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Original Article

Improved vacuum-assisted closure therapy for diabetic wounds that were difficult to heal and accompanied by chronic narrow sinus: a case series of five patients

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Abstract: Objective: To investigate the efficacy of improved vacuum-assisted closure (VAC) therapy for diabetic wounds that are difficult to heal because of the presence of chronic narrow sinuses or cavities. Methods: Five patients met the inclusion criteria and were selected from the Department of Endocrinology, Shandong Provincial Hospital, affiliated to Shandong University. All the patients received improved negative-pressure wound therapy (NPWT) in addition to standard-of-care treatment. We completed intra-subject comparisons of wound growth speed [(the last depth - the depth of the wound)/interval number (mm/day)] to determine treatment effectiveness. Patients were followed up until healing. We recorded visual representations of wound progression and time to full healing. Results: All the subjects demonstrated variable degrees of improvement of wound healing at the last follow-up. Wound healing during NPWT was significantly faster than that observed during standard-of-care treatment. Conclusion: The improved VAC therapy promoted narrow fistula healing in the patients with refractory diabetic foot wounds, but the promotion and application of this technology require additional research.

Keywords: Vacuum-assisted closure therapy, diabetic wounds, chronic narrow sinus

Introduction

Diabetic foot ulcer (DFU) is a common but serious complication of diabetes that produces major economic consequences for patients, their families, and society [1]. The lifetime risk of a person with diabetes for developing a foot ulcer can be as high as 25% [2]. Every 30 seconds, an individual somewhere in the world loses a lower limb as a consequence of diabetes [3]. Over the last decade, the economic cost of diabetes has skyrocketed and was estimated at $174 billion in 2007 and more than $245 billion in 2012 [4]. Of the total costs related to inpatient diabetes care, 20% to 50% may directly relate to DFUs [5].

Fleischmann et al. initially proposed negative-pressure wound therapy (NPWT) in the 1993 German medical literature [6]. Since its inception, NPWT has been applied to various wound types. These include acute, chronic, pressure, and traumatic wounds; wounds associated with resection of space-occupying lesions; infected and noninfected postsurgical wounds; and wounds with exposed prosthetic devices [7-11]. Apelqvist et al. [12] established that incurred medical costs were drastically reduced in post-amputation patients with diabetes who received NPWT, using a vacuum-assisted closure (VAC) system. These patients had lower resource utilization and fewer clinic visits, dressing changes, and surgical procedures, than those who only received standard-of-care moist wound therapy. Negative pressure therapy is becoming a mainstay treatment for both acute and chronic diabetic wounds [13].

Owing to the structural complexities of the foot, diabetic foot injury processes are complicated and highly variable. Penetrating cavities and sinus tracts are common types of damage foot

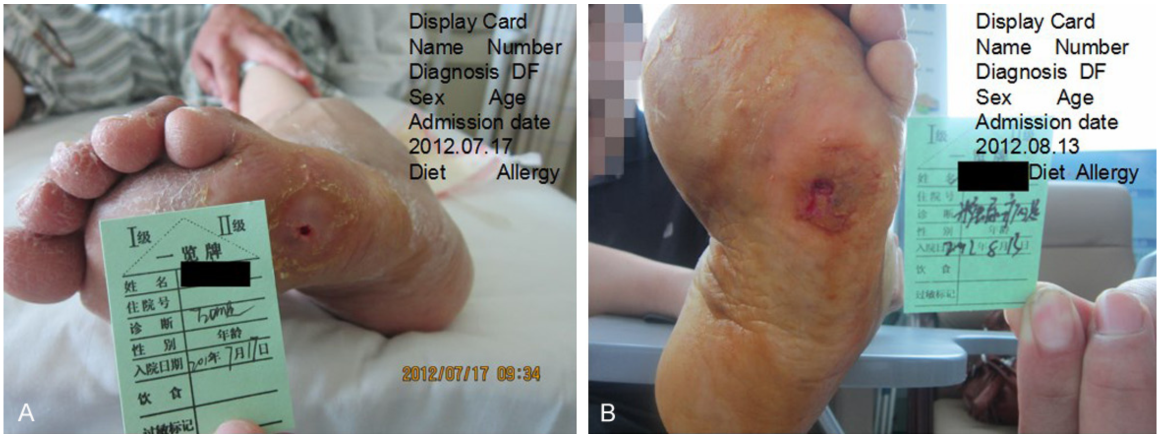

Figure 1. Case 1 pretherapy and post-treatment. A. Foot ulcers size was about 0.3 × 0.4 × 0.9 cm^3. B. The wound had healed.

