Role of negative pressure wound therapy in the management of surgically treated diabetic foot infections: a randomized controlled trial

Ashraf G. Taha, Abdelrahman I. Sayed, Osman M. Ahmed

Department of Vascular and Endovascular Surgery, Assiut University Hospital, Assiut, Egypt

Correspondence to Ashraf G. Taha, MD, PhD, Department of Vascular and Endovascular Surgery, Assiut University Hospital, Assiut 71526, Egypt.
Tel: +20 100 001 3141; fax: +20 88 2333327;
e-mail: a_gamal@aun.edu.eg

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Background
Negative pressure wound therapy (NPWT) has been shown to be an effective and safe adjunctive treatment for chronic diabetic foot ulcers, but its role in surgically treated diabetic foot infection (DFI) has not been clearly evaluated yet. The present study aimed at evaluation of effectiveness and safety of NPWT in the treatment of postoperative wounds of DFI compared with conventional wound dressing (CWD).
Patients and methods
This 8-week randomized controlled study enrolled 80 surgically treated patients with DFI randomized to NPWT (n=40) or CWD (n=40). The study outcomes included changes in wound surface area, time to complete granulation tissue formation (GTF), cessation of wound drainage, wound-related pain, and bleeding. Treatment success was defined as complete healthy GTF without wound drainage.
Results
The wound surface area decreased significantly with NPWT than CWD (39.5 ± 26.5 vs. 14.3 ± 8.9 cm^2, P<0.001) accounting for reduction percentage of 51.0 ± 2.0 versus 19.0 ± 2.0% (P<0.001). In the fourth and sixth week of treatment, 75 and 100% of NPWT patients achieved complete healthy GTF versus 30 and 75% of CWD patients, respectively (P<0.001), with mean time for complete GTF of 30.45 ± 4.6 versus 38.3 ± 1.67 days (P=0.001), respectively. Treatment success was achieved in 100% of NPWT patients versus 75% of CWD (P<0.001). Wound drainage ceased in 100% of NPWT patients versus 65% of CWD (P<0.001) in the sixth week. The mean VAS score was 4.02 ± 0.83 versus 4.0 ± 0.82 (P=0.892) in the first week, and 2.1 ± 0.78 versus 3.0 ± 0.82, (P<0.001) in the fourth week, respectively. No major bleeding occurred in the study.
Conclusions
NPWT is an effective and safe treatment for surgically treated DFI in terms of improved reduction of wound size, faster GTF, and cessation of wound drainage, without increased pain or bleeding as compared with conventional moist wound dressing.

Keywords:
diabetes, diabetic foot infection, negative pressure wound therapy, surgical wounds

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Introduction

Diabetes mellitus is a progressive global health threat, leading to a growing incidence of disabling or even life-threatening diabetic complications, including foot infections [1]. Diabetic foot infection (DFI) is the most common cause of hospitalization and the leading cause of nontraumatic lower extremity amputations [2,3]. Owing to the gravity of this condition, the International Working Group of Diabetic Foot stated that management of DFI should follow a systematic, evidence-based approach to resolve infection, improve the outcomes, and avoid the predicted complications including amputation [4]. This management approach of DFI is founded on prompt diagnosis, proper antimicrobial selection, appropriate surgical intervention when needed, and adequate wound care [4].

Medical literature is rich in studies that have clearly demonstrated the advantages of negative pressure wound therapy (NPWT) as a safe and more effective adjunctive treatment of chronic diabetic foot ulcers (DFUs) than advanced moist wound therapy [5–9]. Using NPWT with chronic DFUs offered faster rates of granulation tissue formation (GTF) [5,7,8] and wound healing [5,6], shorter and fewer hospital admissions [5,9], significant reduction of wound size [5,6], fewer secondary amputations [6,9], and improved quality of life [10]. Therefore, NPWT was recommended by the Society of Vascular Surgery for

chronic DFUs that fail to demonstrate more than 50% wound area reduction after at least four weeks of standard wound care [11]. On the contrary, the role of NPWT in the management of foot surgical wounds following debridement or minor amputations to treat DFI has not been clearly evaluated yet. We hypothesize that the reported advantages of NPWT in the treatment of chronic DFU are continued with its application on surgical wounds resulting from foot debridement or minor amputations to treat DFI.

Aim

The aim of the present study was to evaluate effectiveness and safety of NPWT in the treatment of surgically treated DFI in the clinical practice.

