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Does negative pressure wound therapy with irrigation improve clinical outcomes? A randomized clinical trial in patients with diabetic foot infections

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ABSTRACT

Aim: To compare the efficacy of Negative Pressure Wound Therapy (NPWT) with and without irrigation with 0.1% polyhexanide-betaine.
Methods: We randomized 150 subjects in a 16-week RCT to compare healing in patients with diabetic foot infections. NPWT delivered at 125 mm Hg continuous pressure. NPWT-I were administered at 30 cc per hour.
Results: There were no differences clinical treatment or outcomes: wound area after surgery (18.5 ± 19.0 vs. 13.4 ± 11.1 cm2, p = 0.50), duration of antibiotics (39.7 ± 21.0 vs. 38.0 ± 24.6 days, p = 0.40), number of surgeries (2.3 ± 0.67 vs. 2.2 ± 0.59, p = 0.85), duration of NPWT (148.1 ± 170.4 vs. 114.5 ± 135.1 h, p = 0.06), healed wounds (58.7% vs. 60.0%, p = 0.86), time to healing (56.3 ± 31.7 vs. 50.7 ± 27.8, p = 0.53), length of stay (13.8 ± 6.4 vs. 14.5 ± 11.2 days, p = 0.42), re-infection (20.0% vs. 22.7%, p = 0.69, and re-hospitalization (17.3% vs. 18.7, p = 0.83).
Conclusions: The addition of irrigation to NPWT did not change clinical outcomes in patients with diabetic foot infections.
Clinical trial number: NCT02463487, ClinicalTrials.gov.

Introduction

Negative Pressure Wound Therapy (NPWT) is a singular, innovative therapy that has dramatically changed the care and outcomes of complex wounds. In diabetic foot wounds, there are two randomized clinical trials that evaluate NPWT compared to "standard of care" in surgical wounds and diabetic foot ulcers that demonstrate a higher proportion of wounds that heal, faster healing, and fewer amputations.[1,2] The next advance using NPWT could involve the addition of simultaneous antiseptic irrigation with NPWT. NPWT with irrigation is especially attractive in patients with diabetes and foot infections because the host is usually severely compromised. Patients with diabetic foot infections often have sensory neuropathy, peripheral arterial disease, malnutrition, immunopathy and poor glycemic control.

Animal and clinical studies have demonstrated a significant reduction in quantitative bacterial cultures when NPWT with irrigation is compared to traditional NPWT or standard dressings.[3,4] In a swine model, Davis reported a significant reduction in quantitative bacterial cultures in wounds treated with simultaneous irrigation with normal saline and 0.1% polyhexanide-betaine compared to traditional NPWT and local wound care. In contrast, Phillips and colleagues reported a four fold reduction in quantitative cultures in skin explants treated with 0.1% polyhexanide-betaine and only a one fold reduction with normal saline.[5]

Davis and colleagues subsequently reported data from a

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randomized clinical trial in patients with infected diabetic foot wounds that compared traditional NPWT and NPWT with simultaneous irrigation with normal saline. They did not identify any difference in wound healing, adverse events or time to heal when simultaneous irrigation with normal saline was used. There are several retrospective clinical studies that compare NPWT with antiseptic irrigation and traditional NPWT in patients with infected wounds of mixed etiologies that report improved clinical outcomes.[3,6–8] However, there are no prospective randomized clinical trials that compare the efficacy of NPWT with and without antiseptic irrigation in patients with diabetes and foot infections. The objective of this study was to compare negative pressure therapy with simultaneous 0.1% polyhexanide-betaine irrigation and traditional negative pressure wound therapy in patients with diabetic foot infections.

Methods

This study was a single site, prospective, randomized trial to compare wound healing in patients treated with traditional negative pressure wound therapy (NPWT) (Cardinal Health, PRO, Dublin, OH), and NPWT with simultaneous with 0.1% polyhexanide-betaine irrigation (NPWT-I) (Cardinal Health, PRO, Dublin, OH). All patients had NPWT delivered at 125 mm Hg continuous pressure. Patients who received simultaneous irrigation (NPWT-I) were administered polyhexanide at 30 cc per hour. The study population was comprised of patients who were admitted to hospital with a moderate or severe foot infection that required incision and drainage and parenteral antibiotics and for whom NPWT was indicated. Study inclusion criteria included diagnosis of diabetes based on American Diabetes Association criteria, age $\geq$21 years old, wound size of 5 cm^2–100 cm^2 and ankle brachial indices $\geq$0.5 or toe pressures >30 mmHg. The exclusion criteria included Active Charcot arthropathy, unable to use NPWT at home, untreated bone or soft tissue infection, unable to keep research appointments, and active alcohol or substance abuse.

