Original Article

Comparison of Vacuum-Assisted Closure Therapy and Conventional Dressing on Wound Healing in Patients with Diabetic Foot Ulcer: A Randomized Controlled Trial

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Abstract

Background: Vacuum-assisted closure (VAC) therapy has been shown to be beneficial in a variety of wounds. However, evidence of its benefit in diabetic foot ulcers (DFUs), especially with respect to Indian population, is sparse. **Methodology:** This randomized controlled trial included DFUs of Wagner's Grades 1 and 2. Patients were further stratified with respect to DFU size <10 cm and ≥10 cm. Patients with vascular disease, osteomyelitis, and bilateral DFUs were excluded from the study. The enrolled patients were randomized to receive VAC therapy or conventional dressing. The time to wound healing, granulation tissue formation, and complications such as pain, infection, and bleeding were compared between the two groups. **Results:** A total of sixty patients were randomized, of which 27 in each group were analyzed. The mean time to healing in days was significantly less in VAC group (22.52 vs. 3.85; $P < 0.0001$). Mean time to achieve 75%–100% granulation tissue cover was significantly less in VAC group (23.33 vs. 32.15; $P < 0.0001$). Rate of granulation tissue formation was also found to be significantly better in VAC group (2.91 cm^2/day vs. 2.16 cm^2/day; $P = 0.0306$). There was no difference between the two groups with respect to wound infection and bleeding which are commonly attributed to VAC therapy. VAC therapy group had significantly lesser pain at week 3 (Visual Analog Scale score 3 vs. 4; $P = 0.004$). **Conclusion:** VAC therapy significantly decreases the time to complete wound healing, hastens granulation tissue formation, and reduces the ulcer area compared to conventional dressing. The study did not find any significant increase in the bleeding and infection in the VAC therapy group.

Keywords: *Diabetic foot ulcer, granulation, negative pressure wound therapy, vacuum-assisted closure therapy, wound healing*

Introduction

Diabetic foot ulcers (DFUs) constitute one of the most important complications of diabetes mellitus, with a staggering 25% lifetime risk.[1,2] If not treated promptly, progression of infection and sepsis may necessitate a limb amputation.[3,4] Studies from Western population have shown significant implication of vacuum-assisted closure (VAC) therapy in various wounds including DFUs. Considering the early onset of complications including DFU in Indian diabetic patients due to differences in genetics, lifestyle, culture, socioeconomic status, and health education, the role of VAC therapy needs to be studied to establish the efficacy and safety of VAC in the management of DFUs in an Indian population.

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Patients and Methods

The study was designed as a single-center, prospective, parallel-armed, randomized controlled trial. It was conducted for 2 years at a tertiary care center in South India. The institute's Human Ethics Committee approved the study. Informed consent was obtained from all the patients participated in the study. The entire information recorded was kept confidential, and patients were given full freedom to leave from the study at any point. All ethical principles mentioned in the Declaration of Helsinki were followed in the present study.

With a power of 80%, α error of 5%, and expected difference of 20 days in the time taken for complete granulation cover, the sample size was calculated to be 54 with 27 in each group, using OPENEPI® software version 3 (www.OpenEpi.com). With the expected dropout rate of 10%, the sample size of 30 in each group was taken for the trial.

The study included all diabetic patients >18 years of age admitted with a DFU. The study excluded patients with coagulopathy, venous disease, ulcer with the underlying osteomyelitis, Charcot's joint, and peripheral vascular disease. The study also excluded patients with ulcer with Wagner Grades III and IV and involving both feet.

Stratified block randomization was carried out using a computer program with randomly selected block sizes of four and six. Allocation concealment was ensured using serially numbered opaque sealed envelope technique. Further, after randomization of patients in two groups, the patients in the respective groups were stratified into two groups of ulcer size <10 cm and ≥10 cm in the longest dimension, considering size of ulcer as a known confounding variable.

Initial treatment was done including debridement of the wound, antibiotics (initially empirical and subsequently culture based), and glycemic control. Thirty-four patients with Wagener's Grade II wound and two patients with Wagener's Grade I wound required one or two sessions of surgical debridement in the form of conservative sharp debridement using surgical blade. Antibiotics were given via either oral or intravenous route at the discretion of the treating surgeon. No topical antibiotics were used for the wounds. Once the DFU was deemed "clean" by the treating surgeon, the principal investigator assessed the wound to determine the readiness for VAC therapy. Those patients deemed fit by the principal investigator then received either VAC therapy or conventional dressings by random assignment. Assessment of nutrition was done by monitoring albumin and hemoglobin levels every week. Culture sensitivity was sent at the start of the study and then every week. The DFU area was noted at the start and end of the study. Analgesics were given in equal dose and frequency to patients in both groups.

