





Randomized clinical study to compare negative pressure wound therapy with simultaneous saline irrigation and traditional negative pressure wound therapy for complex foot infections

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ABSTRACT

The aim of this study was to compare the efficacy of different negative pressure wound therapy (NPWT) devices and NPWT with and without simultaneous irrigation in patients admitted to hospital with moderate and severe foot infections. Ninety patients were randomized in a 12-week prospective, randomized noninferiority trial to compare wound healing in patients with moderate and severe infected foot wounds treated with NPWT after surgery. Inclusion criteria included ABI > 0.5 or toe pressures > 30 PVR/mmHg, > 18 years of age and exclusion included active Charcot arthropathy, collagen vascular disease, HIV, and hypercoagulable state. We compared two different traditional devices, NPWT-K (KCI, VAC Ultra) and NPWT-C (Cardinal, PRO), and NPWT-I with saline irrigation (Cardinal, PRO). All patients had therapy delivered at 125 mmHg continuous pressure. In patients who received simultaneous saline irrigation (NPWT-I), the administration rate was 15 ml per hour. The primary outcome was the proportion of healed wounds in 12 weeks. Secondary outcomes included surgical wound closure, number of surgeries, length of stay, and time to wound healing. Continuous data was presented as mean \pm standard deviation. Analysis of variance was used to compare continuous variables and chi-square to compare dichotomous variables with an alpha of 0.05. There were no differences in outcomes among NPWT-I, NPWT-C, and NPWT-K groups in proportion of healed wounds (63.3%, 50.0%, 46.7% $p = 0.39$), surgical wound closure (83.3%, 80.0%, 63.3%, $p = 0.15$), number of surgeries (2.0 ± 0.49 , 2.4 ± 0.77 , 2.4 ± 0.68 , $p = 0.06$), length of stay (16.3 ± 15.7 , 14.7 ± 7.4 , 15.3 ± 10.5 days, $p = 0.87$), time to wound healing (46.2 ± 22.8 , 40.9 ± 18.8 , 45.9 ± 28.3 days, $p = 0.78$). We did not identify any significant differences in clinical outcomes or adverse events between patients treated with different NPWT devices or NPWT with and without irrigation.

INTRODUCTION

Negative pressure wound therapy (NPWT) has dramatically changed the care of complex foot wounds. Compared to standard wound care, patients with diabetic foot wounds that are treated with NPWT are 5.9 times more likely to heal and 4.4 times less likely to require amputation.^{1,2} NPWT involves the delivery of subatmospheric pressure through a vacuum pump connected to a specialized dressing to maintain a closed environment. NPWT increases perfusion to the wound, accelerates granulation tissue formation, reduces edema, and reduces bioburden.¹⁻³

The next advance in clinical outcomes could involve the addition of simultaneous irrigation with NPWT. This approach uses the closed NPWT system and adds the simultaneous

application of continuous irrigation to the wound. This technique allows irrigation solution to cover every part of the wound bed.⁴ It provides better clearance of bacteria from the wound bed compared to traditional NPWT in porcine models.⁵ There are several retrospective studies in patients with wounds of mixed etiologies that compared traditional NPWT and NPWT with irrigation that consistently report improved clinical outcomes.⁶⁻⁹ There are no prospective randomized clinical trials that evaluate the efficacy of NPWT with and without irrigations in patients with foot infections. We hypothesized that foot infections would have better outcomes and fewer complications with the addition of simultaneous irrigation with NPWT. The objective of this randomized clinical study was to compare negative pressure therapy with simultaneous saline