After informed consent was obtained, study subjects were randomized in a 1:1 ratio to be treated with NPWT-I with irrigation or traditional NPWT (PRO Therapy System, Cardinal, Dublin, OH). Patients were enrolled by clinical research coordinators after the study was thoroughly discussed and all questions were answered by the surgeon and research staff. A randomization list was generated by computer program. Randomization was accomplished by having a non-clinical member of the research team place 150 pieces of paper from the randomization list in sealed, opaque envelopes. These envelopes were then opened after successful screening of the patient and before the initiation of therapy. Blinding of the surgeons and patients was not possible to conceal the visual differences in NPWT and NPWT-I.

It is standard practice for our patients to return to the operating room within 48–72 h after the initial surgery for repeated incision and drainage. If residual infection persisted, patients continued to receive NPWT as assigned with subsequent planned return visits to the operating room in 48–72 h per the treating surgeon. Wound closure was determined by the treating physician and based on the absence of soft tissue infection and adequate soft tissue for delayed primary wound closure, local rotational flap, split thickness skin graft, or composite bioengineered tissue coverage (Integra Bilayer Matrix Wound Dressing, Integra Life Sciences, Plainsboro, NJ). The patients were then discharged and followed in the outpatient clinic. If the soft tissue defect could not be closed, we provided NPWT at home, supervised by home health nurses. NPWT with irrigation was not available in the home setting, so both study groups received traditional NPWT when home therapy was needed. Patients were evaluated in clinic every 7–10 days. Wound size was evaluated using a 3D measurement device (inSight, eKare, Fairfax, VA), and wound area and volume reduction were calculated as percent change from baseline.

We evaluated sensory neuropathy with loss of protective sensation with a 10-g Semmes Weinstein monofilament and Vibration Perception Threshold Testing (VPT, Salix, Medical, San Antonio, Texas) at the great toe and medial malleolus. We defined sensory neuropathy as either VPT>25 V or any site missed with 10-g monofilament. We evaluate perfusion with Ankle Brachial Indices (ABI) from the dorsalis pedis and posterior tibial arteries in the treated foot. We used the lowest systolic pressure to define ABI. In addition, we used Skin Perfusion Pressure measurements (SPP) on the dorsum and sole of the involved foot (Sensilase, Väsamed, Eden Prairie, MN Device). SPP is a noninvasive tool to evaluate microcirculation at a depth of about 2 mm. The system uses a laser doppler and pressure cuffs to measure skin perfusion pressure. The patient is placed in a supine position. The cuff automatically inflates to occlude arterial flow. The cuff is then automatically released. Skin perfusion is recorded when the laser doppler identifies blood flow.[9] Peripheral arterial disease was defined as either ABI <0.9 or Skin Perfusion Pressure <30 mm Hg. We defined surgical wound closure as a wound that was surgically closed in the operating room. We defined wound healing as a wound site with complete epithelialization with no drainage, and dehiscence as any part of the wound that was surgically closed that failed to heal when the sutures were removed. We used the Infectious Diseases Society of America criteria to define the presence and severity of diabetic foot infections.[10] Amputation was categorized using an ordinal scale that included the following: no amputation, toe and metatarsal amputation, transmetatarsal amputation/midfoot amputation, below the knee amputation, and above the knee amputation.

Data collected during the study included the following: demographics, comorbidities and history of drug, alcohol, tobacco use, wound location and etiology, wound duration, and surrogate wound outcomes. The primary outcome of this study was the proportion of wounds with complete healing during the 16-week evaluation period, defined as complete epithelialization with no drainage. Secondary outcomes included the number of surgeries, length of hospital stay, proportion of wounds surgical closed, covered with composite bioengineered tissue, or left open before discharge, time to heal, and the number of post-operative infections, need for re-admission, need for further surgery or amputation after discharge from the hospital in each study group.