In the study group, the wound bed was filled with a saline-soaked gauze piece after it was thoroughly cleaned. VAC was applied by placing sterile pads in two layers with a 16Fr Ryle's tube placed between the two layers and then the wound was sealed by a sterile transparent polyurethane sheet. The tube was connected to a wall-mounted suction device and the pressure was set at −125 mmHg [Figure 1]. Mode of NPWT was continuous. This dressing was changed every 48 h. At any point of time during the study, if the treating surgeon noticed any adverse wound parameter, VAC therapy was immediately discontinued.

In the control group, conventional dressing was given. This consisted of placing a saline-soaked gauze piece over the wound bed after cleaning the wound. Two layers of sterile gauze piece were placed on the dressing and secured with roller bandages. The dressing was changed daily, and assessment of the wound was done every 48 h by the treating surgeon for improvement or any adverse wound parameters.

Patients were assessed till complete wound healing (defined as 100% granulation and wound fit for split skin grafting) was achieved [Figure 2]. The primary outcome parameter was time taken to complete wound healing. Secondary outcome parameters were granulation tissue formation using a visual score and complication of bleeding, pain, and infection. Only healthy granulation tissue which appears pink was considered for scoring assessment. The granulation score of 1 was given when no granulation was present. Score 2 was given for <25% of wound covered by granulation tissue and score 3 was given for 25%–74% of wound covered by granulation tissue. Wound with 75%–100% granulation tissue cover was given a score of 4. Pain was assessed using a Visual Analog Scale (VAS) score, which was done 48 hourly and a mean value was calculated for each week and taken for analysis. Bleeding was assessed by the number of times the wound dressing had to be changed (excluding the one which was done every 48 hourly) due to soakage of blood. The total number of dressings changed due to soakage of blood was noted every week and taken for analysis. Infection was assessed by wound culture sensitivity which was sent every week. Besides these, the number of secondary debridement and minor amputations was also noted.

The data were analyzed using SPSS software version 19.0 (IBM SPSS Statistics for Windows, Armonk, NY, IBM Corp., USA) for Windows. Categorical variables were evaluated using Chi-square test or Fisher's exact test. Continuous variables were evaluated using either a

t-test or Mann–Whitney test, based on whether data distribution was normal or nonnormal. $P < 0.05$ was considered statistically significant.

Results

A total of 126 patients were assessed for eligibility. Following the assessment for eligibility, sixty patients satisfying inclusion and exclusion criteria were enrolled into the study and randomized into two groups each with thirty patients. Study Group A received VAC therapy, while the control Group B received conventional dressing. At the end of the study, 27 patients in each group were analyzed [Figure 3].

Age, gender, mean body mass index, hemoglobin, albumin, HbA1c, and diabetic control of patients were comparable between the groups. Average ulcer area and size were comparable between the groups. The number of patients with Wagner Grade 1 and 2 (8 vs. 2 and 19 vs. 25, respectively) was unequally distributed in the two groups ($P = 0.036$) possibly due to the small sample size [Table 1].

The time to complete wound healing was found to be significantly better with VAC therapy (21 days vs. 34 days; $P < 0.0001$). Median time to complete wound healing for DFUs <10 cm was 17.5 days and 30 days ($P < 0.0001$) and for DFUs ≥10 cm, it was 30 days and 39.5 days ($P = 0.0042$) in the study and control groups, respectively. Median reduction in the ulcer area was found to be 10.34 cm^2 and 3.5 cm^2, respectively, between the groups ($P < 0.0001$). Reduction in ulcer area was found to be better with DFUs ≥10 cm (25 cm^2 vs. 6.854 cm^2; $P = 0.0005$) than that of DFUs <10 cm (7.73 cm^2 vs. 3 cm^2, $P = 0.0018$). The number of patients underwent secondary minor amputations and debridement was not statistically significant between the two groups [Table 2].

The mean time to achieve granulation cover of >75% (visual score 4) between the groups was (23.33 days vs. 32.15 days, $P < 0.0001$) statistically significant. Median rate of granulation (cm^2/day) between the groups was (2.4 vs. 1.7; $P = 0.0306$) not statistically significant. However, with stratified analysis, this was not found to be significant for DFUs ≥10 cm ($P = 0.3598$). Pain was comparable with no difference in the two groups in the 1st week ($P = 0.271$), with median VAS of 8.5 in both groups. However, in week 3, the median score was 3 and 4 in the study and control groups, respectively, and this was statistically significant ($P = 0.004$) [Table 3].

