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Original Article

A prospective cohort study of negative pressure wound therapy combined angioplasty for diabetic foot patients with critical limb ischemia

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Abstract: To evaluate the clinical efficacy and security of combined negative pressure wound therapy (NPWT) and percutaneous angioplasty (PTA) in the treatment of diabetic foot ulcers with critical limb ischemia (CLI). We enrolled 97 patients from 142 cases suffered from diabetic foot ulcers into this multi-center prospective cohort study. Patients who were assigned to NPWT-PTA (n=56) or NPWT (n=41) group based on standard off-leading therapy as needed, and were followed-up at 8 weeks and 20 weeks, their ankle-brachial pressure index (ABI), wound area, healing time and adverse events were monitored. A multivariate Cox proportional hazards regression analysis was used to determining the risk factors of wound healing. A greater proportion of wound healing in NPWT-PTA group was observed compared with NPWT group (61.5% *vs* 40.9%, *P*=0.004) at 20 weeks. The time of wound healing was earlier in NPWT-PTA group than NPWT group (48.3±32.8 days *vs* 77.1±27.1 days, *P*=0.009) at 20 weeks. ABI in NPWT-PTA group was higher than NPWT group at both 8 weeks (0.83±0.19 *vs* 0.46±0.15, *P*=0.000) and 20 weeks (0.72±0.17 *vs* 0.53±0.12, *P*=0.000). The decrease of ABI (HR=15.000, 95% CI=2.243-100.333, P=0.005) and increase of wound area (HR=0.926, 95% CI=0.866-0.990, P=0.025) were independent risk factors of wound healing. There was no significant difference in adverse events between the two groups. Combined NPWT with PTA therapy is effective and safe for diabetic foot ulcers with CLI by increasing the level of ABI, and results in a higher proportion of wounds closure.

Keywords: Negative pressure wound therapy, percutaneous angioplasty, diabetic ulcer, critical limb ischemia

Introduction

Diabetic foot wounds are one of the most serious and complex sequelae of diabetes mellitus [1, 2]. Non-healing chronic diabetic wounds are often large and deep with compromised wound healing capacity [3]. Various diabetic foot wound treatments have been reported in the literature, including advanced moist wound therapy [4], treatment with growth factors [5], bioengineered tissue or skin substitutes [6], NPWT (negative pressure wound therapy) [7] and so on.

Over the past several years, NPWT has been applied to treat these complex diabetic wound. It is a noninvasive system that creates a localized subatmospheric pressure environment, accelerates wound healing through creating a moist healing environment, preparing the wound bed for closure, reducing edema, and promoting formation of granulation tissue. And it is the delivery of intermittent or continuous subatmospheric pressure by a special pump to keep a closed environment which is connected to an open-celled, resilient and foam-surface dressing covered with an adhesive drape, and high efficacy of NPWT in treating diabetic foot wound has been elaborated in several studies [8].

Moreover, a recent multicenter study showed that approximate 20% of patients who were newly diagnosed with type 2 diabetes also had peripheral arterial disease (PAD) [9]. At the same time, another European large multicenter

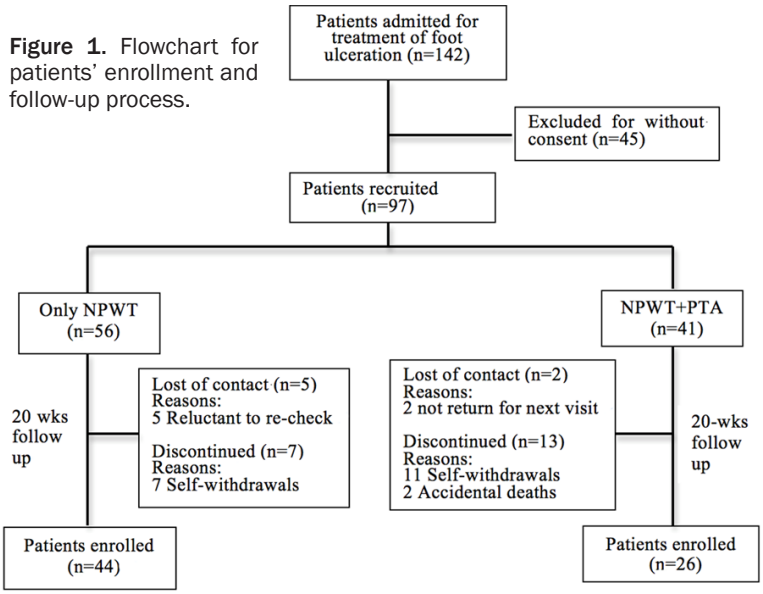

Figure 1. Flowchart for patients' enrollment and follow-up process.

survey (involving more than 1200 diabetic foot patients in 14 highly specialized centers from 10 different European countries) showed that 49% of patients have a preeminent ischemic component which influences the evolution of the diabetic foot pathology, leading to a non-healing wound and eventually a major amputation [10]. Meanwhile, some studies have reported that the successful revascularization of diabetes mellitus (DM) patients with critical limb ischemia (CLI) were beneficial to improve the healing process of diabetic ischemic ulcers [11]. At present, although bypass surgery still plays a significant role in the revascularization of CLI [12], increasing clinical experience over the past two decades shows that endovascular strategies including PTA have low complication rates and high limb salvage rates comparable with bypass surgery [13-16].