In a preliminary study, the proportion of subjects with closed wound was 62% using traditional NPWT and 94% using NPWT polyhexanide irrigation.[7] For the sample size, we used a more conservative estimate of wound closure and estimated 80% wound closure with NPWT with irrigation and 62% for traditional NPWT Using a two-sided Chi-square with alpha of 0.05 and 80% power and a 20% drop out rate, a sample size of 70 subjects per group (total of 150) is required with 62% healing in NPWT group and 80% in the NPWT with irrigation treatment group. In the study, there was a 13.3% drop out rate.

We summarized study variables as means and standard deviations (SD) for continuous variables and proportions or percentages for categorical variables. Continuous variables are presented as median, mean ± standard deviation and dichotomous variables presented as percent. We used Analysis of Variance ANOVA to test for differences in continuous variables. For categorical variables, we used chi square to compare the proportion of outcomes in each treatment arm with an alpha of 0.05, and we used Kaplan Meier analysis to compare closure rates of the tree treatment groups. p-values were reported using the step-up Bonferroni method of Hochberg. We used an adjusted two-sided analysis with an alpha of 0.05. In the intent to treat analysis we used the last observation

carried forward to define the clinical outcomes for patients that were lost to follow up. This study was approved by the UT Southwestern Institutional Review Board (no 092014-016).

Results

A total of 155 subjects were screened and consented in the study between June 2015 and was completed in December 2018 when the final patient completed the follow up period. One patient was excluded because they failed screening, and four withdrew consent before the initiation of therapy. A total of 150 subjects were randomized and analyzed; 75 were randomized to NPWT with continuous irrigation, and 75 patients were randomized to traditional NPWT (Fig. 1). The study was conducted at Parkland Memorial Hospital. There were no differences in demographics, patient characteristic and co-morbidities in the treatment groups (Table 1).

There were no differences in wound characteristics, treatments or outcomes among the traditional NPWT and NPWT-I treatment groups with the exception of the number of surgeries after discharge from the hospital and the type of surgery. The average number of surgeries was significantly more in patients initially treated with NPWT-I (2.2 ± 1.1 vs. 1.3 ± 0.5, p = 0.02, and more patients that received traditional NPWT required incision and drainage (78.9% vs. 33.3, p = 0.01) rather than amputation (Table 2). There were no statistically significant differences for wound area after index surgery (11.4, 18.5 ± 19.0 vs. 9.7, 13.4 ± 11.1 cm^2, p = 0.50), duration of antibiotics (40.0, 39.7 ± 21.0 vs. 32.5, 38.0 ± 24.6 days, p = 0.40), number of surgeries during the index hospitalization (2.0, 2.3 ± 0.67 vs. 2.0, 2.2 ± 0.59, p = 0.85), duration of NPWT treatment (96.0, 148.1 ± 170.4 vs. 72.0, 114.5 ± 135.1 h, p = 0.06), surgical wound closure (78.7% vs. 84.0%, p = 0.40), wound dehiscence of surgically closed wounds (78.0% vs. 63.4%, p = 0.08), proportion of healed wounds (58.7% vs. 60.0%, p = 0.87), time to wound healing (51.0, 56.3 ± 31.7 vs. 42.0, 50.7 ± 27.8 days, p = 0.53), length of hospitalization (13.0, 13.8 ± 6.4 vs. 12.0, 14.5 ± 11.2 days, p = 0.42), re-infection (20.0% vs. 22.7%, p = 0.69), all cause re-hospitalization (34.7% vs. 36.0%, p = 0.86) and foot