The number of patients with different number of change of dressing due to bleeding in weeks 1 and 3 was comparable between the two groups. Furthermore, the number of patients who did not have any episode of bleeding at all was lower with VAC therapy, though this was not statistically significant (14 vs. 16; $P = 0.584$) [Table 4].

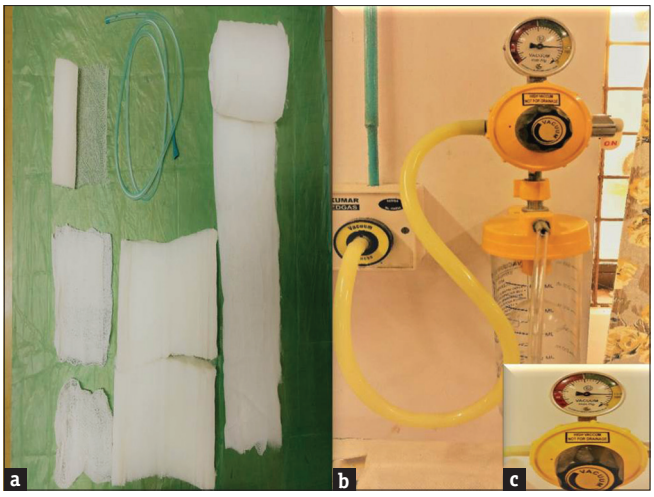

Figure 1: Negative pressure wound therapy (a) Materials used for negative pressure wound therapy in the study; (b and c) Wallmount-based vacuum-assisted closure device with pressure set at 125 mmHg

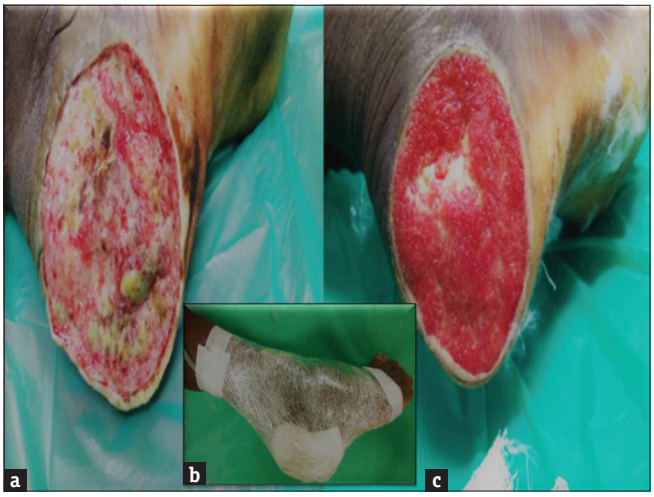

Figure 2: Negative pressure wound dressings (a) Diabetic foot ulcer at the start of negative pressure wound therapy; (b) vacuum-assisted closure therapy for the diabetic foot ulcer; (c) Wound after 15 days of negative pressure wound therapy of the diabetic foot ulcer

