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ORIGINAL ARTICLE

A retrospective cohort study evaluating efficacy in high-risk patients with chronic lower extremity ulcers treated with negative pressure wound therapy

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Key words
Negative pressure wound therapy; Wound healing; Comorbidities; Low extremity chronic ulcers; Early intervention

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Abstract

The purpose of this study was to evaluate the efficacy of negative pressure wound therapy (NPWT) compared with standard of care on wound healing in high-risk patients with multiple significant comorbidities and chronic lower extremity ulcers (LEUs) across the continuum of care settings. A retrospective cohort study of 'real-world' high-risk patients was conducted using Boston University Medical Center electronic medical records, along with chart abstraction to capture detailed medical history, comorbidities, healing outcomes and ulcer characteristics. A total of 342 patients, 171 NPWT patients with LEUs were matched with 171 non-NPWT patients with respect to age and gender, were included in this cohort from 2002 to 2010. The hazard ratios (HRs) were estimated by COX proportional hazard models after adjusting for potential confounders. The NPWT patients were 2·63 times (95% CI = 1·87–3·70) more likely to achieve wound closure compared with non-NPWT patients. Moreover, incidence of wound closure in NPWT patients were increased in diabetic ulcers (HR = 3·26, 95% CI = 2·21–4·83), arterial ulcers (HR = 2·27, CI = 1·56–3·78) and venous ulcers (HR = 6·31, 95% CI = 1·49–26·6) compared with non-NPWT patients. In addition, wound healing appeared to be positively affected by the timing of NPWT application. Compared with later NPWT users (1 year or later after ulcer onset), early NPWT users (within 3 months after ulcer onset) and intermediate NPWT users (4–12 months after ulcer onset) were 3·38 and 2·18 times more likely to achieve wound healing, respectively. This study showed that despite the greater significant comorbidities, patients receiving NPWT healed faster. Early use of NPWT demonstrated better healing. The longer the interval before intervention is with NPWT, the higher the correlation is with poor outcome.

Introduction

Negative pressure wound therapy (NPWT) has been demonstrated to accelerate wound healing successfully in patients with low extremity ulcers (1–5), which were proven by randomised clinical trials (RCT) (6). In many ways, this therapy has revolutionised the clinical paradigm for preserving limbs and healing wounds. V.A.C.® therapy is a form of NPWT that uses Kinetic Concept Inc. (KCI)'s proprietary reticulated open-cell foam construct (NPWT/ROCF). This integrated wound care system was cleared for marketing

Key Messages

- a cohort study of 'real-world' high-risk patients with lower extremity ulcers was conducted using electronic medical records, together with chart abstraction
- 171 patients with NPWT and 171 patients without NPWT were included in this study
- overall, NPWT patients were 2.63 times more likely to achieve wound closure compared to patients without use of NPWT
- NPWT-treated wounds were 3.26 times, 2.27 times and 6.31 times more likely to achieve closure than non-NPWT treated wounds in diabetic ulcers, arterial ulcers and venous ulcers respectively
- wound healing seems to be positively affected by timing of NPWT application. Early NPWT users (within 3 months after ulcer onset) and intermediate NPWT users (4-12 months after ulcer onset) respectively were 3.38 and 2.18 times more likely to achieve wound healing comparing later NPWT user (1 year or later)
- despite the greater significant comorbidities, early use of NPWT demonstrated better healing
- the longer the interval before intervention is with NPWT, the higher the correlation is with poor outcome

by the US Food and Drug Administration in 1995 following which a consensus statement on NPWT (V.A.C therapy) for the management of diabetic foot ulcers was developed.

NPWT is used in the treatment of chronic, acute, subacute, traumatic and dehisced wounds; pressure and diabetic ulcers; partial-thickness burns; flaps; and grafts (1–4,7). The mechanisms of action of NPWT are effective in both the macroenvironment and microenvironment (8,9). This includes providing a moist, closed wound healing environment, drawing wound edges together, removing infectious materials and fluids, reducing oedema, and promoting tissue perfusion and granulation tissue formation, which together help in the preparation of the wound bed for closure by delayed primary or secondary intention. The unique properties of the reticulated open cell foam (ROCF) cause deformation at the epidermal cellular level that stimulates changes in cellular activity. The NPWT through application of V.A.C. therapy has a negative wound expansion effect as well as providing for a metabolic reason for improved wound healing (9).