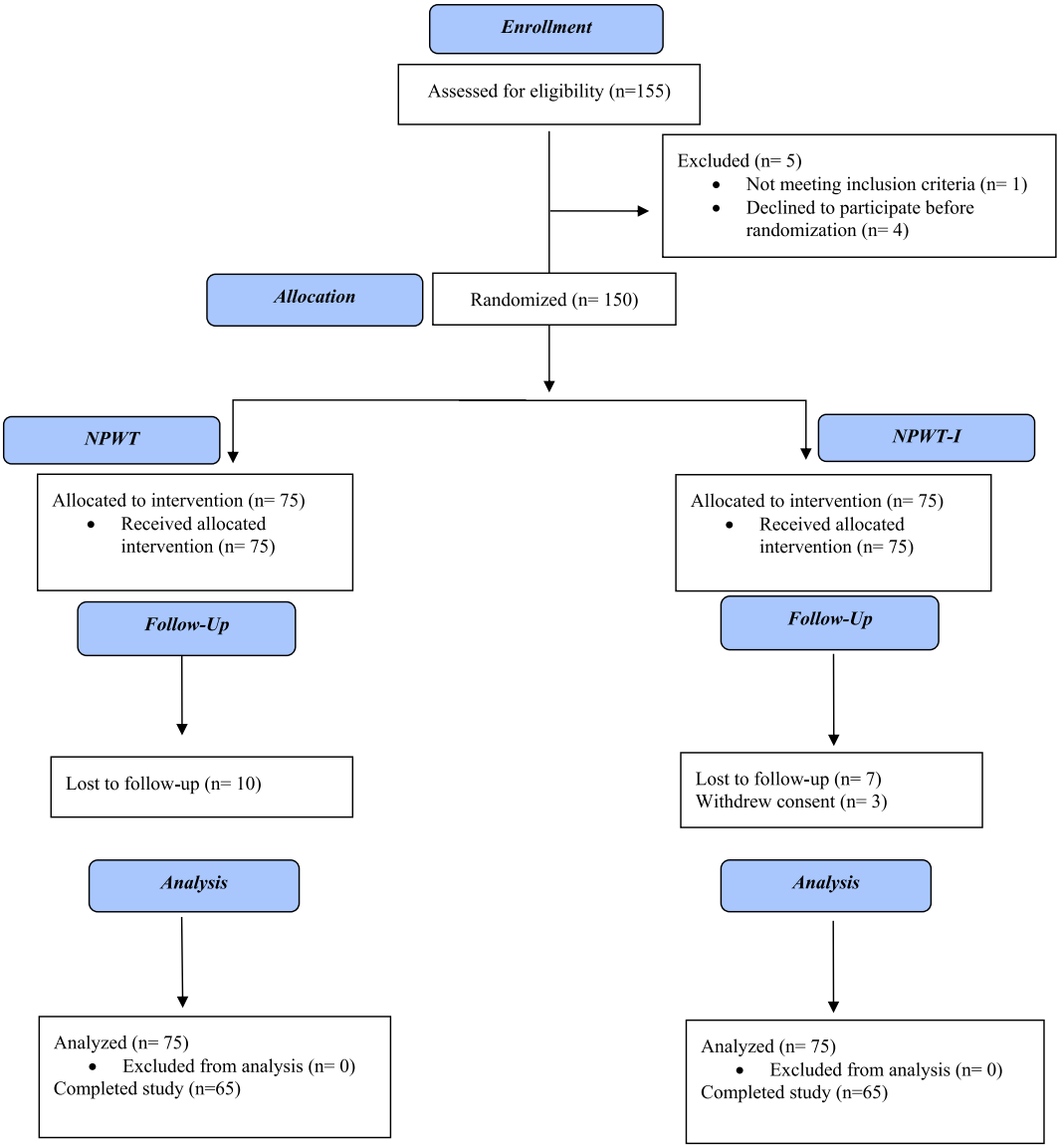

Fig. 1. Consort flow diagram.
Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the enrollment, allocation, follow-up, and analysis of patients.

Table 1
Patient demographics, Co-Morbidities and past medical history.