To our knowledge, there is little known about the efficacy of combined NPWT and PTA to treat diabetic wound with CLI. Therefore, we undertook a prospective cohort study to investigate the effect of NPWT-PTA compared to the therapy of NPWT in diabetic foot patients accompanied by low limb ischemia.

Materials and methods

Study design

We did a prospective cohort study to investigate the efficacy of NPWT-PTA therapy in diabetic foot wound with CLI. Patients flow through each stage of this trial including discontinued patients was described in **Figure 1**. During the course of this study, 142 patients were consented and screened for inclusion from January 2011 to January 2014. Of these, 45 patients were excluded according to the inclusion and exclusion criteria, patients' refusal to participate, and 97 patients were enrolled. Seven patients lost to follow-up because of failed return for next visit or developed gangrene foot, 20 patients discontinued for their self-withdrawal or accidental death. Finally, 70 patients were analyzed.

Inclusion criteria for the study were: the patients age ≥ 18 years with ulcer categorized Wagner grade ≥ 2, presence of CLI (local stenosis > 50% of vessel lumen) according to the criteria of management of Peripheral Arterial Disease in the Trans-Atlantic Inter-Society Consensus Document (TASC II) [12], and evidence of inadequate perfusion (defined as ankle brachial index < 0.7). We excluded patients with wounds resulting from venous insufficiency, burns, untreated cellulitis, untreated osteomyelitis and malignant disease in the wound. A previous PTA in the past months, previous VAC (Vacuum Assisted Closure) therapy in the past 30 days, previous treatments with growth factors or hyperbaric medicine in the past 30 days were also regarded as exclusion criteria. Finally, patients also were excluded if they had no stenosis or occlusion and were being treated with immunosuppressive drugs, corticosteroids, or chemotherapy. Finally, seventy patients were recruited and allocated a treatment. The study protocol was approved by Ethics Committee of Shanghai Sixth People's Hospital and written consent was obtained from all subjects.

Patients data

The cohort study to investigate the efficacy of NPWT-PTA therapy conducted by the Vacuum Assisted Closure (VAC) Therapy system (Weigao medical technology co., China) and PTA in diabetic foot wound with CLI. All patients in NPWT-PTA group were added to evaluate the feasibility and advisability of performing PTA. If this procedure failed, a bypass surgery should be

considered. PTA was performed with contralateral retrograde femoral catheterization. A guide wire was applied to pass through any arterial stenosis or obstructions in NPWT-PTA group, and a Φ3-8 mm balloon catheter was inserted into the stenosis for revascularization. The mean length of the re-canalized segments was 10.6 cm (ranging from 1 to 27 cm). Nitinol stents (eV3 Inc., USA or Opti Med Co. Ger) were placed above the knee if need. For the below-the-knee PTA, a 2.5-3 mm low-profile balloon in a 0.014-inch system (Savy, Cordis Corp., USA) was employed. During the procedure 3000 IU-5000 IU of heparin was infused intravenously. The preoperative medication of acetylsalicylic acid 100 mg or clopidogrel 75 mg daily started at least 72 h before the procedure in the all cases. After the procedure, all patients were prescribed aspirin 100 mg and LMWH (Low-molecular-weight Heparin) 0.8 mg per day.

Patients assigned to the NPWT-PTA and NPWT group all been arranged VAC therapy system for 3-7 days according to standardized treatment guidelines. The subatmospheric pressure in VAC therapy system uses sterile polyurethane or polyvinyl alcohol foam dressing which is fitted to the appropriate size for the wound, then covered with an adhesive drape to create a closed environment. A tube attached to the drape connects to a fluid collection canister contained in a portable, programmable, computer-controlled vacuum pump (negative pressure of -125 mmHg) [17, 18]. Wounds were treated with VAC system until they were closed or until the therapeutic completion of 20 weeks. The difference between two groups was that the patients in the NPWT-PTA group wound receive PTA before or after NPWT. After the PTA, the patients would receive antiplatelet therapy consisted of Aspirin 100 mg/day and clopidogrel 75 mg/day. Patients in two groups were followed-up weekly on an outpatient for the first month, then every two weeks for the second month and every month up to the 20th week.

