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Research Article

A Prospective Observational Multi-Centre Study on the Use of Negative Pressure Wound Therapy in Diabetic Foot Ulcer

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Abstract

The prevalence of Diabetes Mellitus (DM) is increasing all over the world. Diabetic Foot Ulcer (DFU) is one of the major recognized complications. Recent evidence has shown that Negative Pressure Wound Therapy (NPWT) is one of the common methods used to treat DFU. The objectives of this prospective observational study were: (1) to explore the effectiveness of NPWT; (2) to identify any risk factors affecting DFU healing in using NPWT; (3) to make recommendations for daily clinical practice. The study design was an open-label 2-group design, including a conventional group (usual care) and an NPWT group. This study was conducted in 7 orthopaedic centres. The inclusion criteria were a history of DM, age 18 or above, ulcer located at the foot, infection under control, and a Saint Elain Wound Score System score between 12-23. The exclusion criteria were a high bleeding tendency, tumor patients, known autoimmune disease, and uncooperative patients. Each patient was followed for 12 weeks. A total of 125 patients were recruited, 62 in the NPWT group and 63 in the control group. The basic demographics were comparable between the groups. The results showed that the ulcer size, volume, and severity were significantly higher in the NPWT group. The key findings showed that the proportion of wound healing and healing rate was significantly higher in the NPWT group than in the conventional group. In the risk factor analysis, the regression model (adjusted R2=0.715) showed that larger wound size (below 50 cm2) and the use of adjunctive methods were more beneficial for using NPWT in DFU healing. The adjunctive methods included skin grafts, direct sutures, and other progressive wound closure methods. This implies that larger wound size with the help of adjunctive method after NPWT application enhances wound healing in DFU.

Keywords: Diabetic foot ulcer; Negative pressure wound therapy; Wound healing

Background

The prevalence of Diabetes Mellitus (DM) is increasing worldwide. According to the International Diabetes Federation, the global diabetes prevalence in 2019 was 9.3% (463 million people), projected to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [1]. Diabetic Foot Ulcer (DFU) is one of the major complications of DM, occurring not only in Western countries but also in China. A large prospective cohort study found that the annual incidence of ulceration and amputation for DFU patients were 8.1% and 5.1%, respectively [2]. The pathophysiology of DFU is complex and includes motor, sensory, and autonomic neuropathy, leading to skin breakdown ultimately [3]. Because of its complexity and high prevalence, DFU constitutes a significant medical and economic problem. Treatment options include pressure relieving, restoration of skin perfusion, treating infection, glycemic control, and local wound care [4].

Among the local wound care treatments, Negative Pressure Wound Therapy (NPWT) has attracted attention in recent decades. The mechanism of NPWT involves macrodeformation, microdeformation, improving wound perfusion, angiogenesis, granulation formation, exudate control, and bacterial colonization reduction [5,6]. Recent molecular studies have further discovered that patients receiving NPWT upregulate the circulating number of endothelial progenitor cells in venous blood [7], cellular fibronectin, and transforming growth factor β1 expression in local wound tissue [8], and glial cell line-derived neurotrophic factor and their family receptors α-1 and -2 [9]. All of these contribute to the facilitation of granulation formation and accelerate wound healing. Hence, NPWT has become increasingly popular for the clinical treatment of DFU. Many pieces of evidence suggest that NPWT is effective in treating DFU in terms of granulation formation, ulcer size reduction, and ulcer healing [10-12]. However, the evidence is still unclear. Seidel et al., discovered that there was no significant difference in wound closure rate or time to wound closure between NPWT and standard moist wound care in DFU patients [13]. Because of the unclear and conflicting evidence, there is a need to conduct a study to assess the efficacy of NPWT in local settings.

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Literature Review

A systematic search of databases selected for their relevance to wound care and peer review status was conducted, including PubMed and Cochrane CENTRAL, from 2010 to 2020 (Table 1).

	Search Terms
Population	diabetic foot ulcer
Intervention	subatmospheric pressure OR suction dressing OR negative pressure wound therapy OR negative pressure dressing OR vacuum assisted closure
Literature type	systematic review OR meta-analysis OR randomized control trial

Table 1: Search strategy.