	NPWT N = 75	NPWT-I N = 75	p-value
Male	58 (77.3)	59 (78.7)	0.84
BMI (Kg/m^3)	31.6, 32.5 (7.7)	30.2, 31.5 (8.0)	0.25
Race			0.94
Caucasian	21 (28.0)	18 (24.0)	0.58
Native American	1 (1.3)	1 (1.3)	1.00
African American	30 (40)	30 (40)	1.00
Hispanic	23 (30.7)	26 (34.7)	0.60
Substance Abuse History			0.41
Tobacco	35 (46.7)	43 (57.3)	0.19
Alcohol	39 (52.0)	43 (57.3)	0.51
Drugs	13 (17.3)	15 (20.0)	0.68
Foot Ulcer History - All	52 (69.3)	43 (57.3)	0.13
Foot Ulcer History – Study Foot	40 (53.3)	34 (45.3)	0.33
Amputation History	36 (48.0)	28 (37.3)	0.19
Type II Diabetes	68 (90.7)	72 (96.0)	0.20
Coronary Artery Disease	4 (5.3)	5 (6.7)	0.73
Congestive Heart Failure	7 (9.3)	9 (12.0)	0.60
Retinopathy	16 (21.3)	17 (22.7)	0.84
Chronic Kidney Disease	23 (30.7)	32 (42.7)	0.18
End Stage Renal Disease	3 (4.0)	6 (8.0)	0.49
Index Wound Area, cm^2	11.4, 18.5 (19.0)	9.7, 13.4 (11.1)	0.50
Osteomyelitis	61 (81.3)	62 (82.7)	0.83
Lab Values			
White Blood Cell Count (10^9 cells/L)	9.9, 10.5 (4.1)	10.3, 10.9 (4.3)	0.56
Glycated Hemoglobin (%)	9.3, 9.7 (2.9)	9.3, 9.7 (2.5)	0.96
Glycated Hemoglobin (mmol/mol)	78, 83 (8)	78, 83 (4)	0.96
Albumin (g/dL)	3.4, 3.5 (0.8)	3.3, 3.2 (0.6)	0.08
Pre-Albumin (mg/dL)	13.8, 14.5 (7.3)	13.0, 13.6 (6.2)	0.60
Sensory Neuropathy			
Abnormal 10-g Monofilament	64 (85.3)	65 (86.7)	0.81
Vibration Perception Threshold (volt)	41.3, 45.2 (24.2)	42.1, 47.0 (21.5)	0.52
Vibration Perception Threshold >25 (volt)	58 (77.3)	64 (85.3)	0.21
Ankle Brachial Index	1.2, 1.1 (0.2)	1.2, 1.1 (0.2)	0.61
Skin Perfusion Pressures (mmHg)			
Dorsal Medial	63.5, 64.4 (28.5)	66.5, 63.0 (23.1)	0.75
Dorsal Lateral	66.5, 67.6 (24.7)	62.0, 64.1 (26.8)	0.43
Plantar Medial	72.0, 74.8 (21.0)	80.0, 78.3 (22.4)	0.33
Plantar Lateral	80.0, 81.2 (23.8)	81.0, 81.0 (20.4)	0.96

Dichotomous variables are presented as N (%). Continuous variables are presented as median, mean (SD).

specific re-hospitalization (17.3% vs. 18.7%, p = 0.83). Kaplan-Meyer survival analysis was performed to evaluate the time to heal, and there was not a significant difference between the treatment groups (Fig. 2). The median time to heal in patients treated with traditional NPWT (51.0 days) and NPWT with irrigation (42.0 days, Log Rank (Mantel-Cox) p = 0.24).

Discussion

This is the first randomized clinical trial to compare NPWT with and without antiseptic irrigation in patients with moderate and severe diabetic foot infections. The results of this study did not identify any differences in wound healing, the time to heal, wound dehiscence, re-infection, leg amputation, or hospital re-admission based on the type of NPWT treatment. Our results sharply contrast the retrospective studies that compare NPWT with and without irrigation. There are several retrospective studies that compare NPWT with saline or antiseptic irrigation and traditional NPWT in patients with infected wounds of mixed etiologies. All of these studies use a computer-controlled irrigation system rather than continuous irrigation. The computer-controlled approach delivers a predetermined volume of irrigation fluid to the wound bed. NPWT is temporarily stopped and the irrigation is held within the wound bed. After a pre-set time, the NPWT is restarted. The irrigation solution is removed from the wound field, and NPWT continues until the next pre-set sequence of irrigation.[3,6–8] All of the studies using instillation had positive results and reported a variety of outcomes including reduced length of hospitalization, fewer surgeries, faster time to final surgical procedure, a higher proportion of wounds that were surgically closed, faster times to heal, and a higher proportion of healed wounds. Because the retrospective studies included a variety of different wounds etiologies, co-morbidities and locations, it is difficult to compare the studies or generalize the results to patients with diabetic foot infections. All of the patients in the current study had complex diabetic foot infections with multiple comorbidities including sensory neuropathy, poor glucose control, micro and macro peripheral vascular disease, chronic kidney disease, and poor nutrition parameters. We initially hypothesized that a compromised host would get greater benefit from this therapy, but the results of the primary and secondary outcomes in the current study were not statistically different between active and control groups.