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Chronic or traumatic wound, subacute or dehisced wound, partial-thickness burn, ulcer (such as a diabetic or pressure ulcer), flap or graft • Wound presents with full thickness loss of epidermis and dermis • Wound that in the opinion of the investigators will require surgical debridement, and the wound is expected to be a good candidate for NPWT • ABI \geq 0.5 or toe pressures $>$30 PVR/mmHg • Subject is willing and able to abstain from partaking in any other form of treatment for his or her wound throughout the during the active treatment phase of this study, other than the study procedures described herein. • 18 years of age or older 	<ul style="list-style-type: none"> • Does not present with an existing chronic or traumatic wound, subacute or dehisced wound, partial-thickness burn, ulcer (such as a diabetic or pressure ulcer), flap or graft • Subject is unwilling or unable to use the NPWT device at home • Active Charcot arthropathy • Collagen vascular disease • Scleroderma • Nonenteric and unexplored fistula • Necrotic tissue with eschar present after debridement • General skin disorder in the area of the wound such as psoriasis or panniculitis • Malnutrition (defined as BMI $<$ 19) • Hypercoagulable state based on documentation in their medical record • Acute deep vein thrombosis • Current active malignancy in the wound • Current melanoma or history of melanoma at the wound • Current active or history of invasive squamous cell carcinomas at the wound • Sepsis (defined as positive blood culture with leukocytosis) and temperature $>$101.5 at the time of screening • Significant hematologic disorders EXCLUDING anemia • HIV • Deep x-ray therapy • Untreated bone or soft tissue infection • Developmental disability/significant psychological disorder

ABI, ankle brachial indices; NPWT, negative pressure wound therapy.

irrigation and traditional negative pressure wound therapies in patients with infected foot wounds.

METHODS

This study was a single site, prospective, parallel, randomized noninferiority trial to compare wound healing in patients treated with NPWT using three different NPWT approaches, NPWT-K (KCI VAC Ultra, San Antonio, TX), NPWT-C (Cardinal Health, PRO, Dublin, OH), and NPWT-I with simultaneous saline irrigation (Cardinal Health, PRO, Dublin, OH). All patients had NPWT delivered at 125 mmHg continuous pressure. Patients who received simultaneous saline irrigation (NPWT-I) were administered irrigant at 15 ml 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 and exclusion criteria used to determine eligibility are listed in Table 1.

After informed consent was obtained, study subjects were randomized in a 1 : 1 : 1 ratio to be treated with NPWT-K (KCI, San Antonio, TX), NPWT-C (Cardinal, Dublin, OH), or NPWT-I with simultaneous irrigation (Cardinal, Dublin, OH). Randomization assignment was determined from a computer-generated list placed in sealed, prenumbered opaque envelopes. Patients and researchers initially were blinded to randomization status. Randomization was performed prior to treatment initiation. Patients were identified by the clinician authors from their patients and were enrolled by the authors and clinical research coordinators. Once it was determined that the subject qualified for the study in the operating room, the research coordinator opened the assigned randomization envelope, and the NPWT treatment was initiated. Patients, research coordinators, and clinicians were not blinded to the treatment assignment after randomization. NPWT devices were applied in the operating room or at bedside per manufacturers recommendations. The devices were set to deliver NPWT at 125 mmHg. Patients assigned to irrigation (NPWT-I) received normal saline delivered continuously to the wound at a rate of 15 ml/hour.

NPWT dressings were changed every 2 days. Wounds that were not surgically closed or covered at the time of hospital discharge, continued to receive NPWT at home.

The decision for surgery was based on the presence of deep infection or necrosis that required surgical excision per the treating surgeon. It is standard practice for our patients to return to the operating room within 48–72 hours after the initial surgery for repeated incision and drainage. If there continued to be residual infection based on physical examination, patients continued to receive NPWT as assigned with subsequent planned return visits to the operating room in 48–72 hours 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 LifeSciences, 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. Patients were evaluated in clinic every 7–10 days and received NPWT until the study wound was deemed ready for surgical closure for up to 12 weeks. 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 (Salix, Medical, San Antonio, TX) at the great toe and medial malleolus. We defined sensory neuropathy as either VPT > 25 or any site missed with 10 g monofilament. We evaluated 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). Peripheral arterial disease was defined as either ABI < 0.9 or SPP < 30 mmHg. We defined dehiscence as any part of the surgical wound that was surgically closed that failed to heal when the sutures were removed. We defined wound healing as 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 IDSA criteria to define the presence and severity of diabetic foot infections.¹⁰

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 12-week evaluation period defined as complete epithelialization with no drainage. Secondary outcomes included the number of surgeries, length of hospital stay, proportion of wounds surgically closed, covered with composite bioengineered tissue, or left open before discharge, time to heal, and the number of postoperative infections, need for readmission, need for further surgery or amputation after discharge from the hospital in each study group.