The inclusion criteria included English literature, and the outcome focused only on clinical endpoints. Other literature that focused on economic endpoints, biochemistry, and mechanism of action were all excluded. In total, 17 articles were found, and 5 were excluded, including 1 non-English article and 4 articles that focused on molecular action. The included literature is summarized as follows (Table 2) with reference to the Johns Hopkins Evidence-based Practice tool [14].

Category (Level Type)	Total Number of Sources	Overall Quality Rating	Synthesis of Findings Evidence That Answers the EBP Question
Level I	8	A	NPWT was efficacious and safe in treating DFU [11,15-18]
		A	NPWT must be considered as an advanced wound care therapy for post-operative DFU without ischemia [19]
		A	There was low strength of evidence to support NPWT effectiveness in DFU healing [20,21]
Level III	4	B	The pooled result revealed that lower risk of major amputation [RR = 0.23] in NPWT-treated patients [22]
		A	The quality of evidence supporting the use of NPWT was low [23-25]

Table 2: Summary of included studies.

According to the above review, most of the literature supported that NPWT was useful for DFU healing, including systematic reviews, randomized controlled trials, and case studies. However, there were still some pieces of evidence that did not support the argument due to the fair quality of primary studies. In view of the identified gaps, the aim of the present study was to determine whether the application of NPWT enhances the healing of DFU among orthopedic patients. The objectives of the study were to 1) explore the effectiveness of NPWT and 2) identify any risk factors that affect DFU healing under the use of NPWT.

Methodology

This study was designed as an open-label, two-group design. The study sites included seven acute orthopaedic centers in Hong Kong. Both in-patients and out-patients were included. The inclusion criteria were type 2 diabetes mellitus, age 18 or above, ulcer located at or below the malleolus, active infection under control, and a Saint Elian Wound Score System (SEWSS) score between 12 and 23. The score is composed of three clinical parameters: anatomical factors, regional factors that affect healing, and local wound factors [26]. Patients with a high tendency for bleeding, benign or malignant tumors, autoimmune disease, or uncooperative patients were excluded from the study.

Patients were divided into two groups according to the current local practice, based on the clinician's selection. The intervention group received NPWT and usual care, while the control group received only usual care. Usual care was defined as the current local practice on wound care other than NPWT, including skin care, glycemic control, treating infection, and pressure relieving (4). In the control group, moist dressings were applied daily based on local good practice, while NPWT changes were performed every 48-72 hours. The RENASYS NPWT system was used to apply 125 mmHg pressure by the author himself or trained dedicated nursing staff. The wounds were assessed at three fixed time points at weeks 0, 6, and 12 and two flexible time points before and after NPWT. Moreover, wound dimensions in terms of surface area and volume were determined by the Insight® 3D wound management system.

All data collected were analyzed using SPSS Version 23.0. The primary outcome was the proportion of wound healing at weeks 6 and 12. The secondary outcome was the healing rate at the corresponding two time points. The chi-square test was used to compare qualitative data, such as gender, comorbidities, and proportion of wound healing between groups. The independent sample t-test was used to compare quantitative variables, such as age, HbA1c level, albumin level, and healing rate. A multiple regression model was applied for risk factor analysis. A p-value of less than 0.05 was considered significant. The sample size was calculated using the G* Power calculator, with a level of significance of 5% and a power of the test of 80% [27]. The calculated Cohen's effect size was 0.52, and the required sample size for each group was 60, for a total sample of 120.

Results

Overall, we recruited 125 patients from the period of December 2019 to April 2021 (Figure 1): 62 in the intervention group and 63 in the control group. In total, 50 patients in the intervention group and 49 patients in the control group completed the 12-week study period. The reasons for premature termination included amputation, inability to follow up, loss of follow-up, and death. There were no significant differences in premature termination between the two groups (p=0.75).