Object of observing

During each visit, ABI and the area of ulcer and adverse events were evaluated. Before entering the study, all patients underwent a baseline evaluation of the extent and severity of peripheral artery using the ABI, Ultrasonic Doppler technology and either computed tomographic angiography (CTA) or magnetic resonance angiography (MRA). The blood sample was collected to assess serum albumin and HbA_{1c}. If the concentration of albumin ≤ 30 g/L, a nutritionist was consulted and a dietary supplementation was needed. To assess sensory neuropathy, we evaluated patients with vibration perception threshold (VPT) test [19].

The primary objective of this study was to clarify the clinical efficacy of NPWT-PTA therapy system in treating diabetic wound with CLI, so it was needed to assess the time of wound healing and the proportion of healing at 20 weeks. Assessment was based on the date from wound investigations on days 0, 8, and 20 weeks. Complete wound closed was regarded as 100% re-epithelization without drainage.

Secondary aim included assessment of adverse events which defined as any untoward medical occurrences that resulted in death, were life-threatening, extended hospital care, caused significant incapacity or disability. In this study we defined adverse events as deaths, cardiovascular events, cerebral events, minor and major second amputation (excluding the conducted amputation before the time of therapy).

Statistical analysis

Continuous demographic variables were summarized with descriptive statistics (mean ± SD) and compared with a two-sample t test between the two groups. The ABI at 0, 8 and 20 weeks were analyzed using one way ANOVA. Categorical demographic variables were expressed as a proportion of the population and compared with a two-tailed Fisher's exact test.

We analyzed the data of wound healing time in the two groups using a time-to-event strategy with Kaplan-Meier analysis which followed by a log-rank test, and patient not achieving closure was censored using last day of observation. This statistical approach had provided a comparison of the distribution of wound healing time in the two treatment groups. The Cox survival model included terms of age, sex, diabetes duration, serum albumin levels, Serum creatinine, hemoglobin A1c, ALT, AST, C-reactive protein levels, Loss of protective sensation, Ulcer area, Ulcer duration before treatment and ABI, they were used to evaluate covariates (wound healing) and recorded as their hazard ratio with a confidence interval of 95%. The average time to 100% closure of ulcers were

Table 1. Clinical characteristics and risk factors of patients with diabetic foot ulcers with critical limb ischemia

	NPWT	NPWT+PTA	*P*
Patients characteristics			
Cases	44	26	
Age (years)	60.2±10.7	61.8±11.4	0.556
Sex (male/female)	33/11	16/10	0.235
Body-mass index (kg/m^2)	27.0±3.2	25.1±2.8	0.017
Current smoker (n/%)	19/43.2	10/38.5	0.698
Current use alcohol (n/%)	13/29.5	6/23.1	0.557
Type of diabetes			
Type 1 (n/%)	2/4.8	2/8.3	0.624
Type 2 (n/%)	42/95.2	24/91.7	0.624
Diabetes duration (years)	11.5±6.5	12.5±6.8	0.562
Total cholesterinemia (mmol/L)	4.5±1.4	5.0±1.2	0.182
Hypertension (n/%)	32/72.7	17/65.4	0.517
Albumin (g/l)	39.4±9.8	36.5±7.5	0.186
Serum Creatinine (mmol/L)	67.3±20.4	73.0±19.7	0.261
ALT (U/L)	30.5±11.9	36.2±14.5	0.080
CRP (mg/L)	22.7 (0.2, 165.1)	26.2 (4.2, 118.3)	0.729
HbA_{1c} (%)	8.7±3.7	8.0±1.8	0.386
Loss of protective sensation (n/%)*	41/93.2	23/88.5	0.495
Lesion features			
Ulcer duration before treatment (days)	62.3 (7, 360)	83.2 (14, 360)	0.284
Baseline wound area (cm^2)	20.6±16.3	19.2±12.9	0.707
Wagner grade ≤ 4 (n/%)	24/54.5	14/53.8	0.955
Wagner grade > 4 (n/%)	20/45.5	12/46.2	0.955
Ankle-brachial index	0.48±0.15	0.43±0.14	0.102
TASC A-B (n/%)	18/40.9	10/38.5	0.840
TASC C-D (n/%)	26/59.1	16/61.5	0.840

Data are mean ± SD or n (%). *percentage based on available data. ALT: Alanine aminotransferase; CRP: C-Reactive Protein.

calculated at 20 weeks, $P < 0.05$ was considered as significant.

Results

During the study, 70 patients were enrolled in our trial, and the **Table 1** summarized their clinical characteristics at baseline and risk factors. Of the diabetic patients enrolled in this study, the patients in each group were predominantly male and the mean time of diabetes duration was more than 10 years. And the data showed that no statistically significant demographic difference existed between the treatment groups ($P > 0.05$).