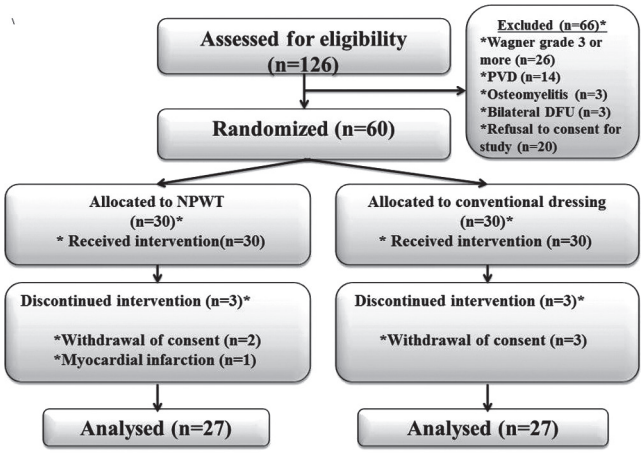

Figure 3: Consort flowchart

Table 1: Baseline demographic parameters between the study groups

Baseline characteristics	VAC (*n*=27)	Conventional (*n*=27)	*P*
Age in years (mean)	55.85 (35-95)	52.89 (28-70)	0.3596
Gender, *n* (%)			
Male	16 (59.26)	15 (55.56)	0.783
Female	11 (40.74)	12 (44.44)	
BMI (kg/m^2) (mean)	22.99	23.26	0.7780
Hemoglobin (g/dL) (mean)	10.28	10.18	0.8163
Albumin (g/dL) (mean)	2.77	2.72	0.5287
HbA1c (mean)	8.74	8.54	0.6525
Wagner grade, *n* (%)			
Grade 1	8 (29.63)	2 (7.41)	0.036
Grade 2	19 (70.37)	25 (92.59)	
Ulcer size, *n* (%)			
≥10 cm	11 (40.74)	10 (37.04)	0.780
<10 cm	16 (59.26)	17 (62.96)	
Ulcer area (cm^2)	70.97	80.44	0.5675

VAC: Vacuum-assisted closure, BMI: Body mass index, HbA1c: Hemoglobin A1c

Table 2: Wound healing parameters between the study groups

Wound healing parameters	VAC (*n*=27)	Conventional (*n*=27)	*P*
Median time to wound healing			
≥10 cm size	30	39.5	0.0042
<10 cm size	17.5	30	<0.0001
Wagner Grade 1	15.5	30	0.0361
Wagner Grade 2	27	34	0.0012
Reduction in ulcer area (cm^2)			
Median reduction	10.34 (0.28-36.85)	3.5 (0.00-25)	<0.0001
≥10 cm size	25 (10-36.85)	6.845 (0-25)	0.0005
<10 cm size	7.73 (0.28-13.25)	3 (0-16.7)	0.0018
Requirement of amputations			
Yes	3	5	0.444
No	24	22	
Requirement of debridement			
Yes	22	24	0.444
No	5	3	

VAC: Vacuum-assisted closure

The commonest organism associated with diabetic foot ulcer was *Staphylococcus aureus*, which was cultivated in the cultures of 35 patients. A total of 28 patients had either no growth or coagulase-negative staphylococci (CONS) during their hospital stay, of which 16 belonged to the study group and 12 belonged to the control group; however, this was not statistically significant.

Table 3: Granulation parameters between the study groups

Granulation parameters	VAC (*n*=27)	Conventional (*n*=27)	*P*
Visual score for granulation			
3	14.52 days	15.04 days	0.5611
4	23.33 days	32.15 days	<0.0001
VAS score for pain			
Week 1	8.5 (7-9)	8.5 (7-10)	0.271
Week 3	3 (2-6)	4 (2-7)	0.004
Granulation tissue formation (cm^2/day)			
Median rate	2.4 (0.79-7.29)	1.7 (0.77-5.5)	0.0306
<10 cm size	2.02 (0.79-5.2)	1.43 (0.77-3.89)	0.0351
≥10 cm size	4.2 (2.37-7.29)	2.766 (1.54-5.5)	0.3598

VAS: Visual Analog Scale, VAC: Vacuum-assisted closure

Table 4: Number of change in dressings due to bleeding between the study groups

Number of change in dressings due to bleeding	VAC (*n*=27)	Conventional (*n*=27)	*P*
Week 1			
0	13	11	0.656
1	8	10	
2	6	5	
3	0	1	
Week 3			
0	25	25	0.579
1	1	2	
2	-	-	
3	-	-	
Bleeding causing soakage			
Yes	14	16	0.584
No	13	11	

VAC: Vacuum-assisted closure

Table 5: Nature of growth found in ulcers between the study groups

Nature of growth	VAC (*n*=27)	Conventional (*n*=27)	*P*
Polymicrobial	8	22	<0.001
Monomicrobial	19	5	
No growth	12	11	0.783
CONS	5	4	0.715
No growth/CONS	16	12	0.276
Escherichia coli	1	13	<0.0001
Gram positive	22	21	0.735
Gram negative	10	23	0.0003
Aerobes	5	6	0.735
Facultative anaerobes	26	27	0.315
Anaerobes	1	0	0.315

VAC: Vacuum-assisted closure, CONS: Coagulase-negative staphylococci

Twenty-two patients in the control group demonstrated polymicrobial growth, while this was

so in only eight patients in the patients receiving VAC therapy ($P \leq 0.001$). *Escherichia coli* growth was significantly less in the study group ($P \leq 0.0001$). Gram-negative bacterial growth was significantly less in the NPWT group ($P = 0.0003$). Most of the patients in both groups demonstrated growth of Gram-positive and facultative bacteria [Table 5].