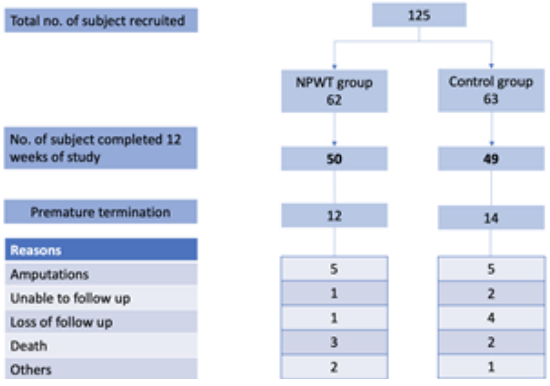

Figure 1: Subject recruitment.

The baseline characteristics were summarized in table 3, and no significance was found between the groups. However, there were statistically significant differences between the groups for the wound-related parameters (Table 4). The initial wound size (p=0.01) and volume (p<0.005) in the NPWT group were statistically larger than in the control group. The size and volume of the NPWT group were also visually bigger (Figure 2). The DFU Severity Score (SEWSS) showed no significant difference between the groups, although the absolute value in the NPWT group was higher. A larger score implied more severity.

		NPWT group	Control group	Statistical test	p value
Number of subjects		62	63		
Gender	M	49	43	Chi square	0.22
	F	13	20		
Age (years)*		61.3 ± 14.5	63.1 ± 14.3	t-test	0.97
Duration of DM (years)*		10.2 ± 10.2	12.1 ± 10.0	t-test	0.29
HbA1c (%)*		8.4 ± 2.9	7.9 ± 2.2	t-test	0.32
Serum WBC (10^9/L)*		11.6 ± 4.4	10.1 ± 4.7	t-test	0.50
Serum albumin (mmol/l)*		29.5 ± 6.9	31.0 ± 7.0	t-test	0.22
Ambulatory status	Outdoor walker	50	47	Chi square	0.61
	Indoor walker	5	7		
	Assist walker	4	2		
	Chair-bound	2	5		
	Bed-bound	1	2		
Peripheral vascular disease	Yes	12	14	Chi square	0.83
	No	50	49		
Heart disease	Yes	16	19	Chi square	0.69
	No	46	44		
Renal disease	Yes	11	17	Chi square	0.28
	No	51	46		

Table 3: Baseline clinical characteristics and biochemical measurement.

* Data presented as mean ± SD

	NPWT group	Control group	Statistics test	p value
SEWSS (DFU score)*	16.4 ± 2.70	15.1 ± 2.5	t-test	0.06
Initial wound size (cm^2)*	23.8 ± 29.7	9.4 ± 15.3	t-test	0.01[a]
Initial wound volume (cm^3)*	14.4 ± 17.9	4.8 ± 8.4	t-test	< 0.005[a]

Table 4: Wound related characteristics.

* Data presented as mean ± SD

[a]p < 0.05

The proportion of wound healing in the NPWT group was significantly higher than in the control group (p=0.04) at week 6, but there was no statistically significant difference at week 12 (Table 5). In terms of the healing rate, the NPWT group showed significantly higher rates for both wound size and volume, but there was no difference at week 12 between the two groups (Table 6). After the wound bed was well-prepared, adjunctive methods were used, which included direct closure by strapping, suturing, the shoelace technique, or skin graft. Interestingly, the use of adjunctive methods was significantly higher in the NPWT group (p=0.002), as shown in table 7.

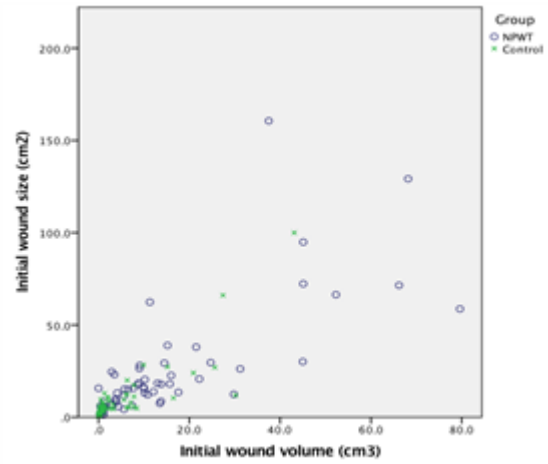

Figure 2: Scattered plot on initial wound size and volume between groups.