Figure 2. Case 2 pretherapy and post-treatment. A. The left foot of the lateral was 0.7 × 0.9 × 0.9 cm^3 ulcer. B. VAC treatment. C. Foot ulcer healed completely.

damage. VAC technology treats soft tissue injury by stimulating tissue repair and accelerating tissue growth [14]. However, in chronic cases with refractory healing and combined narrow and deep damage, traditional NPWT devices cannot adequately apply negative pressure to hard-to-reach damaged tissues and are therefore unable to promote successful healing. We created an improved NPWT device for clinical treatment and compared our device with non-negative pressure approaches to confirm its ability to promote healing of diabetic foot injuries with chronic narrow sinus tracts and cavities.

Materials and methods

Five patients met the inclusion criteria and were admitted to the Department of Endocrinolog of Shandong Provincial Hospital, an affiliate of Shandong University, in 2012. We deidentified all individual patient information during and after data collection. The medical ethics committee of Shandong Provincial Hospital approved this study, and all the patients provided written informed consent for participation.

Inclusion and exclusion criteria

Inclusion criteria: Patients with a diagnosis of diabetic foot injury as per the established criteria [15] and hard-to-heal foot ulcerations with narrow sinuses and cavities were included. All the patients were treated for at least 3 months but showed no improvement.

Exclusion criteria: Patients with serious or acute cardiovascular or neurological disease those who were unwilling and/or unable to com-

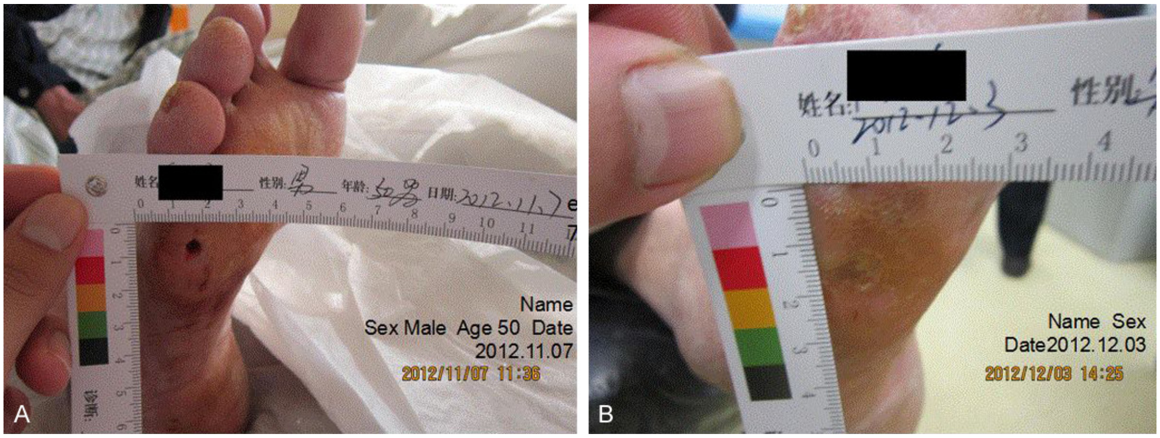

Figure 3. Case 3 pretherapy and post-treatment. A. On the right foot of the lateral was 0.4 × 0.5 × 0.5 cm^3 ulcer. B. Foot ulcer had healed completely.