Efficacy

An example of extreme distal PTA and NPWT was showed in **Figure 2**. All patients PTA-treated in NPWT-PTA group underwent successfully revascularization and negative pressure therapy. Among the 26 procedures in NPWT-PTA group, 2 (7.7%) PTAs were exclusively performed in the proximal segment, 10 (38.5%) exclusively in the infrapopliteal arteries, and 12 (53.8%) exclusively in the femoropopliteal plus infrapopliteal arteries. The initial technical success of PTA was 92.3% in 24 patients (the patients underwent angioplasty were only one) in NPWT-PTA group, the other (2 patients) initially failed PTA procedures required bypass surgery because of suboptimal dilatations in the context of heavy vessel calcifications. The accumulative potencies at 8 and 20 weeks respectively were 96.2% and 84.6%. No patients died during hospitalization, and the procedure rule out any complications in the puncture site.

A greater proportion of wound in NPWT-PTA group healed completely compared with NPWT

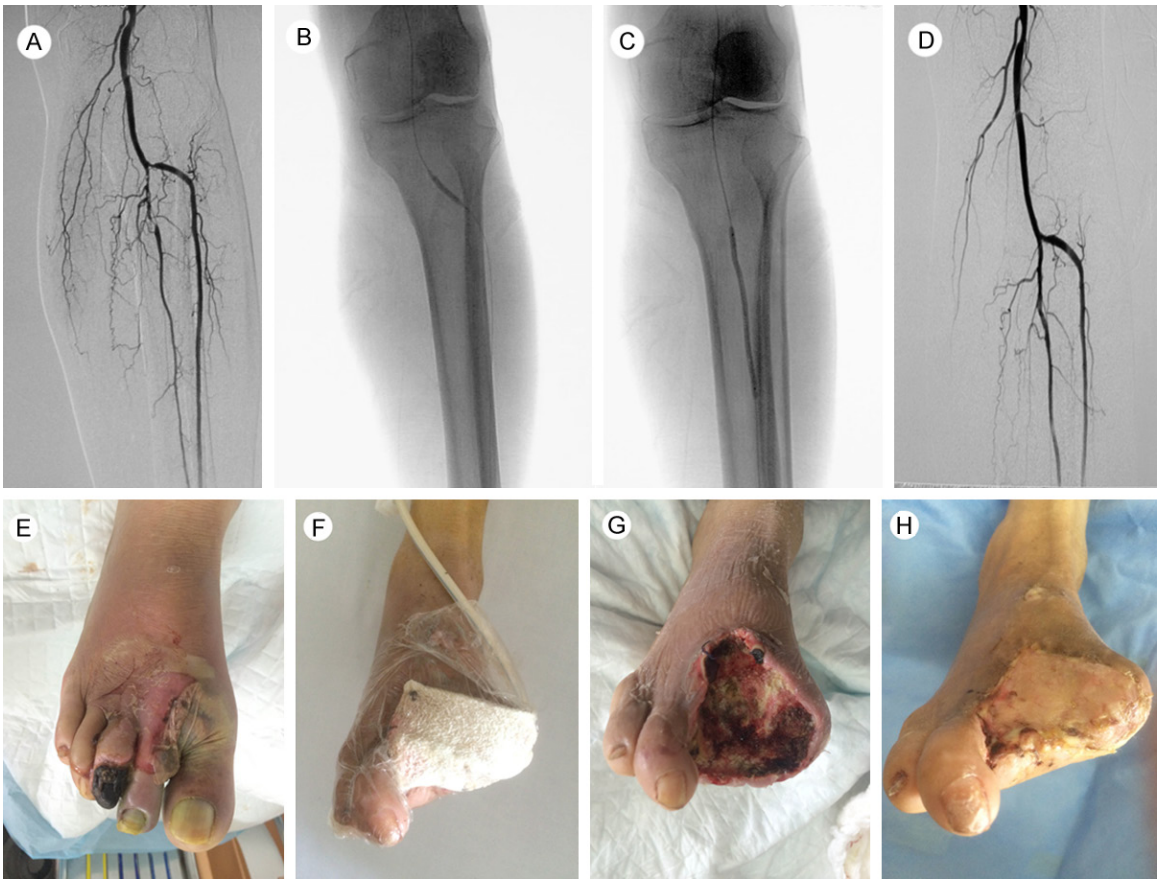

Figure 2. An illustrative case of extreme distal angioplasty (A-D) and NPWT (E-H) in NPWT-PTA group: The distal stenosis of the anterior tibial and peroneal artery below the knee level (A); A percutaneous transluminal angioplasty inflated balloon in the peroneal artery (B); A percutaneous transluminal angioplasty inflated balloon in the anterior tibial artery (C); The outcome of PTA (D); The gangrene of diabetic foot (E); Negative Pressure Wound Therapy (NPWT) system was applied (F); 14 days after NPWT (G); Wound healed after 35 days of NPWT and a split-thickness skin graft (H).