This was a pilot study to obtain preliminary data to assess the efficacy of NPWT with simultaneous irrigation. We planned to use the data to identify the effect size of primary and secondary outcomes to develop a cogent sample size

justification help and plan a larger clinical trial. We summarized study variables as means and standard deviations (SD) for continuous variables and proportions or percentages for categorical variables. We used 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 three 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 this 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 (IRB # 032015-099) and registered with www.ClinicalTrials.gov as NCT02519621.

RESULTS

A total of 93 subjects were screened and consented in the study between April 2016 and January 2018 after the enrollment goal was met. Two patients were excluded because they failed screening, and one withdrew consent before the initiation of therapy. A total of 90 subjects were randomized; 30 were randomized to each of the three treatment groups, NPWT-I, NPWT-C, or NPWT-K (Figure 1). The study was conducted at Parkland Hospital. There were no differences in demographics, wound characteristics or comorbidities in the three treatment groups with the exception of race, CKD, and wound etiology (Tables 2, 3).

There were no differences in outcomes among NPWT-I, NPWT-C, and NPWT-K groups in the proportion of healed wounds (63.3%, 50.0%, 46.7% *p* = 0.39), surgical wound closure (83.3%, 80.0%, 63.3%, *p* = 0.15), number of surgeries (2.0 ± 0.49 , 2.4 ± 0.77 , 2.4 ± 0.68 , *p* = 0.06), length of stay (16.3 ± 15.7 , 14.7 ± 7.4 , 15.3 ± 10.5 days, *p* = 0.87), time to wound healing (46.2 ± 22.8 , 40.9 ± 18.8 , 45.9 ± 28.3 days, *p* = 0.78) and the duration of NPWT (118.2 ± 88.4 , 109.9 ± 101.0 , 134.1 ± 96.9 hours, *p* = 0.61) (Table 4). Finally, a Kaplan–Meier analysis was performed to evaluate the time to heal. There was no significant difference between the treatment groups (Figure 2). The median \pm standard error (95% confidence interval) days to heal for NPWT-I, NPWT-C, or NPWT-K was 43.0 ± 9.4 (24.5–61.5), 41.0 ± 6.3 (28.6–53.4), 42.0 ± 13.1 (15.3–51.2). The log Rank comparison is *p* = 0.69.

DISCUSSION

The goal of this pilot study was to compare NPWT with simultaneous irrigation to traditional NPWT approaches. This is the first randomized clinical trial to compare NPWT with irrigation and traditional NPWT in infected foot wounds. We included two devices that provided traditional NPWT without irrigation. One of the devices was the predicate for the NPWT device we used with irrigation in this study, and the second is considered the market leader for NPWT and was the first NPWT device to be commercialized. We did not identify any difference in surgical wound closure or wound healing during the 12-week evaluation period in patients that received NPWT-I (63.3%), NPWT-C (50.0%), and NPWT-K (46.7%). While the proportion of