Chronic wound patients often have multiple comorbidities such as diabetes, peripheral arterial disease or compromised immune systems, which may lead to impaired wound healing (10). The goal of therapy in these patients was to optimise the wound healing environment by stabilising the conditions that impede wound healing and to facilitate active and aggressive wound care (11,12).

RCTs are considered to be the gold standard in generating major evidence for a clinical intervention (13,14). However, 'real-world' patients are clinically complex and present with multiple comorbidities, as well as various underlying aetiologies and compliance challenges. RCT-proven therapies may fail to be effective in 'real-world' patients. This might be attributed to RCT designs that do not reflect the complex issues faced in clinical practice and are limited by the challenges of designing such studies displaying wound heterogeneity (15). Use of practice-based evidence (PBE) and observational study data in a real-world setting may provide supplement important clinical insights that are generally missing in RCTs (16,17). Therefore, the purpose of this study was to evaluate the efficacy of NPWT compared with non-NPWT patients. We selected real-world patients with multiple comorbidities across the continuum of care settings, for the study population. This population will not be allowed in a traditional RCT. This study has demonstrated that despite the greater significant comorbidities, patients receiving NPWT healed faster.

Patients and methods

Data source

We conducted an Institutional Review Board (IRB)-approved retrospective cohort study at the Boston Medical Center, a 508-bed, academic medical center and the primary teaching affiliate for Boston University School of Medicine.

We used information from the electronic medical records during the period 2002–2010. This database contains longitudinal patient health information including demographics, medical diagnoses (ICD-9) and inpatient procedures (ICD-9 or CPT coded) (Table 1).

Additional information, such as ulcer history, ulcer start date, ulcer end date, ulcer size, duration of NPWT, wound grade, type of surgical procedures, history of lower extremity ulcers (LEUs), and major or minor amputation, was identified through chart review of Boston University Medical Center (BUMC) medical records by trained medical professionals (Table 1).

Table 1 Data source and collection

Data obtained or confirmed by chart reviewing
- History of smoking, alcohol consumption, minor amputation, major amputation, infection and malignancy
- Date of podiatric and vascular clinic visit, hospital admission date, hospital discharge date, and primary diagnosis of admission
- Ulcer start date, location of ulcer, size of ulcer, type of ulcer (diabetic arterial, venous and/or others), NPWT start date, ulcer status at the end of study (healed, unhealed or loss of follow-up), ulcer grade, palpable pulse, vascular status, infection (culture, imagine, pathology reports)
- Minor amputation, major amputation, and surgical incision and drainage during study period

Data obtained from electronic medical records including ICD-9 codes
- Medical record number, date of birth, gender, race
- Diabetes (250).XX
- Peripheral arterial disease (440·20, 440·21, 440·22, 440·23, 440·24, 443·81,443·9, 454·0)
- Coronary heart disease (410·0–410·9, 411·0, 411·1, 412, 413·0, 413·1, 414·10, 414·11, 414·12, 414·8, 414·9)
- Congestive heart failure (428·0)
- Chronic renal disease (585, 586)
- Hypertension (401.X)

Study subjects

This study included 342 patients with LEUs, who were treated with or without NPWT. Patients with LEUs were identified from the BUMC Data Warehouse, whereas those with an ICD-9 diagnostic code indicating LEU were considered in either cohort. ICD-9 and CPT codes were then used to exclude patients based on inclusion/exclusion criteria (HIV-positive, sickle-cell disease, active malignancy with chemotherapy, age less than 18 years, traumatic and burn ulcers).

NPWT Cohort: A query of the BUMC Data Warehouse was used to identify patients who had a chart entry indicating NPWT. Each patient's chart was reviewed to confirm the use of NPWT and to identify the index ulcer (the ulcer that received the NPWT application) as some patients had multiple ulcers – not all receiving NPWT applications. Before being entered into the cohort, the patient who was identified as having a LEU had their chart reviewed to confirm that NPWT was maintained for a minimum of 7 days.

Non-NPWT Cohort: A query of the BUMC Data Warehouse identified patients who did not have chart entries indicating NPWT. Before entering into the cohort, these patients had their charts reviewed to confirm that the LEU identified did not receive NPWT. These patients were matched for age, sex, and ulcer surgical incision and drainage (I/D) with the NPWT cohort.

Outcome and follow-up

Ulcer healing was the outcome of interest in this study and was a dichotomous variable with healed and unhealed as the factors. The study period was from the first clinic visit date of the index ulcer to the last clinic visit date. The final date of the index ulcer was defined as either the date on which the index ulcer achieved complete healing (event) or the last clinic visit date on which the index ulcer was described in a clinic note (right censored).