([61.5%] *vs* [40.9%], *P*=0.004) at 20 weeks. The time of wound healing, based on the complete ulcer closure (100% re-epithelization), was faster in NPWT-PTA group than NPWT group (48.3±32.8 *vs* 77.1±27.2, *P*=0.009) at 20 weeks. And the duration of therapy of NPWT in NPWT-PTA group was 33.12±15.86 days (means ± SD) versus 45.34±23.24 days in NPWT group (*P*=0.021).

ABI was assessed both before and after PTA. **Figure 3A** showed that a significant improvement of ABI in NPWT-PTA group were detected after the PTA, peaking at 8 weeks (0.83±0.19 *vs* 0.46±0.15, *P*=0.000), 20 weeks (0.72±0.17 *vs* 0.53±0.12, *P*=0.000) after the PTA, it still was significantly higher than the baseline (**Figure 3A**). There was no significant difference was detected when it in NPWT group during the treatment (**Figure 3B**).

The healing time of complete ulcer closure in NPWT-PTA group was 83.5±10.0 days (95% CI 63.9-103.2). Healing time in NPWT group was 114.3±5.3 (95% CI 103.8-124.7) days; the Kaplan-Meier median time to complete ulcer closure was 70.0±30.0 (95% CI 11.3-128.8, P=0.023) days (**Figure 3C**). In separate multivariate Cox proportional hazards regression models, the decrease of ABI (HR=15.000, 95% CI=2.243-100.333, P=0.005) and the increase of wound area (HR=0.926, 95% CI=0.866-0.990, P=0.025) were significant risk increasing factors for days of wound healing (**Table 2**). The survival function at mean of covariates was showed in **Figure 3D**.

Safety

After adequate preparation of wound bed, 15.4% (4 of 26) NPWT-PTA-treated ulcers and