Figure 4. Case 4 pretherapy and post-treatment. A. The ulcer size was about 0.9 × 0.6 × 0.9 cm^3. B. VAC treatment. C. The ulcer had healed well.

ply with all study-related procedures, or those for whom NPWT was contraindicated were excluded.

Design proposal

We compared our improved NPWT with the standard-of-care treatment in all the patients. As patients with chronic, severe diabetic foot injuries often demonstrate narrow-wound sinuses and cavities, traditional NPWT cannot conduct negative pressure into these hard-to-heal regions, thereby rendering the device less effective for wound healing. We improved the traditional NPWT device by removing the negative pressure dressing (sponge) that typically contacts with the wound. This results in the negative pressure drainage tube directly contacting the wound cavity (either a parallel or mergence cavity; **Figures 2B** and **4B**) to achieve a higher-magnitude and more direct-negative intra-articular pressure, thereby stimulating and inducing granulation tissue growth into the cavity or sinus.

Our improved NPWT device was compared with a standard-of-care treatment that involved education on controlling blood glucose level, standard wound treatment (surgical debridement, removal of necrotic tissue and foreign bodies, dead space exposure, etc), nerve nutrition, strategies to improve circulation, anti-infection measures, and so on.

During the improved NPWT therapy, the patients received intermittent NPWT. The average durations of a single course of NPWT and intermittent NPWT was 5 to 7 days, and 3 to 5 days, respectively. The negative-pressure drainage condition involved an intermittent negative

Table 1. Patient parameters

	Initial wound size (cm^3)	Initial wound locations	Vascular interventions during therapy	VAC* cycles	Status of last follow up
Case #1	0.3 × 0.4 × 0.9	Left plantar	None	1	Healed
Case #2	0.7 × 0.9 × 0.9	Left dorsal	Angioplasty with balloon dilation and stent	2	Healed
Case #3	0.4 × 0.5 × 1.0	Right plantar	None	1	Healed
Case #4	0.9 × 0.6 × 1.5	Right plantar	None	2	Healed
Case #5	1.0 × 1.1 × 2.6	Right heel	None	4	Healed

*Vacuum-Assisted Closure.

Table 2. The wound growth rate comparison

	Growth rate during the VAC (mm/day)	Growth rate of none VAC (mm/day)	*P* values
Case 1	0.633	0.189	-
Case 2	0.576 ± 0.006	0.161 ± 0.015	0.023
Case 3	0.720	0.200	-
Case 4	0.540 ± 0.015	0.167 ± 0.023	0.010
Case 5	0.518 ± 0.003	0.153 ± 0.006	<0.001

pressure of approximately 125 mmHg, a negative pressure treatment for 3 minutes, and an intermittent negative pressure for 3 minutes.

We recorded the speed of wound growth [(the last depth - the depth of the wound)/interval number (mm/day)] before and after each treatment phase (improved NPWT or standard-of-care treatment).

Statistical analysis

We used the SPSS 21.0 statistical software. Data are presented as means and standard deviations. We used paired sample *t* tests to compare wound growth speed during both improved NPWT and standard-of-care treatments. Statistical significance was determined as *p* values of <0.05.

Results

This study included five patients. The patient parameters are presented in **Table 1**. All were patients with diabetic foot ulcers featuring narrow sinuses and penetrating cavities.

Case 1

Our first case was a 43-year-old male patient with a history of diabetes for >1 year. His medical history was significant for poliomyelitis, dyslipidemia, poor blood glucose control, and glycosylated hemoglobin 9.8%. His diabetic foot ulceration burst 8 months prior to presentation. He was treated, though unsuccessfully, at a local clinic prior to presenting to our facility in July 2012. On admission, the size of his foot ulcer was approximately 0.3 × 0.4 × 0.9 cm^3 (**Table 1**, **Figure 1A**). After confirming that NPWT was not contraindicated, he was treated with both improved NPWT, and standard-of-care treatment. Owing to the better wound healing in the patients who underwent clinical observation, only one period of treatment was performed. During the improved NPWT phase, the speed of his wound healing was 0.633 mm/day faster than that observed during the standard-of-care phase (0.189 mm/day; **Table 2**). He was discharged on July 27, 2012, whereupon he continued oral medications and standard-of-care treatment. At his follow-up appointment on August 13, 2012, his wound had healed (**Figure 1B**).

