. Therefore, our findings suggest that TTT can be served as an effective treatment for non-diabetic recalcitrant leg ulcers. This is in accordance with the findings of our previous study which found outstanding clinical effects of TTT on recalcitrant diabetic foot ulcers [11]. Nevertheless, the ulcer healing rate of the current study (78.6%, 33 of 42) is lower than the previous study (96%, 131 of 136) [11]. This discrepancy may be mainly attributed to two reasons. First, atherosclerosis-induced leg ulcers which comprise a high portion (90.5%, 38 of 42) of the ulcers in the present study have different characteristics from some diabetic foot ulcers. Atherosclerosis influences not only small vessels but also large arteries (eg, anterior and posterior arteries and peroneal artery) and thus leads to severe tissue ischemia or necrosis. In contrast, in some patients with diabetic foot ulcers, there are still tissue perfusion at different levels, particularly in those complicated by infections (ie, wet gangrene) – otherwise the bacterial cannot survive [11,18]. Our previous study demonstrated that TTT stimulated regeneration of small vessels at the foot and recanalization of the small and medium arteries, while the changes in the structure of calcified large arteries were not obvious [11]. Thus, the effect of TTT on atherosclerotic leg ulcers may not as good as some diabetic foot ulcers. Second, the follow-up duration of the current study is shorter (1-year) than the previous one (2-year) and it is anticipated that some ulcers would heal later. In contrast to the previous study, the major amputation and recurrence rates did not reach significance although they tended to be lower in the TTT group. This is probably because of the smaller sample size of the present study (n = 42 in the TTT group and n = 43 in the control group) than the previous one (n = 136 in the TTT group and n = 137 in the control group).

A previous study showed that only 1.5% (4 of 273) of patients with recalcitrant diabetic foot ulcers recruited from our department underwent revascularization [11], probably because of the cost of the surgery and lack of acceptance. Consistently, no patient in the TTT group of the present study received revascularization. However, most patients in the control group underwent revascularization. This is not unanticipated because they were from the department of vascular surgery and treated by vascular surgeons. Against this, the TTT group still had a higher healing rate in a shorter time. Therefore, the effect of TTT on recalcitrant non-diabetic foot ulcers is underestimated.

The protocol of TTT established previously is primarily for recalcitrant diabetic foot ulcers, and good clinical outcomes (ulcer healing, limb salvage, and recurrence) were attained [11]. Considering that diabetic and non-diabetic share some similar characteristics (eg, chronic and ischemic), the same surgery protocol was applied. For example, after TTT surgery we performed only open wound dressing and used no special treatments such as growth factor, hyperbaric oxygen [28], or flap reconstruction. According to international guidelines, some of the special treatments have no solid effect while are expensive and high cost for patients [7,8]. However, we cannot exclude the possibility that the application of some special treatments may accelerate ulcer healing or improve the outcome. We believe that TTT is crucial, but adjunctive treatment treatments may help to maximize the effect. This needs further

Figure 3. This figure shows the effects of TTT on a recalcitrant atherosclerotic ulcer. This 57-year-old female had the ulcers on her left foot persisting for more than 6 years, with the forefoot and the heel involved. A–C: Before debridements, the first toe had been amputated, with the exposure of the head of metatarsal bone and necrosis of the surrounding tissues. The third toe was necrotic. D–F: During the operation, the devitalized tissue was removed and the third toe was amputated. G–I: Six weeks after the operation, the ulcers were completely healed.

investigation.