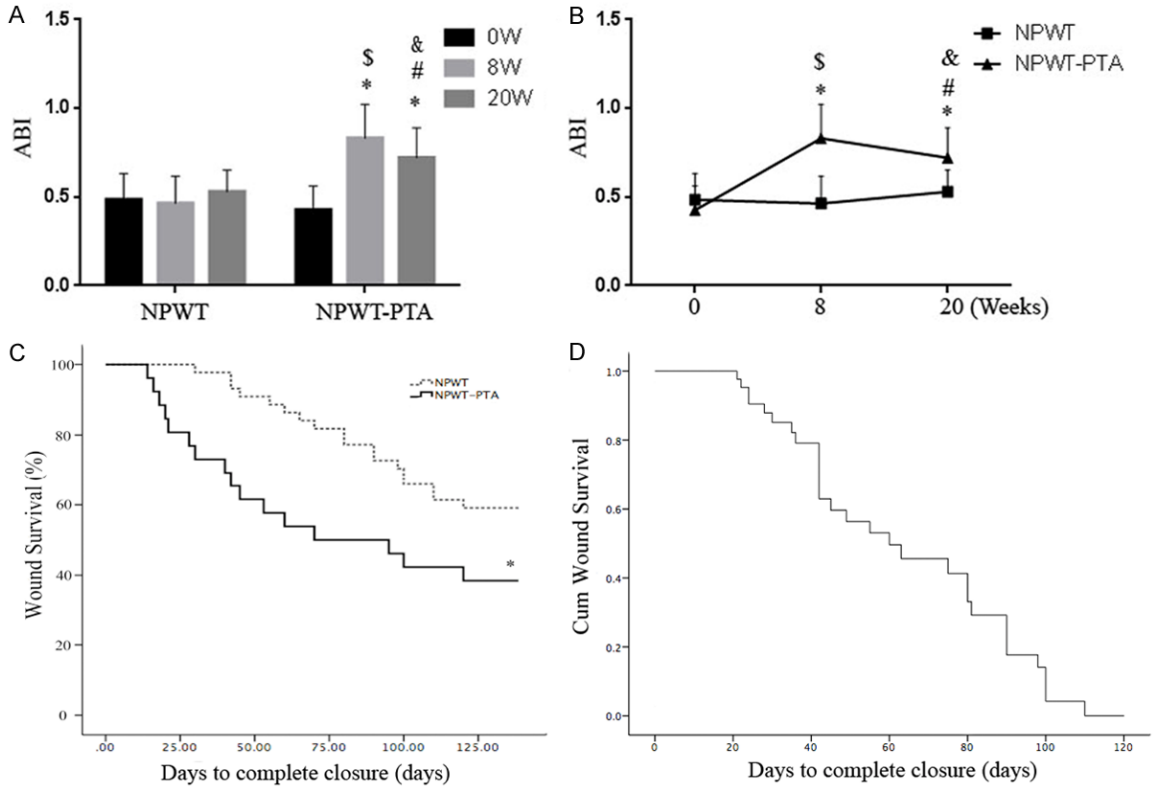

Figure 3. ABI values in the two groups before and after therapy. A significant improvement of ABI in NPWT-PTA group were found after the PTA (A); There was no significant difference was found when it in NPWT group during the treatment (B). Kaplan-Meier estimates for time to complete ulcer closure (P=0.023). Continuous line: NPWT-PTA group; dash line: NPWT group (C). Survival Function at mean of covariates (D); *P < 0.05 when compared with the corresponding controls; #*P* < 0.05 when compared with the ABI at 8 week in NPWT-PTA group; &*P* < 0.05 when compared with the ABI at 0 week in NPWT-PTA group; $*P* < 0.05 compared with the ABI at 0 week in NPWT-PTA group.

Table 2. Hazard ratio of Patients with Diabetic Foot Ulcers with Critical Limb Ischemia

	Hazard ratio (95% CI)	*P*
Baseline wound area (cm^2)	0.926 (0.866-0.990)	0.025
Ankle-brachial index	15.000 (2.243-100.333)	0.005
Age (years)		NS
Sex (male/female)		NS
Diabetes duration (years)		NS
Albumin (g/l)		NS
Serum Creatinine (mmol/L)		NS
ALT (U/L)		NS
AST (U/L)		NS
CRP (mg/L)		NS
HbA_{1c} (%)		NS
Loss of protective sensation (n/%)		NS
Ulcer duration before treatment (days)		NS

NS: No Significance; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-Reactive Protein.

13.6% (6/44) NPWT-treated ulcers were surgically closed after skin grafts transplantation. No major second amputation was observed in the NPWT-PTA group. **Table 3** displays treatment-related rates for healing time, skin graft, deaths, minor second amputation, major second amputation, cardiovascular event and cerebral event at 20 weeks. In all other categories, no significant statistically differences were observed.

Discussion

This trial assessed the outcomes in diabetic foot ulcer with critical limb ischemia (CLI) through NPWT combined with PTA, and our results firstly revealed that the NPWT combined with PTA gained a higher wound healing ratio, a shorter ulcer healing time, a higher ABI, and potential trend towards

Table 3. The Comparison of Adverse Events in the two groups

	NPWT (n=44)	NPWT+PTA (n=26)	*P*
Skin graft (n/%)	6/13.6	4/15.4	0.840
Deaths (n/%)	2/4.5	2/7.7	0.584
Minor second amputation (n/%)	5/11.4	4/15.4	0.908
Major second amputation (n/%)	3/6.8	0/0	0.453
Cardiovascular event (n/%)	0/0	0/0	1
Cerebral event (n/%)	0/0	1/3.8	0.789

Minor second amputation: amputation below foot; Major second amputation: amputation above foot.

reducing the risk of major second amputation than NPWT in the patients with diabetic foot ulcerations. And it seemed to be a quite safe therapy, with no significant differences observed in proportion and distribution of adverse events compared with controlled group.

This study has unique characteristics that distinguish it from previous trials as followed: firstly, we reported that the therapy NPWT combined with PTA has an obvious advantage to improve the diabetic wound healing and blood supply of foot; secondly, the ulcers enrolled into this trial were larger and more complex than previously reported. The ulcers in previous study mainly focused on superficial neuropathic foot ulcers [20-22]. Thirdly, little was known that a prospective cohort trial included controlled group. And in this study, the negative controlled group (NPWT) had been set up to synthetically compare the therapeutic effect of NPWT-PTA.

The results indicated the difference in proportion of healing between treatment groups at the end of trial. The main reason attributed to the severity of these ulcers which posed a larger size, a deeper depth and accompanied with the presence of pre-existing infection. Such wounds needed debridement because they enable removal of devitalized and necrotic tissue. NPWT system in conjunction with debridement could contribute a lot advantages to the wound healing process [23]. And major clinical trials have observed that NPWT therapy delivered through the VAC system seems to efficiently stimulate a robust granulation tissue response compared with other therapies [24, 25]. As reported in this study, the wounds treated with NPWT had achieved faster wound closure. This result paralleled the findings reported by Peter et al who determined that NPWT was as safe as and more efficient than moist healing dressing for the treatment of diabetic foot ulcers [26]. The difference to ours was that their therapies were without PTA during the therapy of NPWT.