Case 2

The second patient was a 59-year-old man with a 14-year history of diabetes. His medical history was additionally remarkable for coronary atherosclerotic heart disease and glycosylated hemoglobin 9.2%. He presented with a diabetic left foot ulcer that burst more than half a year prior. On presentation to our hospital in November 2012, his left foot ulcer measured 0.7 × 0.9 × 0.9 cm^3. He showed double lower limbs, violet-red foot skin (**Table 1**, **Figure 2A**), cool skin temperature, and worsening condition of the left foot.

As is the case with patients with large sinus cavity ulcerations, the patient was given a simple suture pull after debridement to promote wound healing. During the improved NPWT, his rate of wound healing was 0.576 ± 0.006 mm/day, faster than that observed during the standard-of-care phase (0.161 ± 0.015 mm/day, p

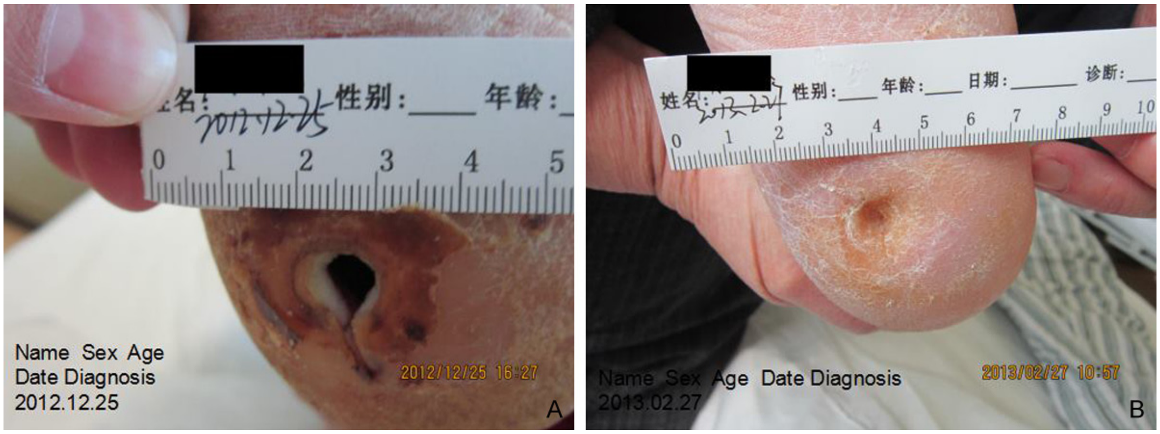

Figure 5. Case 5 pretherapy and post-treatment. A. At the bottom of the right foot ulcer: about 1.0 × 1.1 × 1.1 cm^3. B. The wound had healed.

= 0.023; **Table 2**). He was discharged in late November, by when his foot ulcer had healed completely (**Figure 2C**).

Hospitalization is necessary for patients whose lower limb arterial computed tomography angiography finding conforms to abdominal aorta and double lower limb atherosclerosis, multiple luminal stenosis, and arterial occlusion. The lower extremity arterial angioplasty, simple balloon dilatation of the left knee artery, and superficial femoral artery stent implantation were performed smoothly. The improvement of the lower extremity circulation was beneficial to the patients with foot ulcer healing.

Case 3

A 50-year-old man presented for treatment of a right foot ulceration in November 2012. He had a diabetes history of >10 years. His medical history was additionally significant for hypertension and dyslipidemia. His glycated hemoglobin level was 10.9%. His right foot ulceration measured 0.4 × 0.5 × 0.5 cm^3 and featured a small amount of seepage without purulent secretion (**Table 1**, **Figure 3A**). Culture of the foot ulcer secretions revealed *Pseudomonas aeruginosa*, so the appropriate antibiotic treatment was started. On November 7, we determined that the patient was a candidate for NPWT and started improved NPWT. During clinical observation, his ulceration improved markedly, with clearly visible granulation tissue growth. During the improved NPWT phase, the wound healing rate was 0.720 mm/day faster than that observed during the standard-of-care treatment phase (0.200 mm/day; **Table 2**). The patient continued to take oral medications and received standard-of-care treatment after discharge. At his follow-up visit on December 3, 2012, his foot ulcers had healed completely (**Figure 3B**).