Patients and methods

This present study is a single-center, prospective, parallel-armed randomized controlled trial (RCT) that was conducted at the Department of Vascular and Endovascular Surgery, Assiut University Hospital, from November 2019 till November 2021. Institutional Review Board approval was obtained for the present study, and informed consent was obtained from all study patients. This study has been registered with ClinicalTrials.gov, number NCT04093635.

The study included 80 adult patients presenting with DFI (Wagner grades III–V) [12] who had received surgical debridement or minor amputations within 12 h before enrollment. Criteria of the Infectious Disease Society of America were used to define infection severity [13]. Patients with Charcot arthropathy, impalpable pedal pulses, extensive foot infection or gangrene requiring major amputation, coagulopathy, or bilateral DFI were excluded from the present study. Patients on corticosteroids, immunosuppressive medications, or chemotherapy were also excluded. Block randomization was performed using a computer-generated list. Allocation concealment was done using serially numbered opaque sealed envelopes. Patients were randomized to treatment arms in a 1 :1 ratio to NPWT (group A) or conventional moist wound dressing [conventional wound dressing (CWD) group B].

In the operating room, all patients underwent urgent surgical debridement of all infected and necrotic tissues and/or bones under regional or general anesthesia. Swabs for culture and antibiotic sensitivity were obtained during the initial debridement. Parenteral broad-spectrum antibiotics were started empirically after debridement and were continued according to the results of culture and sensitivity testing. Strict glycemic control was achieved during the study period and was initiated using crystalline insulin guided by the level of random blood glucose then by the endocrinology department.

Following the initial debridement, the initial wound surface area (WSA) was assessed. WSA was calculated by multiplying the longest diameter by the perpendicular diameter using a measuring tape. All patients were initially maintained on daily CWD according to International Working Group of Diabetic Foot guidelines in the form of comprehensive wound wash with physiological saline and then covered with sterile gauze and nonadherent dressing and roller bandages [4]. No topical antibiotics were used during the study.

Patients, treating physicians, and researchers were initially blinded to the treatment group that the patients were assigned to. Randomization was done in the second postoperative day after the initial surgical debridement to confirm the wound readiness for treatment initiation, including adequate hemostasis and complete removal of all infected and necrotic tissues. At patient randomization, treatment was assigned based on the next sequentially labeled envelope. After opening the assigned randomization envelope, NPWT was initiated in group A patients, whereas group B patients continued the same CWD till the end of the study.

As per manufacturer recommendation, application of NPWT and all subsequent foam dressing changes started with thorough wound cleaning with saline wash followed by placement of open-pore (400–600 μm) black polyurethane ether foam that is cut to fit the size and shape of the wound cavity. The foam was sealed with a transparent polyurethane adhesive drape to completely cover the foam and about 3–5 cm of the surrounding skin. A suction tube was inserted into a 1.5-cm hole located at the center of the drape and then connected to the canister tubing. The tubing clamps were opened and the suction device (Lifotronic NP800/200; Lifotronic Technology, Shenzhen, China) was powered on and set to intermittent suction pressure of 125 mmHg with on and off cycles of 5 and 2 min, respectively.

Dressing change was done every 72 h in group A patients and every 24 h in group B. Unless wound complications had occurred or there was another indication for continued hospitalization, all patients were discharged after second dressing change to continue receiving NPWT or CWD at home supervised by home nurses. Wound assessment was done in the outpatient clinics every week for wound

improvement or appearance of any complications such as increasing infection, pain, bleeding, or appearance of pus or offensive odor. In both treatment groups, if infection or slough appeared in the wound, additional surgical debridement was done using a surgical blade.

Wound assessment was continued until completion of the eighth weeks of treatment (regardless the wound condition at that time point) or until complete coverage of the wound bed with clean granulation tissue and without any discharge. NPWT was finished in group A patients when complete GTF was achieved with disappearance of wound discharge. Excessive wound bleeding, aggravated wound infections, or maceration of the surrounding skin are indications of termination of NPWT in the present study [14].

The primary outcomes were changes in WSA, time to complete GTF, cessation of wound drainage, and treatment success. Treatment success was defined as 100% wound coverage with healthy granulation tissue without further drainage and the wound is ready for skin grafting or spontaneous closure. If the wound did not show complete GTF by the end of the eighth week, this was considered treatment failure. The secondary outcomes are the number of secondary debridement/amputation procedures, bleeding, and pain assessment. Bleeding was assessed by counting the number of unplanned dressing changes (UPDC) due to soakage with blood during the first week. Wound-related pain was assessed using visual analog scale (VAS) every 48 h during the first and fourth weeks of treatment.