However, the majority of patients have a severe ischemic component which influences the evolution of the diabetic foot pathology, leading to a non-healing wound and eventually a major amputation [10]. Thus the successful revascularization is far more important to the final diabetic wound healing. At present, although bypass surgery still plays a significant role in the revascularization of CLI [12], increasing clinical experience over the past two decades shows that endovascular strategies (PTA) has low complication rates and high limb salvage rates comparable with bypass surgery [13-16]. In this study, we have a low-risk and efficient procedure in PTA, and we found that combination of NPWT and PTA had more advantage to improve wound healing compared with only NPWT treatment. This could explain the reason why the high level of blood supply of foot in NPWT-PTA group which was achieved by opening specific pathways of flow. Meantime, depending soly on the PTA was inadequated. Active infection may induce further hypoxia and tissue loss which means revascularization would be in vain.

In this study, Cox proportional hazards regression models showed that the decrease of ABI and the enlargement of wound area were significant risk increasing factors. And our results found that PTA treatment in NPWT-PTA group significantly increased the ABI of wound tissue compared with NPWT group at 8 weeks, and also at 20 weeks, and in line with that described by Nylaende et al who claimed that the ABI at 3 and 12 months were highly significantly improved in favor of PTA in the patients who diagnosed as peripheral arterial occlusive disease without diabetes [27], the difference between our study was that their treatment didn't include the NPWT. Also, these data were confirmed by Aust et al who had found that a targeted peripheral vessel reopening before debridement helped to improve chronic lower extremity wounds [28]. However, the difference in our study is that the debridement in the latter

observation was the treatment without negative pressure wound therapy, and the applied wound was not diabetic foot.

A greater percentage of patients in NPWT group underwent a major second amputation (above foot) during the observing period. This different rate of second amputation probably resulted from the rapid and higher proportion wound healing. PTA could also contribute to the avoidance of the second major amputation, because it can improve significantly blood supply of foot, and it is a major independent prognostic factor for the major amputation [29]. Reiber et al believed that the major amputation (above-the-ankle) rate in patients who successfully underwent PTA is lower than the literature data [30], as it also showed in our study. We assumed that PTA has increased the likelihood of successfully conducting minor second amputations, which would decrease the probability of major second amputation.

Limitations

This study has some potential disadvantages that are inherent to the procedure studied. The most important aspect is that this study was confined by the small number of cases in the two groups as well as by its retrospective nature; Secondly, although effective in improving the early and medium period outcomes, PTA posed a poor long-dated patency rate, resulting from the evolution of the underlying pathology that causes recurrences very frequent in diabetic patients; Thirdly, percutaneous oxygen pressure examination was not applied during the study.

In summary, the present study confirmed that NPWT-PTA combination was an efficient and safe strategy for the diabetic foot ulcer accompanied with critical limb ischemia. Treatment with NPWT-PTA System results in a higher proportion of wounds closure, shorter healing time, more adequate blood supply of foot, and a potential trend towards reduced risk for major second amputation than with sole NPWT therapies. Meantime it was a quite safe therapy. In the future, we will investigate the effect about length of hospital stay, cost efficacy, and quality of life in postoperative patients. We look forward to further understanding the NPWT-PTA Therapy System and improve the treatment for diabetic foot ulcer with critical limb ischemia in the near future.

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Disclosure of conflict of interest

None.

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References

[1] Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005; 293: 217-228.

[2] Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. Diabetes Care 2003; 26: 1435-1438.

[3] Armstrong DG, Frykberg RG. Classifying diabetic foot surgery: toward a rational definition. Diabet Med 2003; 20: 329-331.

[4] Wiwanitkit V. Vacuum-assisted closure and moist wound dressing in diabetic foot. J Cutan Aesthet Surg 2013; 6: 173.

[5] Ram M, Singh V, Kumawat S, Kumar D, Lingaraju MC, Uttam Singh T, Rahal A, Kumar Tandan S, Kumar D. Deferoxamine modulates cytokines and factors to accelerate cutaneous wound healing in diabetic rats. Eur J Pharmacol 2015; 764: 9-21.

[6] Martson WA, Hanft J, Norwood P, Pollak P. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: re-