Statistical analysis

We compared the baseline characteristics of non-NPWT and NPWT patients as shown in Table 2. A *t*-test was used for continuous variables, whereas a chi-square or Fisher's exact test for categorical variables.

Incidence rate (IR) with 95% confidence intervals (CI) was calculated for all patients with ulcers and then stratified by types of ulcers. To adjust for all potential confounders (diabetes, peripheral arterial disease, chronic kidney disease, coronary heart disease, etc.), we constructed multivariable-adjusted COX proportional hazard models to evaluate dichotomous ulcer closure outcome. In addition, we performed subgroup analyses in NPWT patients by examining whether timing of NPWT application after the onset of index ulcer is associated with outcomes using a separate confounder-adjusted COX proportional hazard model. All data manipulation, programming and analyses were performed using SAS 9.1 Statistical Software (SAS Institute Inc., Cary, NC).

Results

Patient characteristics of two groups at baseline

On the basis of confirmation from chart review of NPWT use, 171 patients were confirmed to be NPWT patients and 171 non-NPWT patients matched for age, gender and surgical I/D procedure were selected for the non-NPWT cohort.

Table 2 depicts the baseline characteristics of NPWT and non-NPWT patients. Age, gender, location and grade of ulcer are almost the same for both groups. However, there are more diabetic (81·8% versus 69·4%, $P < 0{\cdot}05$) and arterial ulcers (66·7% versus 34·9%, $P < 0{\cdot}01$) in NPWT group than non-NPWT group. Fewer patients had infections during the study period in the NPWT cohort than in the non-NPWT cohort (79·5% versus 91·1%, $P < 0{\cdot}05$). As for comorbidities, associated with the severity of patient's overall medical condition, more subjects in the NPWT group had chronic renal disease and a history of smoking than in the non-NPWT group. In addition to these comorbidities, we examined disease severity-related variables, such as number of outpatient clinic visits during the study period, total number of comorbidities and history of minor and major amputation. We found that 94·7% of NPWT patients had at least one inpatient ulcer service compared with 66·7% of non-NPWT patients did ($P < 0{\cdot}01$). In contrast, 71·9% of NPWT patients had five or more outpatient clinic visit during their study period compared with 87·7% of non-NPWT patients.

In summary, overall the subjects enrolled in the NPWT cohort showed a greater proportion of diabetes, peripheral arterial disease and comorbidities.

IRs and adjusted hazard risk of different types of wound healing in NPWT patients

Table 3 demonstrates the IR of wound healing at the end of the study period. For all subjects regardless of ulcer type, 43·0 (95% CI = 35·91–51·51) wounds were healed per 100 person-years without NPWT, whereas 90·51(95% CI = 75·63–108·32) wounds were healed per 100 person-years with NPWT. The IRs of wound healing for each type of ulcer are also shown in Table 3.

Potential confounders in this study include comorbidities (i.e. diabetes, peripheral arterial disease, coronary heart disease, chronic kidney disease, congestive heart failure, stroke, smoking, etc.). We also considered other variables associated with disease severity as additional potential confounders. Table 4 summarises unadjusted and adjusted hazard ratios of wound healing. After adjusting for potential confounders, comorbidities and other variables associated with disease severity, NPWT patients had 2·63 times (95% CI = 1·87–3·70) likelihood of a wound closure compared with that of non-NPWT patients. Moreover, when ulcer healing is reviewed by ulcer type NPWT patients with diabetic ulcers had greater incidences of wound healing (HR = 3·26, 95% CI = 2·21–4·83), arterial ulcers (HR = 2·26, CI = 1·56–3·78) and venous ulcers (HR = 6·31, 95% CI = 1·49–26·6) compared with that of non-NPWT patients.