Statistical analysis

SPSS software, version 19.0 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, New York, USA) was used for statistical analysis. χ^2 test or Fisher's exact tests were used for categorical variables, whereas *t* test or Mann–Whitney tests were used for continuous variables. *P* value less than 0.05 was considered statistically significant.

Results

A total of 80 patients with DFI who received surgical debridement with or without minor amputations were randomized to receive NPWT (*n*=40) or CWD (*n*=40). Patients' demographics, comorbidities, laboratory findings, and baseline lesion characteristics were comparable between the two treatment groups (Table 1).

Table 2 shows changes in the WSA in the two treatment groups. The mean decrease in the WSA upon completion of the study was significantly higher in the NPWT than in the CWD group (39.5 ± 26.5 vs. 14.3 ± 8.9 cm^2, *P*<0.001). The percentage of WSA reduction was also significantly higher in the NPWT group (51.0 ± 2.0%) compared with the CWD group (19.0 ± 2.0%, *P*<0.001).

Regarding the time to complete GTF, 75% of NPWT patients and 30% of CWD patients (*P*<0.001) achieved complete healthy GTF in the fourth week, which increased to 100 and 50%, respectively, at the end of the sixth week (Fig. 1). By the end of the study period, treatment success was achieved in 100% of NPWT (*n*=40) compared with 75% (*n*=30) in CWD patients (*P*=0.001). In the successfully treated patients, the mean time to complete GTF was 30.45 ± 4.6 versus 38.3 ± 1.67 days (*P*=0.001), respectively.

In terms of cessation of wound drainage, 100% of NPWT patients stopped wound drainage by the end of the sixth week compared with 65% of CWD patients (*P*<0.001). None of the study patients continued wound drainage beyond the eighth week (Fig. 2).

After the initial surgical treatment, eight (20%) CWD patients required another surgical debridement compared with six (15%) patients in the NPWT group. Secondary minor amputations were needed in two (15%) CWD in the form of transmetatarsal amputations. None of the NPWT patients required secondary amputations.

Pain assessment during the first week was comparable between the two treatment groups, with mean values for VAS score of 4.02 ± 0.83 in NPWT versus 4.0 ± 0.82 in CWD (*P*=0.892). In the 4th week, the mean VAS score was significantly lower in NPWT group (2.1 ± 0.78) than the CWD group (3.0 ± 0.82, *P*<0.001). In terms of bleeding assessment, the number of UPDC was comparable between the two groups. During the first week of the study, 80 and 85% of NPWT and CWD patients did not need any UPDC, 15 and 10% needed only one UPDC, whereas the remaining 5 and 5% needed two UPDC, respectively (*P*=0.794).

Discussion

Diabetes-related lower extremity complications are a leading cause of infection, hospitalization, and amputation, yet these outcomes are readily preventable [15]. Acute DFI, even with a relatively mild severity, usually causes major morbidity. The condition is even worse with moderate or severe infections as about 20% of those patients will have some form of amputation

Table 1 Patients' demographics and baseline lesion characteristics

	NPWT (*N*=40) [*n* (%)]	CWD (*N*=40) [*n* (%)]	*P* value
Age (years)			
Range	35–64	45–66	0.103
Mean±SD	53.2±8	56.9±5.6	
Sex			
Male	16 (40)	18 (45)	0.652
Female	24 (60)	22 (55)	
Current smoker	8 (20)	6 (15)	0.556
Hypertension	20 (50)	24 (60)	0.369
Chronic kidney disease	4 (10)	6 (15)	0.499
Ischemic heart disease	12 (30)	18 (45)	0.166
Previous limb revascularization	10 (25)	12 (30)	0.617
Laboratory findings			
Hemoglobin (mg/dl)			
Range	9.8–14.4	7–13.8	0.137
Mean±SD	11.5±1.5	10.8±1.4	
Glycated hemoglobin (mg/dl)			
Range	7–14	8–13	0.311
Mean±SD	10.3±1.9	9.8±1.8	
Total leukocytic count (10^3)			
Range	10–28.9	12.6–28.4	0.249
Mean±SD	17.4±5.2	19.2±4.7	
Lesion characteristics			
Infection severity[1]			
Moderate	11 (27.5)	14 (35)	0.630
Severe	29 (72.5)	26 (65)	
Wagner class			
Class III	38 (95)	38 (95)	0.999
Class IV	2 (5)	2 (5)	
Lesion site			
Toes	2 (5)	4 (10)	
Sole	16 (40)	14 (35)	
Dorsum of the foot	6 (15)	8 (20)	0.605
Heel	10 (25)	6 (15)	
Foot lesion extending to the leg	6 (15)	8 (20)	