Case 4

A 39-year-old man with diabetes and obesity sustained a nail injury to his foot in late November 2012. Upon presentation at our hospital, he denied having hypertension or coronary atherosclerotic heart disease. His glycosylated hemoglobin level was 8.4%. On admission, the ulcer size was approximately 0.9 × 0.6 × 0.9 cm^3, and showed bloody exudate. The surrounding skin was not red and swollen (**Table 1**, **Figure 4A**). Bacterial culture of the patient's wound secretion revealed coagulase-negative Staphylococcus, and the appropriate antibiotic treatment was started. We introduced the patient to the improved NPWT, during which his average wound healing rate was 0.540 ± 0.015 mm/day, faster than that observed during the standard-of-care phase (0.167 ± 0.023 mm/day, $p = 0.010$; **Table 2**). He was followed up as an outpatient, and by January of the following year, his wound had healed well (**Figure 4C**).

Case 5

Our final patient was a 51-year-old man with a 15-year diabetes history. His medical history was remarkable for hypertension and obesity. He demonstrated a right foot ulceration, which was treated for >4 months at a local hospital but with little improvement. In December 2012, he presented to our hospital for treatment of his ulcer, at the bottom of the right foot ulcer. At presentation, the ulcer measured approximately 1.0 × 1.1 × 1.1 cm^3 and had no purulent secretions (**Table 1**, **Figure 5A**). Magnetic resonance (MR) scanning revealed changes to the right tarsal and surrounding soft tissue. Bacterial cultures of his wound secretions were positive for *E.coli*, and he was started on appropriate antibiotic treatment. During his hospitalization, the patient exhibited nasal congestion, cough, and a small amount of white phlegm, among other symptoms. He was afebrile and his symptoms were considered suggestive of an upper respiratory tract infection. After oral treatment with Qingkailing granules, his symptoms improved after 7 days.

The patient received four sessions of improved NPWT, which appeared to have contributed to the significant wound healing. During the improved NPWT, the wound healing rate was 0.518 ± 0.003 mm/day, faster than that observed during the standard-of-care phase (0.153 ± 0.006 mm/day, $p<0.001$; **Table 2**). At his follow-up appointment in February 2013, his wound had healed (**Figure 5B**).

Discussion

Diabetic foot ulcers are severe complications of diabetes, and their occurrence closely relates to vascular lesions, neuropathy, and infection [16]. Diabetic foot wounds are difficult to treat. Healing is usually inadequate and takes a long time, often leading to amputation. Diabetes is the leading cause of non-traumatic foot amputations worldwide [17, 18]. Traditional treatments involve continual debridement and administration of anti-infection drugs. The process is long and frequently delays the optimal timing of treatment. Other symptoms such as abscess and osteomyelitis further complicate recovery. Other common treatment methods include skin substitutes, hyperbaric oxygen therapy, gene therapy using synthetic growth factors, and stem cell therapy [19]. Timely and effective ulcer healing is critically important for avoiding amputation and other serious complications, and for restoring body shape and function. For patients with diabetic foot wounds, earlier application of effective treatment improves overall prognosis.

NPWT, applied in the treatment of diabetic foot ulcers, is a new and effective technology. It features a drainage tube with a built-in medical foam material for covering the wound and uses a semipermeable membrane drainage area to seal and isolate the wound from the outside wound environment. The wound, coupled with the negative-pressure source, effectively drains. Compared with the standard-of-care wound dressing treatments, application of NPWT requires fewer switching times, is less painful, and shortens hospitalization and wound healing time [20].