sults of prospective randomized trial. Diabetes Care 2003; 26: 1701-1705.
[7] Li X, Liu J, Liu Y, Hu X, Dong M, Wang H, Hu D. Negative pressure wound therapy accelerates rats diabetic wound by promoting agenesis. Int J Clin Exp Med 2015; 8: 3506-3513.
[8] Schintler M. Negative pressure therapy: theory and practice. Diabetes Metab Res Rev 2012; 28: 72-77.
[9] Faglia E, Caravaggi C, Marchetti R, Mingardi R, Morabito A, Piaggesi A, Uccioli L, Ceriello A. Screening for peripheral arterial disease by means of the ankle-brachial index in newly diagnosed type 2 diabetic patients. Diabet Med 2005; 22: 1310-1314.
[10] Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, Edmonds M, Holstein P, Jirkovska A, Mauricio D, Ragnarson Tennvall G, Reike H, Spraul M, Uccioli L, Urbancic V, Van Acker K, Van Baal J, Van Merode F, Schaper N. High prevalence of ischemia, infection and serious comorbidity in patients with diabetic foot disease in European. Baseline results from the Eurodiale study. Diabetologia 2007; 50: 18-25.
[11] Alexandrescu V, Hubermont G, Philips Y, Guillaumie B, Ngongang Ch, Coessens V, Vandenbossche P, Coulon M, Ledent G, Donnay JC. Combined primary subintimal and endoluminal angioplasty for ischemic inferior-limb ulcers in diabetic patients: 5-year practice in a multidisciplinary 'diabetic-foot' service. Eur J Vas Endovasc Surg 2009; 37: 448-456.
[12] Norgreen L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group, Bell K, Caporusso J, Durand-Zaleski, Komori K, Lammer J, Liapis C, Novo S, Razavi M, Robbs J, Schaper N, Shigematsu H, Sapoval M, White C, White J, Clement D, Creager M, Jaff M, Mohler E, Rutherford RB, Sheehan P, Sillesen H, Rosenfield K. Inter-Society Consensus for the management of peripheral arterial disease (TASC II). Eur J Vasc Endovasc Surg 2007; 33 Suppl 1: S32-S55.
[13] Blevins WA, Schneider PA. Endovascular management of critical limb ischemia. Eur J Vasc Endovasc Surg 2010; 39: 756-761.
[14] Conrad MF, Kang J, Cambria RP, Brewster DC, Watkins MT, Kwolek CJ, LaMuraglia GM. Infrapopliteal balloon angioplasty for the treatment of chronic occlusive disease. J Vasc Surg 2009; 50: 799-805.
[15] Romiti M, Albers M, Brochado-Neto FC, Durazzo AE, Pereira CA, De Luccia N. Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. J Vasc Surg 2008; 47: 975-981.
[16] Adam DJ, Beard JD. Cleveland T, Bell J, Bradbury AW, Forbes JF, Fowkes FG, Gillepsie I, Ruckley CV, Raab G, Storkey H; BASIL trial participants. BASIL trial participants. Bypass versus angioplasty in severe ischemia of the leg (BASIL): Multicentre, randomized controlled trial. Lancet 2005; 366: 1925-1934.
[17] Banwell PE. Topical negative pressure therapy in wound care. J Wound Care 1999; 8: 79-84.
[18] Banwell PE, Teot L. Topical negative pressure (TNP): the evolution of a novel wound therapy. J Wound Care 2003; 12: 22-28.
[19] Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005; 28: 956-962.
[20] Veves A, Sheehan P, Pham HT. A randomized, controlled trial of Prompgran (a collagen/ oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. Arch Surg 2002; 137: 822-827.
[21] Veves A, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. Apligraf Diabetic Foot Ulcer Study. Diabetes Care 2001; 24: 290-295.
[22] Marston WA, Hanft J, Norwood P, Pollak R. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. Diabetes Care 2003; 26: 1701-1705.
[23] Saxena V, Hwang CW, Huang S, Eichbaum Q, Ingber D, Orgill DP. Vacuum-assisted closure: microdeformations of wounds and cell proliferation. Plast Reconstr Surg 2004; 114: 1086-1096.
[24] Armstrong DG, Attinger CE, Boulton AJ, Fryberg RG, Kirsner RS, Lavery LA, Mills JL. Guidelines regarding negative pressure wound therapy in the diabetic foot: results of the Tucson expert consensus conference. Ostomy Wound Manage 2004; 50 Suppl: 3S-27S.
[25] Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomized controlled trial. Lancet 2005; 366: 1704-1710.
[26] Blume PA, Ayala J, Walters J, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers. Diabetes Care 2008; 31: 631-636.
[27] Nylaende M, Kroese AJ, Morken B, Stranden E, Sandbaek G, Lindahl AK, Arnesen H, Seljeflot I. Beneficial effects of 1-year optimal medical treatment with and without additional PTA on inflammatory markers of atherosclerosis in patients with PAD. Results from the Oslo Balloon

Angioplasty versus Conservative Treatment (OBACT) study. Vasc Med 2007; 12: 275-283.
[28] Aust MC, Spies M, Guggenheim M, Gohritz A, Kall S, Rosenthal H, Pichlmaier M, Oehlert G, Vogt PM. Lower limb revascularization preceding surgical wound coverage-an interdisciplinary algorithm for chronic wound closure. J Plast Reconstr Aesthet Surg 2008; 61: 925-933.
[29] Pecoraro RE, Ahroni JH, Boyko EJ, Stensel VL. Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. Diabetes 1991; 40: 1305-1313.
[30] Reiber GE. The epidemiology of diabetic foot problem. Diabet Med 1996; 13: S6-S11.