This study is novel because there are very few prospective studies in patients with moderate and severe diabetic foot infections, and there are few randomized clinical trials that evaluates NPWT in diabetic foot infections. Many of the outcomes in this study such as dehiscence, re-infection, antibiotic utilization, and hospital re-admission have not been reported in other NPWT studies.

Infection is a common complication in patients with diabetes and foot wounds. Re-infection after hospitalization for a diabetic foot soft tissue or bone infection effects 32%–50% of patients during the year following the index hospitalization.[11–13] Therefore, we anticipated a high rate of postoperative complications. The re-

Table 2
Index admission and post-discharge outcomes.

	NPWT N = 75	NPWT-I N = 75	p value
Index Hospitalization Outcomes			
Surgeries During Admission			0.43
Incision and Drainage	28 (37.3)	34 (45.3)	0.32
Amputation Foot	46 (61.3)	40 (53.3)	0.32
Amputation Leg	1 (1.3)	1 (1.3)	1.00
Number of Surgeries	2.0, 2.3 (0.67)	2.0, 2.2 (0.59)	0.85
Hours of NPWT	96.0, 148.1 (170.4)	72.0, 114.5 (135.1)	0.06
Length of Stay (days)	13.0, 13.8 (6.4)	12.0, 14.5 (11.2)	0.42
Time to Surgical Closure (days)	6.0, 7.3 (5.6)	5.0, 6.6 (5.6)	0.18
Wound Status at Discharge			0.69
Surgically Closed	59 (78.7)	63 (84.0)	0.40
Wound Covered	10 (13.3)	8 (10.7)	0.60
Wound Open	6 (8.0)	4 (5.3)	0.52
Outcomes After Hospital Discharge			
Wound Dehiscence	46 (78.0)	40 (63.4)	0.08
Duration of Antibiotics (days)	40.0, 39.7 (21.0)	32.5, 38.0 (24.6)	0.40
Healed at End of Study	44 (58.7)	45 (60.0)	0.87
Time to Heal (days)	51.0, 56.3 (31.7)	42.0, 50.7 (27.8)	0.53
New Ulcer Formation	12 (16.0)	18 (24.0)	0.22
Re-Infection	15 (20.0)	17 (22.7)	0.69
Hospital Re-Admission All Cause	26 (34.7)	27 (36.0)	0.86
Hospital Re-Admission Foot	13 (17.3)	14 (18.7)	0.83
Number of Surgeries after Discharge[a]	1.0, 1.3 (0.5)	2.0, 2.2 (1.1)	**0.02**
Surgery after Discharge	19 (25.3)	15 (20.0)	0.44
Incision and Drainage	15 (78.9)	5 (33.3)	**0.01**
Amputation Foot	3 (15.8)	5 (33.3)	0.23
Amputation Leg	1 (5.3)	5 (33.3)	0.06

Dichotomous variables are presented as N (%). Continuous variables are presented as median, mean (SD). Amputation refers to the highest level of amputation performed during index hospitalization or during the follow-up period.

[a] Outcomes after hospital discharge number of surgeries is based on patients who had surgery in follow up. There were 19 and 15 patients for the NPWT and NPWT-I groups, respectively.

infection and foot specific re-admission rates were 22.7% and 17.3%, respectively, in patients treated with NPWT-I and 20.0% and 18.7% in patient treated with traditional NPWT during the 16-week evaluation period. Armstrong and Lavery reported the results of an RCT that compared NPWT to standard wound care for large surgical wounds after foot amputation in people with diabetes over a 16-week period. The incidence of infection was 9.4% in patients that received standard wound care and 16.8% in patients that received traditional NPWT.[2]