Distraction osteogenesis is accompanied by angiogenesis in the surrounding tissues [10,22]. Furthermore, TTT mediates neovascularization in the foot of patients with diabetic foot ulcers which is frequently complicated by atherosclerosis using CTA and CT perfusion [11]. In this study, we found an increase in small vessels in both the calf and the foot after TTT. Thus, this result is consistent with previous studies [10,11,22]. Moreover, as the foot ulcer is distant to the corticotomy position, the findings of the current study and the previous one [11] together suggest that TTT may have a systemic effect in promoting angiogenesis in the presence of a distant limb ulcer. Additionally, studies reported similar pathogenesis (lack of capillaries) and the healing process in artery ischemic and venous ulcers from a microcirculatory point of view using laser Doppler perfusion imager and capillary microscopy [29]. Therefore, TTT may have enhanced the healing of artery ischemic and venous ulcers via stimulation of angiogenesis and neovascularization and consequently improvement of microcirculation. On the other hand, lower limb ischemia is complicated by hypoxia, inflammation, edema, increased pressure, and vasospasm in bone marrow as well as increased intraosseous pressure. These factors together contribute to lower limb syndromes including rest pain and low temperature. The relief of pain and an increase in temperature of the lower limb was observed as early as 2 days after TTT when neovascularization is generally considered not having occurred. Thus, corticotomy in TTT may function as an "open window" effect resulting in decreasing the bone marrow pressure and relieving the vasospasm. However, this hypothesis needs to be tested in the future.

Operation on limbs in ischemia raises the concern about whether the incision or osteotomy would lead to postoperative skin or soft tissue

Figure 4. This figure shows the effects of TTT on a recalcitrant venous ulcer on the lateral calf of a 60-year-old man. The ulcer persisted for more than 8 years, and the size was 5 cm × 3 cm, with the depth reaching the tibial cortex. It was also complicated by infections (A) Necrosis and swelling of the ulcer edge were obvious before surgery (B) Four weeks postoperatively, the wound was much cleaner, with minimal swelling and the granulation tissue was evident. Note the external frame attached (arrow) (C) Eight weeks postoperatively, the wound was much smaller, with epithelization at the wound edge (D) The ulcer was completely healed at 16 weeks postoperatively.

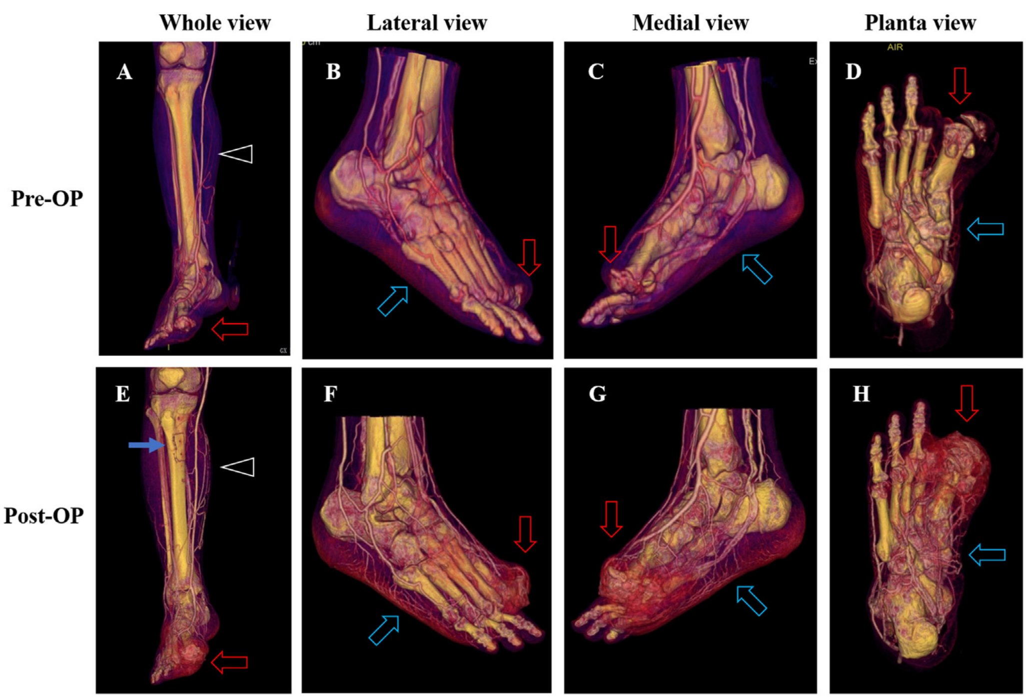

Figure 5. Representative CT angiography images from a patient with atherosclerotic foot ulcer at the first toe treated with TTT. Compared with preoperative status (A–D), 4 weeks operatively (E–H) the ulcerated feet displayed more small vessels at the calf (white arrowheads; blue solid arrow in E indicates the position of corticotomy), the planta (blue arrows), and the toes (red arrows), separately. Some small arteries became visible postoperatively compared with preoperatively, suggesting patency after TTT. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