No. of wound healing		NPWT group	Control group	Statistics test	p value
Week 6	Yes	17	8	Chi-square	0.04[a]
	No	38	48		
Week 12	Yes	10	10	Chi-square	0.80
	No	22	30		

Table 5: Proportion of wound healing.

[a]p < 0.05.

Healing rate		NPWT group (n = 55)	Control group (n = 56)	Statistics test	p value
Week 6	Size (cm^2/ day)*	0.57 ± 0.97	0.08 ± 0.25	t-test	0.001[a]
	Volume (cm^3/ day)*	0.38 ± 0.56	0.11 ± 0.31	t-test	0.002[a]
Week 12	Size (cm^2/ day)*	0.19 ± 0.24	0.12 ± 0.19	t-test	0.20
	Volume (cm^3/ day)*	0.17 ± 0.24	0.08 ± 0.22	t-test	0.10

Table 6: Healing rate at week 6 and week 12.

*Data presented as mean ± SD

[a]p < 0.05

In addition, the majority of the wounds were in the category of wound size below 50 cm^2 and a healing rate between 0 to 1 cm^2/ day. When selecting this group of patients, the correlation in the NPWT group was 0.81 (Figure 3). Hence, this group of patients was chosen for risk factor analysis. The results showed that the initial wound size and the use of adjunctive methods were correlated with the wound healing rate at week 6 (adjusted R^2=0.72).

Adjunctive method	NPWT group (n = 62)	Control group (n = 62)	Statistics test	p value
No	37	53		
Yes	25	9	Chi-square	0.002
Skin graft	18	3		
Direct suture	6	6		
Progressive wound closure/ strapping/ shoe-lace	1	0		

Table 7: Use of adjunctive methods.

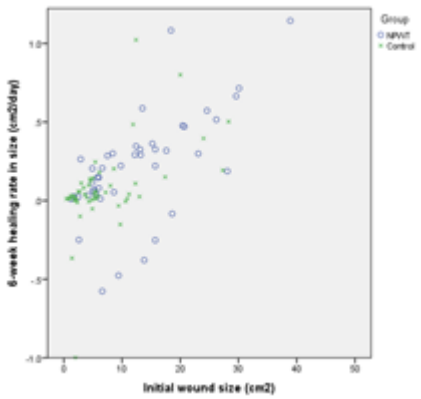

Figure 3: Initial wound size versus healing rate in terms of wound size at week 6.

Discussion

We presented our prospective observational study on the effectiveness of using NPWT in 125 patients with DFU. Since the selection method was based on the current clinical decision by orthopaedic nurses and doctors, the wound status was not evenly distributed between the NPWT and control groups. Importantly, the NPWT group had a significantly larger size and volume of wounds. In a similar observational study, the wound size in the NPWT group was also significantly larger [27]. Not surprisingly, most clinicians select larger DFUs for NPWT. In our present study, the proportion of healing and healing rate was significantly higher in the NPWT group at week 6. Similar studies have found that NPWT results in faster wound healing than conventional treatment. James et al., demonstrated that the mean time to healing in days was significantly less in the NPWT group [12]. Additionally, the NPWT group led to early reduction in wound size compared to the control group after 8 to 14 days of application [10,11,27].

The relatively short-term effect of NPWT in DFU was obvious. NPWT achieves its positive wound healing effects through multiple mechanisms. The suction creates a contraction force, which results in wound approximation and macro-deformation. In addition, the force can facilitate cell migration, angiogenesis, and perfusion changes, resulting in micro-deformation [5]. Recently, research has further studied the molecular effects of NPWT on DFU. NPWT up-regulates vascular endothelial growth factor and fibroblast growth factor 2, while the expression of inflammatory cytokines is down-regulated [28]. Yang et al., discovered that NPWT facilitates the expression of cellular fibronectin and transforming growth factor-β1 in DFU, which can facilitate granulation formation [8]. Borys et al., identified four genes differential expression that may contribute to the NPWT effect on DFU [9]. Yang et al., demonstrated that NPWT significantly decreased the expression of interleukin-6, tumor necrosis factor α, and inducible nitric oxide synthase, as well as nuclear factor-κB p65 expression, and increased the expression of activating transcription factor-3 during DFU healing [29].