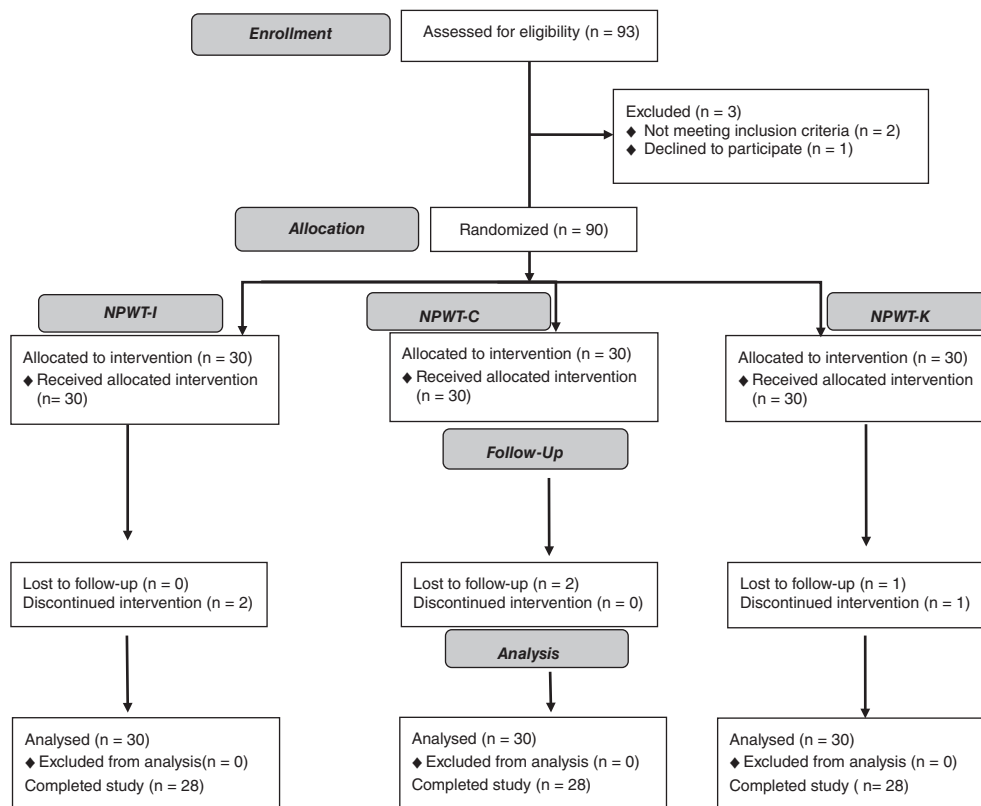


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the enrollment, allocation, follow-up, and analysis of patients.

wounds that healed in the NPWT-I groups was higher than the treatment groups with traditional NPWT without irrigation, the difference was not statistically significant ($p = 0.39$). No difference was identified between the two groups that received NPWT without irrigation. This was expected as it has been described in the two RTCs that evaluate a head to head comparison of NPWT device brands in complex diabetic foot wounds.^{11,12}

Our result did not show any benefit when simultaneous irrigation was provided with NPWT as compared to NPWT alone. There are several retrospective studies using NPWT and irrigation that include mixed patient populations with infected wounds with various etiologies, so their results are difficult to compare to foot infection outcomes or generalize to other patient populations. The vast majority of the patients in the current study included patients with diabetes with peripheral sensory neuropathy, peripheral vascular disease, osteomyelitis, hyperglycemia, chronic kidney disease, and malnutrition. Patients with diabetes are often severely compromised hosts that are prone to poor healing and reinfection.

Our rationale to use saline was based on the work of Kim and colleagues. In a randomized clinical trial, Kim compared NPWT with saline ($n = 49$) and NPWT with 0.1% polyhexanide and 0.1% betaine irrigation ($n = 51$) in patients with infected wounds of mixed etiologies. Kim found no difference in clinical outcomes (surgical closure, length of hospitalization, and number of surgeries) with the exception of the time to surgical closure (5.7 vs. 7.7 days, $p = 0.04$).¹³

Most retrospective NPWT irrigation studies do not include reports of adverse events such as wound dehiscence, reinfection, readmission, or amputation.^{6–9,14–16} Dehiscence after delayed primary closure was high in every treatment arm in this study. Table 4 shows wounds with dehiscence as a proportion of subjects randomized in each treatment arm. However, when this is evaluated as a percent of wounds that were surgically closed, the overall rate of wound dehiscence was 75%. We defined dehiscence as any part of the surgical wound that was surgically closed that failed to heal, so even if a small part of the wound did not heal, it was reported as dehiscence. We were unable to identify any published data to reference the likelihood of partial or complete wound failure and postoperative infection after a foot amputation or surgery for infection. Several studies report postoperative infection but not the rate of surgical site dehiscence. In a prospective cohort study, Wukich and colleagues reported that 30% of diabetic patients developed infection following below the knee amputation¹⁷ and 29% developed infection after ankle fusion.¹⁸ However, the rate of dehiscence without infection was not reported separately.