Discussion

A considerable proportion of patients with diabetes mellitus develop DFUs. The incidence of DFU ranges from 1% in the West to as high as 11% in African populations.[5] DFUs comprise the most common cause of nontraumatic amputation preceding as high as 85% of the cases.[6,7] Mortality rate among DFU patients is almost twice than in diabetics without DFU. It was found that the cost of care in patients with DFUs was over five times higher in the 1st year than in diabetics without foot ulcers.[8] This is mainly due to the long duration of hospital stay needed in DFU patients.

Application of NPWT to Wagner Grade 3 ulcers which include deep ulcers with abscess, osteomyelitis, and joint sepsis encloses the wound infection and may form an abscess.[4,9] Further, a significant number of patients with Wagner Grade 3 DFUs in our system present with infection, sepsis, and nonfunctioning ankle joints and often end up with amputation. Hence, the present study analyzed Wagner Grade 1 and 2 DFUs. However, considering the fact that both the grades are superficial, it is less likely to have a considerable impact on the time to complete wound healing, taking into account that the size of ulcers was equally distributed. Further, when stratified analysis was done to assess the effect of Wagner grade on time to complete healing, the results were still in favor of VAC therapy.

The time to complete wound healing was significantly better in the VAC therapy group as compared to conventional dressing. Similar results were obtained when comparison was done between the two groups stratifying the patients based on ulcer size. The time to complete healing in VAC group was significantly better in both DFU of <10 cm and ≥10 cm compared to the conventional dressing group; however, efficacy was more evident in the DFUs <10 cm ($P < 0.0001$) than the DFUs ≥10 cm ($P = 0.0042$). This can be attributed to the fact that time to healing is directly proportional to the size of the ulcer.

In a study by Armstrong and Lavery, median time to complete closure was 56 days in VAC therapy group against 77 days in the conventional saline dressing group.[10] Blume *et al*. demonstrated that a greater proportion of DFUs who received VAC therapy achieved complete skin closure or 100% reepithelization.[11] Singh *et al*. showed mean time to complete wound closure of 41.2 days and 58.9 days in VAC therapy group and conventional group, respectively.[12] Vaidhya *et al*. in a similar Indian study of sixty patients with DFU showed a time to healing of 17.2 days in VAC therapy group as compared to 34.9 days in conventional dressing group.[13]

Faster healing in NPWT is attributed to macrodeformation, wound environment stabilization and decrease in edema, microdeformation leading to increased cellular proliferation and angiogenesis, and decreased bacterial load, all of which lead to enhanced granulation cover. When comparing with the results of Armstrong and Lavery and Singh *et al*., our time to healing was achieved in lesser number of days in both the study and control groups.[12] This is because the end points in the latter studies were defined by spontaneous complete closure, i.e., 100% reepithelization. The disadvantage of having complete closure as an end point is that this may not be achieved in all wounds, as the wound size differs considerably between patients; also, majority of the DFUs are wider and longer than deeper unlike the postoperative wounds which take prolonged period for complete spontaneous closure. In none of the latter studies did all patients reached spontaneous closure. Further waiting for a wound to fully epithelize requires prolonged hospital stay which adds on to the cost of treatment.

Reduction in ulcer area was found to be more significant in ulcers ≥10 cm compared to those <10 cm. NPWT enhances wound contraction by macrodeformation due to the centripetal forces acting at the wound–foam interface.[12] The extent of macrodeformation is dependent on the deformability of the wound tissue.[14] Thus, in the present study too, wound contraction was more significant for ulcers >10 cm which were more deep and hence responded better to the macrodeformation effect of NPWT. Liu *et al*. in a recent systematic review and meta-analysis on the effect of NPWT in DFUs showed that NPWT significantly reduces DFUs compared to standard dressing.[15] McCallon *et al*. in their studies showed a reduction by 28.4%, 16.4%, and 23.6% in DFUs who received NPWT.[16] An Indian study by Nain *et al*. showed similar results as the present study with mean reduction in ulcer area by 16.14 cm^2 and 5.98 cm^2 in DFUs treated with NPWT and conventional dressing, respectively.[17]

Although few studies have shown NPWT to reduce the need of re-amputations, there is no explainable direct correlation of re-amputations with NPWT.[11,18] Other studies by Sepúlveda *et al*. show no difference with respect to amputations.[19] In the present study, all the

wounds were well debrided at initial presentation and hence most of them did not require further secondary amputations in both groups.