The incidence of wound healing was high in both traditional NPWT and NPWT with simultaneous irrigation (58.7% and 60.0%), and the average time to heal the wound was fast (56.3 and 50.7 days). However, the wound healing process involved surgical closure of the wounds in the vast majority of patients (78.7% and 84.0%), with dehiscence of at least part of the wound occurring in the majority of the wounds that were surgically closed (NPWT 78.0% and NPWT-I 63.4%). The dehisced wounds healed by secondary intention. The current study results are similar to Armstrong's NPWT RCT in which 56% subjected that received traditional NPWT healed in 16 weeks.[2] Despite the large wound size after the index surgery, the time to heal in this study was similar to most randomized clinical studies of phase 3 or 4 diabetic foot ulcers that report median time to heal of 42–65 days for ulcers that are 2–3 cm in diameter.[14–16]

There are several limitations and sources of bias in this study. Selection bias is likely in this study. Parkland Hospital is a safety net hospital that serves a population that is disproportionately poor, unfunded, and comprised of minorities compared to the general population in the United States. However, despite barriers to access transportation and medical care, we had a low dropout rate (13.3%) that was the same in both treatment arms. The results of this study cannot be generalized to other techniques that use NPWT and irrigation. Additional work is needed to understand the role of different irrigation solutions, different sponge configurations, the rate of flow for continuous irrigation, the timing of irrigation, and the characteristics of patients that are most likely to benefit from this therapy.

Another potential limitation was the inclusion criteria used for peripheral arteria disease. We used ankle brachial indices $\geq$0.5 or toe pressure >30 mm Hg to identify peripheral arterial disease. ABIs are a common inclusion criterion in diabetic foot RCTs. However they are often unreliable because of Monckeberg's arteriosclerosis or calcification of the tunica media. Peripheral artery pressures are often falsely elevated, or the arteries are not compressible. Toe pressures may not be available because a high percentage of study patients will have experienced a previous amputation, or the study ulcer and infection site include the great toe. We used Skin Perfusion Pressure measurements in this study to better characterize the study population. Several studies have reported that SPP >30 mm/Hg were associated with increased likelihood of healing.[17] In our study the median and mean SPP were >60 m/Hg (Table 1).

NPWT was usually not used the entire duration of the study as reported in Table 2. Patients that received simultaneous irrigation had fewer hours of NPWT on average, however the difference in the two groups was not significant (Table 2, 148.1 vs 114.5 h). It is not uncommon for NPWT to be interrupted. NPWT is often removed in the hospital for testing such as MRI, ultrasound or vascular studies. NPWT is routinely stopped when there is peri-wound macerated, so the surrounding tissue is not damaged by reapplication of the occlusive dressing. Patients and nurses on the floor sometimes stop therapy if the seal is lost or if the device is keeping the patient awake. In addition, surgeons often stop therapy the morning of surgery to avoid peri-wound maceration when delayed primary wound closure is planned. We recorded the hours of utilization; however, we did not record the reason for the interruption in therapy in this study.