The process to treat and evaluate complex diabetic wounds is difficult. It is a heterogeneous group with multiple comorbidities including poor nutrition, renal disease, peripheral arterial disease, and poor glucose control. Most of the wounds can be surgically closed, and a high proportion of surgically closed wounds fail some part of the incision. There is a smaller group of patients that heal by secondary intention or the wound is covered with bioengineered or

Table 2. Patient demographics, comorbidities, and past medical history

	NPWT-I	NPWT-C	NPWT-K	<i>p</i> -value
Subjects	<i>N</i> = 30	<i>N</i> = 30	<i>N</i> = 30	
Sex: male	23 (76.7)	25 (83.3)	26 (86.7)	0.59
BMI (kg/m ³)	32.0 (9.5)	33.24 (7.2)	32.0 (9.6)	0.82
Race				<0.01*
Caucasian	1 (3.3)	10 (33.3)	4 (13.3)	<0.01*
African descent	9 (30.0)	4 (13.3)	1 (3.3)	0.02*
Hispanic	20 (66.7)	16 (53.3)	24 (80.0)	0.09
Substance abuse				
Tobacco (past or current)	15 (50.0)	18 (60.0)	16 (53.3)	0.35
Alcohol	13 (43.3)	20 (66.7)	21 (70.0)	0.13
Drugs (past or current)	2 (6.7)	7 (23.3)	8 (26.7)	0.20
Lab values				
White blood cell count	9.6 (3.6)	11.0 (4.3)	11.3 (4.1)	0.23
Glycated hemoglobin	9.6 (3.0)	9.6 (2.8)	10.9 (5.9)	0.38
Albumin	3.3 (0.4)	3.3 (0.5)	4.2 (4.5)	0.29
Prealbumin	14.9 (6.3)	13.9 (7.6)	13.0 (7.3)	0.66
Sensory neuropathy				
Abnormal 10-g monofilament	26 (86.7)	26 (86.7)	25 (83.3)	0.61
Vibration perception threshold (volt)	46.7 (22.1)	46.4 (21.0)	49.4 (21.4)	0.84
Vibration perception threshold >25 (volt)	25 (83.3)	24 (80.0)	23 (76.7)	0.96
Ankle brachial index	1.1 (0.19)	1.1 (0.12)	1.1 (0.29)	0.85
Skin perfusion pressures (mmHg)				
Dorsal medial	57.9 (22.7)	60.0 (21.1)	61.5 (21.2)	0.82
Dorsal lateral	56.5 (19.8)	69.8 (24.4)	64.6 (21.8)	0.08
Plantar medial	67.8 (23.5)	77.5 (19.5)	69.0 (20.9)	0.19
Plantar lateral	69.1 (24.5)	77.6 (25.0)	68.2 (30.9)	0.36
Ulcer history	22 (73.3)	17 (56.7)	17 (56.7)	0.44
Ulcer history—study foot	11 (40.7)	8 (29.6)	8 (29.6)	0.41
Amputation history	14 (49.2)	9 (29.0)	8 (26.7)	0.24
Diabetes	29 (96.7)	27 (90.0)	27 (90.0)	0.70
Type II	28 (93.3)	27 (90.0)	26 (86.7)	0.64
Coronary artery disease	2 (6.7)	1 (3.3)	1 (3.3)	0.63
Congestive heart failure	4 (13.3)	5 (16.7)	2 (6.7)	0.48
Retinopathy	4 (13.3)	3 (10.0)	2 (6.7)	0.71
Chronic kidney disease	8 (26.7)	2 (6.7)	1 (3.3)	0.01*
End stage renal disease	4 (13.3)	1 (3.3)	0	0.06

*Data presented as average (standard deviation) or number of subjects (percent of group). NPWT, negative pressure wound therapy.

composite materials or skin grafts. Complex surgical wounds are a segment of diabetic foot wounds that are the most expensive to treat with high recidivism of wounds and infections. It is also the least studied and the least amenable to evaluating a single treatment in a RCT. We plan to use the pilot data from this study to develop a sample size justification that can evaluate treatment subgroups (surgically closed vs. open wounds).