NPWT causes mechanical strain at the wound–foam interface, which deforms the cytoskeleton-activating cascades bringing about cellular proliferation and angiogenesis.[20] Increased levels of fibroblast growth factor, transforming growth factor-β, fibroblast proliferation, α-smooth muscle actin, interleukin-8, and vascular endothelial growth factor are implicated in the enhancement of granulation tissue formation in NPWT.[21,22] VAC therapy also creates a suitable environment by decreasing edema and bacterial load which would otherwise impede granulation. Time to achieve scores of 3 and 4 was comparatively less in VAC, this was significant only for VAS score 4. The possible reason as to why values were not significant in terms of VAS score 3 could be the wide range of 25%–75% granulation used in score of 3. Armstrong *et al*. showed that the median time to achieve 76%–100% granulation was almost twice as faster using NPWT than conventional dressing (median time of 42 days vs. 84 days).[10] Singh *et al*. showed the mean time to appearance to 100% granulation tissue as 15.1 days in the NPWT group, while it was 21.5 days in those who received conventional dressing.[12] In a Spanish study by Sepúlveda *et al*., the mean time to achieve 90% granulation was 18.8 days and 32.3 days in the NPWT group and conventional dressing group, respectively.[19] The present study also found that the median rate of granulation tissue formation was found to be statistically significant.

Pain in NPWT is thought to occur due to negative suction. During the change of dressing, the granulation tissue which grows into the foam's pores gets disrupted and may cause pain. Week 3 was chosen in the present study because the median time to healing was 21 days and 34 days in the study and control groups, respectively, which approximated to about 3 weeks. At the first presentation, all wounds being infected and covered with slough and necrotic tissue required extensive debridement, thus leading to more pain in all patients initially.

Only few studies compared pain between NPWT and conventional dressing in DFUs.[23,24] Pain was significantly less in the NPWT group in the present study. This could be possibly due to less number of dressings required in the VAC group. NPWT group patients required half the number of dressings as compared to those in the control group as dressing was done once in 2 days in NPWT group. This was stated as the cause of less pain in NPWT by Nather *et al*.[24] Other reason for lesser pain could be the use of gauze-based NPWT in the present study.[24] Foam is more adhesive and poriferous, hence granulation tissue grows into it, and thus at the time of dressing change, wound bed gets disrupted. Use of gauze-based NPWT has been shown to produce less pain by Fraccalvieri *et al*. and Dorafshar *et al*.[23,25] Faster growth of granulation tissue in NPWT group covered the raw wound bed faster and hence also contributed to lesser pain than in the control group.

Hemorrhage is one of the most feared complications of NPWT and been responsible for 12 deaths since 2007.[12] However, such life-threatening bleeding has been reported only when NPWT was applied for sternal wounds. Major bleeding in NPWT on DFUs is mostly due to improper hemostasis following debridement, exposed large blood vessels, and high set negative pressure, all of which are avoidable causes. In the present study where VAC therapy was done by trained surgical residents, there was no significant bleeding reported. No previous studies compared the bleeding complications between the two groups. Stress should be placed on controlling hemostasis after debridement and before applying VAC therapy to avoid bleeding complications. In addition the set negative pressure should be constantly monitored to avoid bleeding from the superficial blood vessels due to trauma associated with negative suctioning.

S. aureus was the common organism grown (23.3%).[12,24,26] There are studies showing NPWT to decrease bacterial load and infection; however, Armstrong and Lavery reported infection as an adverse event.[10] Inadequate debridement, retention of foam, air leak, sealing of any underlying infection, and bleeding due to NPWT which serves as a culture medium are attributed to cause or worsen infection in NPWT. Though studies including the present study show beneficial effect of NPWT on wound microbiology, NPWT should not be considered a substitute method to control infection.[27,28]

Limitations

A larger sample could have avoided the unequal distribution of Wagner's grade between the two groups. Although stratified analysis of the primary outcome variable based on grade showed significant positive outcome, this analysis could have been avoided had both Grade 1 and 2 DFUs been equally distributed by stratification in the study groups. Although bleeding was assessed, the methodology could not be made objective due to logistic reasons. Other important aspects which could have made the study more meaningful could be comparison of cost, quality of life, and patient satisfaction.

Conclusions

The present randomized controlled trial reports that VAC therapy is effective and safe in DFUs. It significantly

reduces the time to complete wound healing by hastening granulation tissue formation without any increase in the incidence of complication such as bleeding and infection.

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Conflicts of interest

There are no conflicts of interest.

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