necrosis or infection or osteomyelitis at the operation site. However, no such complications were found in the current study as well as in the previous study which focusing on diabetic foot patients. This is probably because TTT induces neovascularization in the osteotomies cortex and the surrounding soft tissues as well as evident by the CTA which consequently increases perfusion and enhances tissue healing and anti-infection. Previous studies using Ilizarov's technique of horizontal tibial fragment distraction to treat Buerger's Disease (Thromboangiitis Obliterans) reported complications such as 3.3% (2 of 60 patients) of perioperative tibial fracture [30] and 6.7% (2 of 30 patients) of osteomyelitis [31], separately. In contrast, we found no tibial fracture or osteomyelitis at the corticotomy site in this study. This discrepancy is probably because a much smaller osteotomy area was adopted in our surgical protocol (1.5 × 5.0 cm^2) than previous studies (3 × 12 cm^2) [30, 31].

The present study displays the outcomes of TTT from patients with recalcitrant non-diabetic foot ulcers; good outcomes from patients with milder ulcers were also attained (data not shown). Based on this, we suggest the application of TTT to patients with ulcers of University of Texas grade 2-B and above (wound penetrating to the tendon, capsule, bone, or joint with infection and/or ischemia) and without occlusion or stenosis ≥80% of the lumen of the large arteries of the lower extremity. If the occlusion or stenosis ≥80% of the lumen of the large arteries is present, it is recommended to perform revascularization before TTT to maximize its effect. Or, if a wound is still not healing well after other treatments, we suggest considering using TTT. Additionally, if the leg ulcer is combined with one or more organ damages or failures such as chronic kidney disease and coronary heart disease, a multidiscipline therapy including the TTT technique is suggested. On the other hand, we suggest against the application of TTT to ulcers complicated by acute limb ischemia in which limbs are immediately threatened or are irreversibly damaged and resultant major tissue loss or permanent nerve damage is inevitable [32,33]. In these situations, immediate revascularization or primary amputation is required [32].

This study has several limitations. First, it was non-randomized and selection bias is a concern, but we believe that selection bias is not serious because the patients in both groups were consecutively recruited with the same criteria by different physicians in different departments. Even so, the findings of the present study still need to confirm in future randomized studies. Second, the two groups of patients received debridements and wound care in different departments, thus it was questioned whether the treatments were sufficiently matched for comparison. Treatment differences may have led to the bias of our findings. As the debridements procedure and wound care regimen were the same in the two departments, we do not consider this limitation serious. Third, this is a retrospective study, and computed tomography perfusion was not performed for some patients, and thus the data of leg or foot were not available for analysis. A prospective study is needed in the future to investigate the association of TTT with perfusion and leg ulcer healing. Last, as there are much fewer studies or guidelines focusing on non-diabetic leg ulcers than on diabetic foot ulcers [11], some evaluation methods (such as Texas University wound classification system) [18] originally developed for diabetic foot ulcers were adopted. The methods require validation in patients with non-diabetic foot ulcers although their application facilities the comparison of the current study with the previous one focusing on diabetic foot ulcers [11].

In conclusion, we found that TTT facilitates the healing of recalcitrant non-diabetic leg ulcers and reduces the healing time compared with conventional surgeries. These findings suggest TTT as an effective treatment for recalcitrant non-diabetic leg ulcers. The mechanism may be associated with the neovascularization in the ulcerated foot induced by TTT and consequently increased perfusion. Additionally, the procedure of TTT is relatively simple. Future large population studies will be needed to confirm the effectiveness and safety of the procedure.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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