CWD, conventional moist wound dressing; NPWT, negative pressure wound therapy. [1]According to classification of Infectious Disease Society of America [13]

Table 2 Changes in wound surface area in the two treatment groups

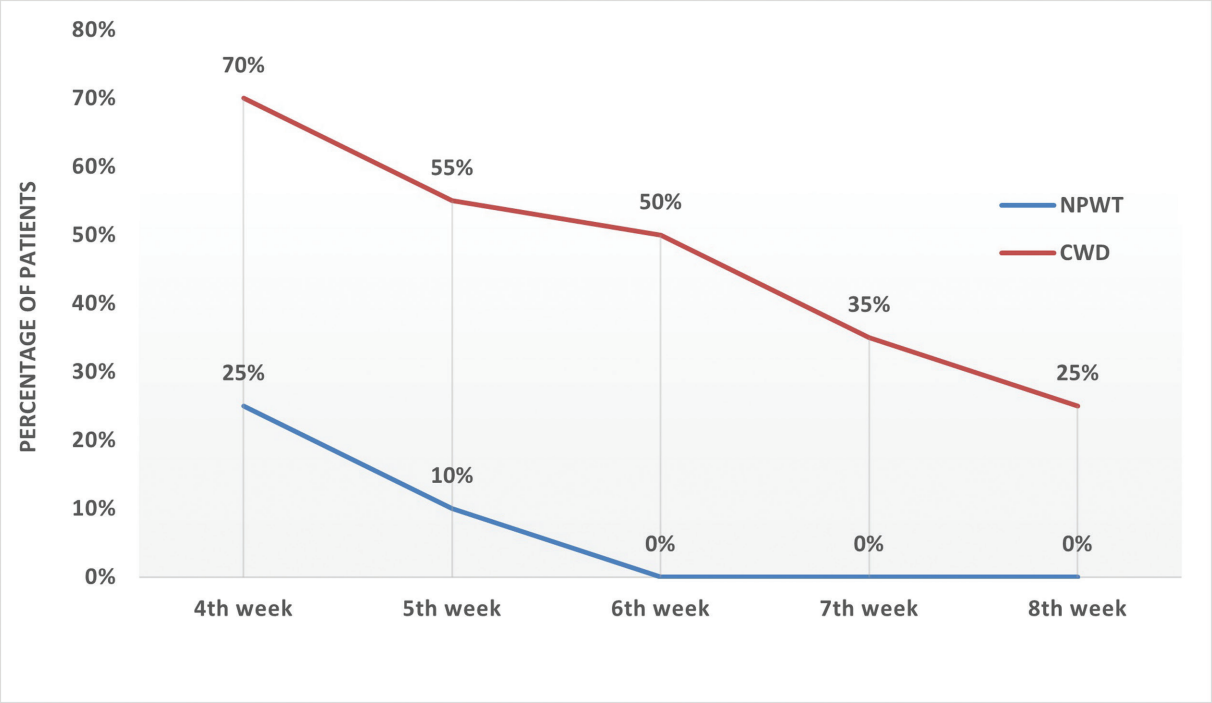
	NPWT	CWD	*P* value
Initial WSA (cm^2)			
Range	16–180	20–170	0.840
Mean±SD	77.5±51.9	75.2±47.2	
WSA on completion (cm^2)			
Range	7.8–88.2	16.2–137.7	0.002
Mean±SD	37.9±25.4	60.9±38.3	
Decrease in WSA (cm^2)			
Range	8.16–91.8	3.8–32.3	<0.001
Mean±SD	39.5±26.5	14.3±8.9	
Percentage of decrease in WSA			
Range	50–51%	19–21%	<0.001
Mean±SD	51.0±2.0%	19.0±2.0%	

CWD, conventional moist wound dressing; NPWT, negative pressure wound therapy; WSA, wound surface area.

[16]. Prevalence of DFI in patients with newly diagnosed DFU is substantially high, reaching up to 58% as reported by a large study from 10 European countries [17].