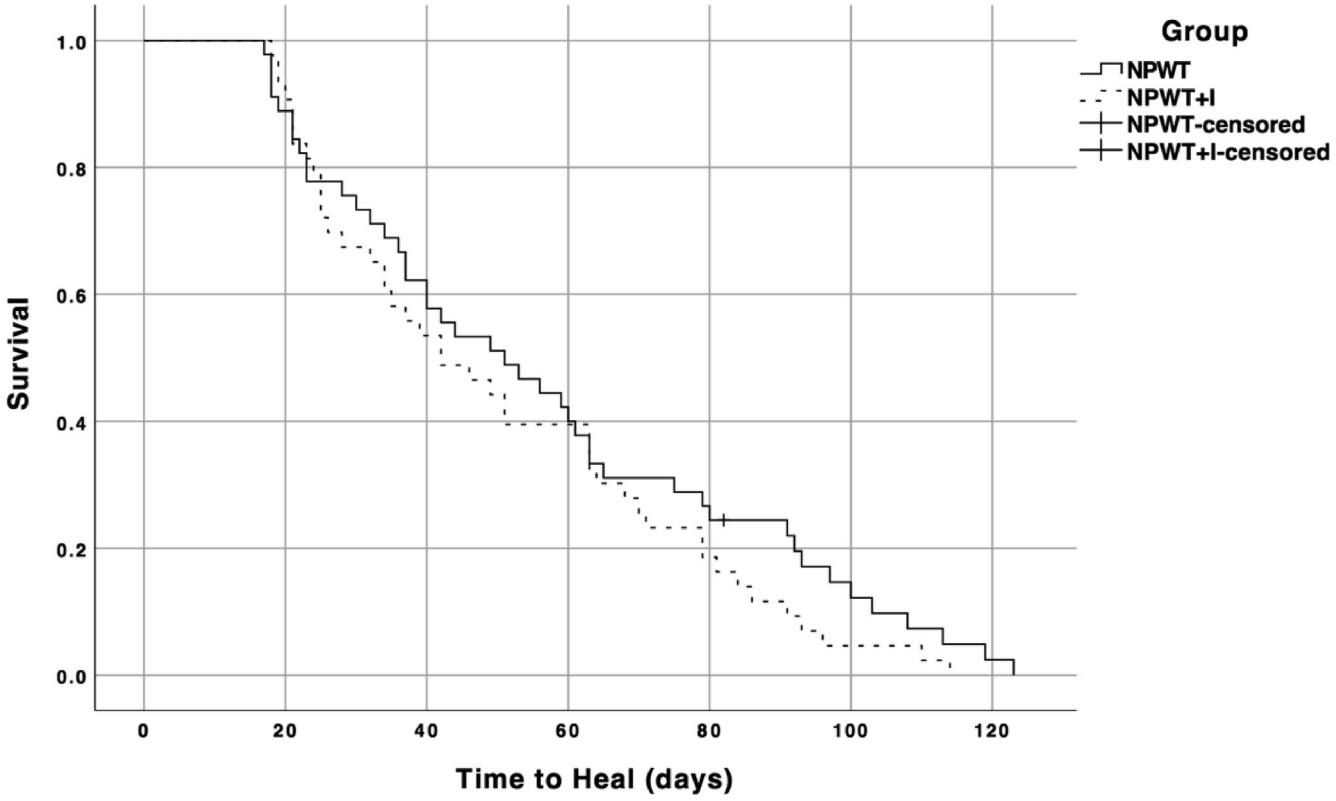

Fig. 2. Kaplan-meier survival analysis – days to heal.
There was not a significant difference in the median time to heal in patients treated with traditional NPWT (51.0 days) and NPWT with irrigation (42.0 days, Log Rank (Mantel-Cox) $p = 0.24$).

It has been suggested that constant irrigation would not reach every part of the wound. However, Davis and colleagues published bench top work that demonstrates that continuous irrigation with 125 mm Hg pressure provides a constant flow of solution that reaches every part of the wound, including fistulas.[18] Other types of antiseptic solutions may be more effective. Studies with polyhexanide report that it is not cytotoxic while still maintaining good antibacterial properties, which was part of our rationale in selecting it for the study.[19]

Conclusion: We did not identify any differences in clinical outcomes with traditional NWPT or NPWT with 0.1% polyhexanide-betaine irrigation at 30 cc per hour with continuous irrigation. NPWT with irrigation did not provide any additional benefits over standard NPWT. This is the first prospective randomized clinical trial using simultaneous irrigation with an antiseptic in patients with diabetic foot infections. Davis and colleagues[20] reported the results of a small randomized clinical trial that compared simultaneous irrigation with normal saline (15 cc per hour) in patients with diabetic foot infections. They reported similar results; there were no differences in clinical outcomes when simultaneous irrigation was added to traditional NPWT.

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Declaration of competing interest

LAL has research funding from Cardinal Health, KCI, EO2 Concepts, Osiris Therapeutics, Avazzia, Pluristem Therapeutics, Inc., and consulting agreements with EO2 Concepts, Cardinal Health, Bayer, Medline Industries, Boehringer Ingelheim, Medimmune.

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LAL developed the study design, collected data, contributed to the manuscript, participated in data analysis and is the guarantor of this work. KED and PAC contributed to the manuscript and participated in data analysis. JL, DF, KB, and OKO contributed to the manuscript.

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