NPWT can improve local blood circulation. Patients with diabetic foot lesions lack vitamin C, amino acids, and other nutrients in local tissues. These deficiencies seriously impair wound healing. Within a few minutes of starting NPWT, blood vessels dilate, causing blood supply to the tissues to multiply as the partial pressure of oxygen increases to the wound tissue. NPWT increases blood flow to the skin by vasomotor mediators [21], promoting healing nutrients and growth factors, and reactivating chronic wound tissue.

NPWT can promote angiogenesis and proliferation. Microdeformation at the wound interface activates vasculogenic growth factors. The endothelial progenitor cell (EPC) is the marker of healing and repair, and NPWT can increase its systemic concentration. Seo et al. [22] noted significant increases in systemic EPC in patients treated with NPWT, reflecting underlying angiogenesis and repair.

During NPWT, the wound is maintained in a relatively closed environment, which reduces the possibility of repeat infection. Bacterial infection may damage and extend the wound healing stages of inflammation, inhibit leukocyte function, prevent granulation tissue formation, and interfere in other ways with the normal wound healing process [23]. Negative pressure exerts both direct and indirect damage to bacteria. Bacteria struggle to survive under negative pressure conditions. Bacterial cell walls can be damaged because of the negative pressure and die. Moreover, improvement in blood circulation induced by negative pressure increases white blood cell migration into the wound. White blood cells can be produced under minimum oxygen concentrations and kill bacteria.

NPWT reduces local edema while removing seepage, purulence, and necrotic tissue from the wound. NPWT facilitates the merger of wound tissue with surrounding tissue to reduce wound tension, increasing epidermal growth and coverage. Stone et al. [24] proved that NPWT effectively absorbs the fluid surrounding the wound and reduces the localized accumulation of lactic acid, reducing lactic acid-induced apoptosis.

NPWT promotes granulation tissue growth. Albuquerque [25] believes that vascular endothelial cells and fibroblasts can directly sense the stimulation from NPWT on the wound surface. The mechanical stimulation of the cell is converted to a biological signal that activates cell growth, enabling decreases in intracellular cyclic adenosine phosphate, protein kinase A, and prostaglandin E2 levels. Cyclic adenosine phosphate acts as a signal transduction factor, and its decrease can promote the synthesis and proliferation of DNA so that at the cellular and molecular levels, cytokines, the cytoskeleton system, protein kinase, and so on mediate a series of cascading effects on tissue. Vacuum Sealing Drainage (VSD) can enhance the migration and activation of macrophages, induce tissue cell proliferation, and increase wound granulation tissue growth. In addition, the wound has many inhibiting tissue repair materials such as inflammatory factors and matrix metalloproteinases (MMPs). Stechmiller et al. found that after the application of NPWT, the inflammatory factors in the fluid that drained from the wound significantly decreased. Greene et al. [26] found reduced volume of MMPs in wound tissue after NPWT, which sped up tissue repair.

NPWT treats diabetic foot ulcers in common wounds, with good outcome. However, for cases with narrow sinuses or cavities, the traditional NPWT methods cannot produce sufficient negative pressure toward the narrow sinus, thereby reducing healing. We improved NPWT by removing the negative-pressure dressing (sponge) from the wound. We directly connected the negative-pressure drainage tube to the wound cavity (parallel or mergence cavity) to achieve a direct intra-articular negative pressure, thereby stimulating and inducing granulation tissue growth, in the cavity. This study involved 5 patients who completed 10 treatment cycles to promote foot wound healing. We found that wound healing during NPWT was significantly faster than that observed during the standard-of-care treatment. Research has shown that improved NPWT technology is suitable for treating diabetic foot ulcers. However, the technique still requires further research, including larger-scale clinical studies with randomized treatment assignment.

Conclusions

NPWT is an economical and effective treatment for diabetic foot ulcers. The improved NPWT technology is suitable for treating diabetic foot ulcers with refractory narrow sinuses and cavities.

Disclosure of conflict of interest

None.

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