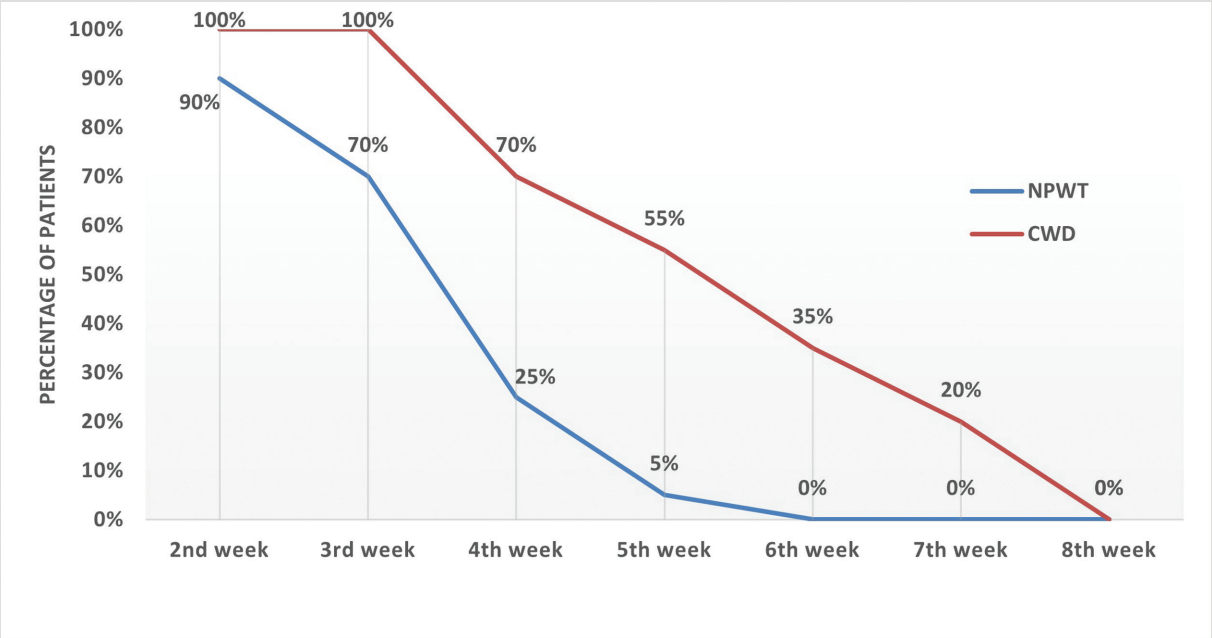
Despite the numerous reports on the advantages of NPWT on chronic DFU, the vast majority of RCTs on NPWT did not include patients presenting with surgical wounds for treatment of acute DFI. In contrast

Figure 1



Percentage of patients without 100% granulation tissue formation at each time point.

Figure 2



Percentage of patients with persistent wound drainage at each time point.

to the chronic wounds of DFU, surgical wounds to treat acute DFI are intended to salvage the foot and leg, and therefore, they are usually larger and deeper wounds, leaving exposed bones and tendons in areas with pre-existing infection. Such complex surgical wounds may behave differently with NPWT than do chronic wounds of neuropathic DFU, in terms of both treatment effectiveness and safety. A unique feature of the present trial is restricting the study participants exclusively to patients with acute moderate and severe DFI requiring urgent surgical debridement or minor amputations, which served well with the main goal of the present trial.

Another strong feature in the present trial is the similarity between the two treatment groups regarding

baseline patient and wound characteristics, which led to a solid ground for outcome comparison between the two groups. In the present study, distribution of infection severity and the initial WSA were comparable between NPWT and CWD groups. On study completion, NPWT showed a significantly superior WSA reduction than CWD (51.0 ± 2.0 vs. 19.0 ± 2.0%, P<0.001). In agreement with this observation, a meta-analysis study of six RCTs consisting of 389 patients found that NPWT reduced DFU area more effectively than conventional dressing group (95% confidence interval: 8.50–15.86, P<0.00001) [18]. Other RCTs also reported significant WSA reduction with NPWT compared with CWD [5,6,19].