Not surprisingly, the wound healing rate in terms of size and volume was not significant at week 12 in our study. The average duration of NPWT application was 15.5 ± 11.5 days, which was relatively short. Due to the short duration of NPWT application, unhealed ulcers were changed to other methods when NPWT was no longer beneficial clinically. In addition, healed ulcers were excluded from the week 12 analysis. Therefore, there was no significant difference at week 12, even though the absolute values of both healing size and volume were higher in the NPWT group. This phenomenon is echoed by a German DiaFu-RCT study. Seidel et al., found that the time to complete healing in the NPWT group was lower than in the standard moist wound care group in week 5, but there was no significant difference in week 16, even though the absolute value in the NPWT group was lower [13].

The use of adjunctive methods, including direct suture, progressive closure devices, shoelace technique, and strapping, was significantly higher in the NPWT group than in the control group. The mechanism of action of NPWT includes macrodeformation through three-dimensional shrinkage of the surrounding tissue, drainage of extracellular fluid resulting in decreased edema, and microdeformation, which produces shearing and deformation on the cells [30]. This is the reason why using NPWT makes it easier to directly close wounds through sutures and different closure devices. Ka Kagia et al., compared the combination of NPWT and the shoelace technique with the control group in fasciotomy wounds, and the evidence supports the combination of methods having a significantly shorter wound closure time [31]. Netto et al., demonstrated the associated use of progressive tension sutures and NPWT in large degloving wounds. With the help of the combined method, the wound surface area and volume were minimized quickly [32]. In addition, NPWT also facilitates skin grafting afterward since it can facilitate cellular proliferation, angiogenesis, and granulation formation. Liu et al., studied the effect of NPWT from a molecular perspective. They demonstrated that NPWT may suppress NLRX1 expression through the upregulation of miR-195 expression, which, in turn, can promote angiogenesis in the granulation tissue [33]. Maranna et al., further supported this clinically. They found that the time for 100% granulation tissue coverage was significantly shorter in the NPWT group than in the control group [10]. This is the reason why the use of skin graft was significantly higher in the NPWT group than in the control group in our study.

In the present regression analysis, we found that a larger wound size (less than 50 cm2) and the use of adjunctive methods affected the 6th week healing rate. Seidel et al., supported that a relatively large diabetic foot wound size was more beneficial when using NPWT. Their study reported that larger wounds achieved wound closure within 16 weeks in the NPWT group faster than in the control group. However, there was no significant difference in small wounds between the groups [13]. Not surprisingly, larger wounds can stretch the surrounding skin more easily than smaller wounds [30] resulting in a more obvious healing rate and wound closure. Besides, the use

of adjunctive methods, including different closure devices, strapping, or suture techniques during and after NPWT, can further assist in decreasing wound defects and enhancing wound healing. Therefore, our present study supports that both a larger wound size and the use of adjunctive methods are the two crucial factors that enhance DFU healing. Considering the limited resources in healthcare settings, NPWT is recommended to prioritize larger wound sizes (below 50 cm2) and the use of adjunctive therapy during and after NPWT treatment in DFU healing.

In our present multi-center study, we had two major limitations. First, there were few points for reassessment. We only assessed every participant at weeks 1, 6, and 12. Some participants had already achieved complete ulcer healing between week 6 and 12. Second, in this prospective observational study, there was no randomization or concealment.

Conclusion

Our study highlights the effect of NPWT in DFU healing. The proportion of wound healing, wound size, and volume reduction were significant after several weeks of NPWT treatment. Additionally, both the initial wound size and the possibility of using adjunctive methods are important considerations for the outcome of DFU healing. It is suggested that clinicians consider these factors before commencing NPWT to enhance the clinical outcome of DFU healing.

Compliance with Ethical Standards

Conflicts of interest: The author have no conflicts of interest to declare.

Ethical approval: All the procedures performed involving human subjects were in accordance with 1964 Helsinki declaration and its later amendments or comparable standards.

Informed consent: Verbal consent was obtained from all individual participants included in the study.

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