Infection is a common complication in elective surgery, Charcot reconstruction, and in prospective studies of

diabetic foot ulcers. The incidence of infection has to be evaluated with consideration for the time of exposure. In the current study, we evaluated patients for 12 weeks. In patients admitted to hospital for moderate and severe foot infection, the rate of reinfection is about 50% in the next year.¹⁹ Therefore, we expected a high rate of postoperative complications. Our study population experienced a 15.6% infection rate overall during a 12-week evaluation period. If the rate of reinfection remained constant, our reinfection would be similar to Wukich and colleagues reinfection

Table 3. Wound etiology and characteristics

	NPWT-I	NPWT-C	NPWT-K	<i>p</i> -value
Subjects	<i>N</i> = 30	<i>N</i> = 30	<i>N</i> = 30	
Wound type				0.05
Diabetic ulcer	26 (86.7)	16 (53.3)	20 (66.7)	0.02*
Puncture	1 (3.3)	11 (36.7)	6 (20.0)	0.01*
Trauma	1 (3.3)	1 (3.3)	2 (6.7)	0.77
Surgical wound	2 (6.7)	1 (3.3)	0 (0.0)	0.36
Other	0 (0.0)	1 (3.3)	2 (6.7)	0.36
Wound duration (days)	55.5 (112.8)	37.9 (71.3)	47.2 (76.6)	0.75
Starting wound area cm ²	13.9 (13.7)	19.7 (20.9)	16.8 (22.8)	0.52
Starting wound volume cm ³	13.7 (15.5)	18.1 (25.3)	12.9 (14.9)	0.54
Type of infection				0.99
Soft tissue infection	6 (20.0)	6 (20.0)	7 (23.3)	
Osteomyelitis	24 (80.0)	24 (80.0)	23 (76.7)	

Data presented as average (standard deviation) or number of subjects (percent of group). NPWT, negative pressure wound therapy.

Table 4. Wound outcomes

	NPWT-I	NPWT-C	NPWT-K	<i>p</i> value
	<i>N</i> = 30	<i>N</i> = 30	<i>N</i> = 30	
Outcomes during index hospital admission				
Surgeries during admission				0.53
Incision and drainage	8 (26.7)	11 (36.7)	12 (40.0)	0.53
Amputation foot	20 (66.7)	17 (56.7)	15 (50.0)	0.42
Amputation leg	2 (6.7)	2 (6.7)	3 (10.0)	0.86
Number of surgeries	2.0 (0.49)	2.4 (0.77)	2.4 (0.68)	0.06
Hours of NPWT	118.2 (88.4)	109.9 (101.0)	134.1 (96.9)	0.61
Length of stay (days)	16.3 (15.7)	14.7 (7.4)	15.3 (10.5)	0.87
Time to surgical closure (days)	5.4 (4.3)	5.9 (4.7)	6.4 (4.7)	0.71
Wound status at discharge				0.34
Surgically closed	25 (83.3)	24 (80.0)	19 (63.3)	0.15
Wound covered	3 (10.0)	4 (13.3)	6 (20.0)	0.53
Wound open	2 (6.7)	2 (6.7)	5 (16.7)	0.33
Outcomes after hospital discharge				
Duration of antibiotics (days)	25.6 (20.2)	27.8 (20.3)	31.0 (23.3)	0.67
Healed at end of study	19 (63.3)	15 (50.0)	14 (46.7)	0.39
Time to heal (days)	46.2 (22.8)	40.9 (18.8)	45.9 (28.3)	0.78
Wound dehiscence of patients surgically closed	16 (53.3)	20 (66.7)	15 (50.0)	0.39
New ulcer formation	5 (16.7)	1 (3.3)	4 (13.3)	0.23
Reinfection	5 (16.7)	4 (13.3)	5 (16.7)	0.92
Hospital readmission all cause	7 (23.3)	13 (43.3)	7 (23.3)	0.15
Hospital readmission foot	4 (13.3)	4 (13.3)	4 (13.3)	1.00
Subsequent surgeries	5 (16.7)	6 (20.0)	6 (20.0)	0.93
Incision and drainage	3 (10.0)	2 (6.7)	4 (13.3)	0.69
Amputation foot	1 (3.3)	4 (13.3)	1 (3.3)	0.20
Amputation leg	1 (3.3)	0	1 (3.3)	0.60