In the present study, NPWT showed a significantly faster GTF than in CWD (30.45 ± 4.6 vs. 38.3 ± 1.67 days, P=0.001). Moreover, more patients achieved 100% GTF with NPWT than CWD, which started as early as during the fourth week of treatment (75 vs. 30%, respectively). Similar observation was noted in a recent RCT on chronic DFU (Wagner classes I and II), which reported a threefold shorter time for complete GTF with NPWT compared with saline dressing (14.82 ± 7.30 vs. 44.57 ± 9.29 days, P <0.001) [5]. The superior GTF rates reported in the latter trial compared with ours may reflect the differences between the healing rates of chronic wounds of Wagner I and II grades in that trial as opposed to the complex surgical wounds of acute DFI of Wagner III and IV grades of the present study. Nevertheless, our rates compare favorably to those reported in a study on wounds of partial foot amputation, which also showed a significantly faster GTF rate with NPWT than CWD (42 vs. 84 days, P=0.002) [20]. Several other studies have demonstrated the benefit of NPTW in terms of accelerated GTF [7,8,19].

Similar to observations reported by earlier studies [8,21], the present trial showed that more patients stopped wound drainage with NPWT than in the CWD groups, which may indicate a better drainage effect of NPWT. Cessation of wound drainage along with complete GTF were the criteria of treatment success in the present study, which was significantly higher in NPWT than CWD group (100 vs. 75%, P=0.001).

The observed advantages of NPWT in the present study did not come at the expense of increased treatment-related adverse event, including pain or hemorrhage. Pain assessment in the present study was done during the first and fourth week of treatment to assess tolerance to pain when the wounds are still fresh, raw, and devoid of any granulation tissue compared with older wounds covered with granulation tissues. During the first week, NPWT showed similar mean values for VAS score to those observed with CWD. During the fourth week of treatment, wounds were expected to form granulation tissue that could have grown into the pores of the foam dressing and may cause pain due to its disruption with dressing change. However, the mean values for VAS score during the fourth week were significantly lower with NPWT compared with CWD (2.1 ± 0.78 vs. 3.0 ± 0.82, P<0.001), which comes in agreement with observations reported in a recent RCT [19]. In both treatment groups of the present study, VAS scores were lower during the fourth week than in the first week indicating that covering the wound bed with granulation tissue helped decrease pain sensation. Moreover, the faster GTF together with the fewer dressing changes with NPWT may have contributed to the decreased pain as compared with CWD.

Another concern about using NPWT in acute surgical wounds was the possibility of increased bleeding owing to the suction effect on recent wounds. The US Food and Drug Administration reported 12 deaths associated with NPWT between 2007 and 2011 owing to acute hemorrhages [18]. One of the important requirements for using NPWT is minimizing bleeding risk in the form of adequate wound hemostasis without any exposed vessels or coagulation dysfunction [14]. In the present study, patient randomization was carried out in the second postoperative day to ensure that any potential source of bleeding is well controlled; hence, none of the study patients experienced significant bleeding. Dressing soakage with blood was observed only during the first week of treatment in the present study, with a maximum of two UPDC in 5% of NPWT and 5% of CWD groups.

Increasing infection that led to secondary minor amputations was noted in two patients in the CWD group (5%) as opposed to 0% in the NPWT patients. None of the study patients required major amputations. Other studies have also reported fewer amputations with NPWT as compared with CWD [6,20]. The comparable rates of wound-related adverse events between NPWT and CWD have been also reported in several studies [18,22,23].

The main limitation in the present study is that all study patients continued their treatment at home. Although dressing changes were supervised by home nurses, this would not guarantee their strict commitment to our wound dressing protocol, especially in CWD patients. This, however, was not a major concern with NPWT as device processing and dressing changes were only allowed by qualified technicians provided by the supplier. Treatment at home, although might have caused some bias in our results, it still presents a

'real world' clinical practice of the local wound care of diabetic foot patients.

Investigating other important factors such as assessment of the role of NPWT and CWD in bacterial clearance and performing cost analysis of both dressing types could have added more value to the present study. All NPWT supplies were provided free of charge by our institution to the patients on admission and with every subsequent dressing change after discharge, which precluded an accurate cost analysis. Assessment of bacterial load reduction, however, required weekly testing for culture and antibiotic sensitivity on an outpatient basis and could not be done because of financial constraints.

Conclusions

Despite the study limitations, we are able to conclude that NPWT is a useful adjunctive wound treatment in surgically treated acute DFI. Effectiveness and safety of NPWT on surgically treated DFI has been shown in the present RCT in terms of significantly improved wound size, faster GTF, and cessation of wound drainage, without increased pain or bleeding as compared with CWD.

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Conflicts of interest

There are no conflicts of interest.

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