Table 2 Baseline characteristics of patients

	Non-NPWT patients	NPWT patients	*P* value
Age, mean (SD)	61·3 (14·5)	60·8 (14·4)	>0·05
Gender, *N* (%)			
Male	99 (57·9)	99 (57·9)	>0·05
Female	72 (42·1)	72 (42·1)	>0·05
Race, *N* (%)			
White	62 (36·7)	76 (44·4)	
Black	70 (41·4)	69 (40·4)	
Hispanic	30 (17·8)	19 (11·1)	
Others	7 (4·1)	7 (4·1)	>0·05
Ulcer Location, *N* (%)			
Dorsal	33 (19·3)	29 (16·9)	
Plantar	37 (21·6)	36 (21·1)	
Toe	15 (8·8)	60 (35·2)	
Heel	36 (21·1)	19 (11·1)	
Leg	50 (29·2)	27 (15·7)	>0·05
Ulcer grade*, *N* (%)			
I	67 (39·2)	85 (49·7)	
II	100 (58·5)	85 (49·7)	
Undefined	4 (2·3)	1 (0·6)	>0·05
Type of ulcer, *N* (%)			
Diabetic ulcers	118 (69·4)	140 (81·8)	<0·05
Arterial ulcers	59 (34·9)	114 (66·7)	<0·01
Venous ulcers	18 (10·6)	15 (8·8%)	>0·05
Pressure ulcers	17 (10·1)	23 (13·45)	>0·05
Disease severity			
Type of comorbidities			
Infection, *N* (%)	154 (91·1)	136 (79·5)	>0·05
Coronary heart disease, *N* (%)	74 (43·3)	79 (47·9)	>0·05
Cerebrovascular disease, *N* (%)	18 (10·5)	6 (3·5)	<0·05
Diabetes, *N* (%)	130 (76·0)	140 (84·9)	>0·05
Peripheral arterial disease, *N* (%)	67 (39·2)	51 (30·9)	>0·05
Chronic renal disease, *N* (%)	48 (28·1)	82 (49·7)	<0·01
Congestive heart disease, *N* (%)	66 (38·6)	49 (29·7)	>0·05
Smoking, *N* (%)	59 (34·5)	67 (40·6)	>0·05
History of minor amputation, *N* (%)	22 (12·87)	24 (14·4)	>0·05
History of major amputation, *N* (%)	15 (8·8)	14 (8·4)	>0·05
Number of comorbidities, *N* (%)			
0 through 1	40 (23·4)	34 (19·9)	
2 through 4	108 (63·2)	100 (58·5)	
5 or more	23 (13·4)	37 (21·6)	>0·05
Health service utilisation			
Inpatient ulcer service, *N* (%)	114 (66·7)	162 (94·)	<0·01
5+ outpatient ulcer service, *N* (%)	150 (87·7)	123 (71·9)	<0·01

NPWT, negative pressure wound therapy.

*Grade I, superficial ulcer involving skin only; Grade II, deep ulcer involving muscle/tendon/bone.

Timing of NPWT application on wound closure

Few studies have demonstrated the association between the timing of NPWT application and a wound-healing outcome. A previous study conducted on the efficacy of NPWT application on *acute* traumatic wounds receiving early NPWT (within first 48 hours of wound onset) demonstrated a better healing outcome than those wounds receiving late NPWT (after first 48 hours of wound onset) (18).

To examine the relationship between application timing and ulcer healing, we defined ulcer onset as the date the ulcer was recorded for *the first time* in a clinical note. Ulcer onset date is equal to the 'index ulcer start date'. We then divided NPWT subjects into three categories based on days between onset of ulcer and application of NPWT (shown in Table 5). Early NPWT users are defined as those who received NPWT within 3 months of ulcer onset, intermediate NPWT users within 4–12 months of ulcer onset, and late NPWT as 1 year or later after ulcer onset. The achievement in wound healing seems to be affected by timing of NPWT application. Early NPWT users had a 3·38 (95% 1·68–6·82) times greater likelihood of achieving wound healing than later NPWT users, whereas intermediate NPWT users had a 2·18 (0·94–5·07) times greater probability of healing when compared with the same. In summary, early intervention of NPWT yields more healing benefits than late intervention, which implicates a new practice guide to achieving better outcomes.

Table 3 Incidence rate of wound closure

Type of ulcer	Group	No of patients	Person-years	No of events	Event rates per 100 person year
All ulcers	non-NPWT	171	274·36	118	43·01 (35·91–51·51)
	NPWT	171	131·47	119	90·51 (75·63–108·32)
All ulcers by grade					
Grade I	non-NPWT	67	77·41	51	65·88 (50·07–86·69)
	NPWT	85	56·51	61	107·95 (83·99–138·74)
Grade II	non-NPWT	100	194·41	65	33·43 (26·22–42·63)
	NPWT	85	74·96	58	77·96 (59·81–100·08)
Type of ulcers					
Diabetic ulcers	non-NPWT	118	205·65	80	38·9 (31·25–48·43)
	NPWT	140	112·01	94	83·92 (68·56–102·72)
Arterial ulcers	non-NPWT	59	102·89	37	35·96 (26·05–49·63)
	NPWT	114	99·54	78	78·36 (62·56–97·83)
Venous ulcers	non-NPWT	18	30·69	14	45·62 (27·02–77·03)
	NPWT	15	7·79	12	154·04 (87·48–271·24)
Pressure ulcers	non-NPWT	17	16·77	13	77·52 (45·01–133·51)
	NPWT	23	11·96	17	142·14 (88·36–228·65)

NPWT, negative pressure wound therapy.

Table 4 Unadjusted and adjusted hazard ratio (HRs) of wound closure*

	Unadjusted HRs (95% CI)	Adjusted HRs (95% CI)
All ulcers	2·25 (1·73–3·96)	2·63 (1·87–3·70)
All ulcers by grade		
Grade I	1·85 (1·26–2·69)	2·73 (1·61–4·62)
Grade II	2·54 (1·77–3·65)	2·74 (1·78–4·21)
Type of ulcers		
Diabetic ulcers	2·38 (1·75–3·23)	3·26 (2·21–4·83)
Arterial ulcers	2·33 (1·57–3·48)	2·27 (1·56–3·78)
Venous ulcers	4·90 (1·72–13·59)	6·31 (1·49–26·6)
Pressure ulcers	2·19 (1·03–4·66)	1·72 (0·43–6·95)

*Non-NPWT as a reference group.

Discussion

RCTs are considered to be the gold standard in generating evidence for a clinical intervention (13,14). However, over time, there has been a shift in considering RCTs as the sole source of primary evidence in the development of standard clinical practice (17). While RCTs remain important, 'real-world' patients are clinically complex, they present with multiple comorbidities, varying underlying aetiologies, compliance challenges, and sometimes RCT-proven therapies fail to be effective on these real-world patients. An RCT cannot reflect the complex issues faced in clinical practice and are limited by the challenges of designing such studies displaying wound heterogeneity. Use of PBE and observational study data in a real-world setting can provide important clinical insights that are generally missing from RCTs (17). Observational clinical studies that reflect real-world factors can be better suited to examine the complexity of chronic wound development and healing.

In this study, 171 NPWT patients and 171 non-NPWT patients reflected real-world patients in the continuum of care settings. These patients had multiple comorbidities, multiple clinic visits and ulcer-related inpatient service (hospitalisation). We collected patients' data starting from 2002 and followed these patients for up to 8 years. This lengthy study period is far greater than most RCTs. RCTs that have demonstrated NPWT accelerated wound healing followed subjects from between a few weeks to a few months, with some of the wounds not achieving complete wound closure. This retrospective cohort study provides supplementary clinical outcomes to RCTs as most patients do not likely satisfy their inclusion and exclusion criteria.

There is a new understanding of how important it is to look at the sickest among us. In fact, there are researchers looking into the impact on our health care system if we were to treat the most severe patients with the most aggressive treatment. It has become critical to understand how effectively and efficiently use of advanced wound care can lower overall health care expenses (19–29).

To our knowledge, the results obtained from 'real-world' patients have not been compared with the findings from other studies (case report, randomised trials, etc.). However, as most observational studies, here we also have to discuss limitations of this study. In this retrospective study, we used electronic medical data and also data collected via chart review. While there are advantages to obtain data by conducting chart review, when compare to prospective data collection such as in a RCT, such as relatively inexpensive methodology of obtaining data, ability to capture conditions where there is a long latency between exposure and disease, ability to study rare occurrences and ability to generate hypotheses that can then be tested prospectively. However, disadvantage of chart abstraction is that reviewers are limited by incomplete documentation, unrecoverable or unrecorded information, difficultly interpreting information, problematic verification of information and variance in the quality of information recorded by medical professionals (30–32).

In conclusion, this study showed that despite the greater significant comorbidities, patients receiving NPWT treatment healed faster. Early use of NPWT demonstrated better healing. The longer the interval before intervention with NPWT, the greater correlated with poor outcome.

Table 5 Hazard ratio (HR) of wound closure by timing of NPWT application

NWPT application after ulcer onset	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*P* value
3 months or less	3·11 (1·58–6·12)	3·38 (1·68–6·82)	<0·01
3–12 months	1·83 (0·82–4·06)	2·18 (0·94–5·07)	0·07
12 months or more	1·0 (reference)	1·0 (reference)	NA

NA, not applicable; NPWT, negative pressure wound therapy.

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