Data presented as average (standard deviation) or number of subjects (percent of group). Amputation refers to the highest level of amputation performed during index hospitalization or during the follow-up period. NPWT, negative pressure wound therapy.

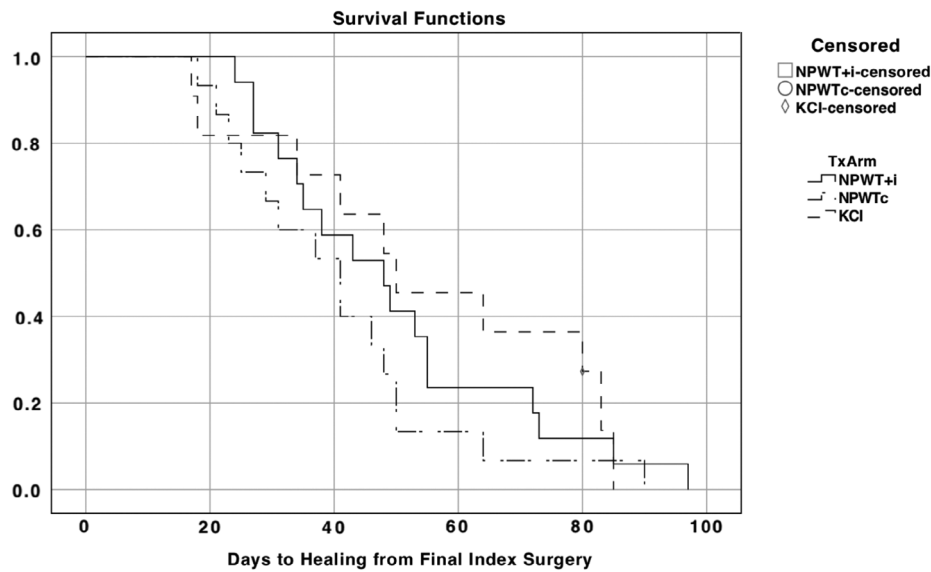


Figure 2. The median \pm standard error (95% confidence interval) days to heal for NPWT-I, NPWT-C, or NPWT-K was 43 ± 9.4 (24.5–61.5), 41.0 ± 6.3 (28.6–53.4), 42.0 ± 13.1 (15.3–51.2). The log rank comparison is $p = 0.69$.

findings over the course of a year. Armstrong and Lavery reported the results of a RCT that compared NPWT to standard wound care for large surgical wounds after foot amputation in people with diabetes in a 16 week study. The incidence of infection was low in both treatment arms (9.4% SOC vs. 16.8% NPWT).²⁰ Armstrong and Lavery's results contrast the current RCT in several important ways that may simply reflect the evolution of NPWT in surgical wounds. Both studies included large wounds (20.7 vs. 16.8 cm²). However, in the current RCT, NPWT was applied immediately after surgery and the majority of wounds were closed during the index hospitalization. In the Armstrong and Lavery study, wounds were present for several months before NPWT was used, and a minority of wounds were surgically closed (11% vs. 16%).

The main limitation of this study was the small sample size. This was a small, exploratory study. One of our underlying goals was to use this information to plan a larger clinical trial, identify outcomes that could be improved with irrigation, and develop a cogent sample size justification for a future study. The current study was not powered to determine differences in wound healing because of the small sample size, so the data is not sufficiently robust to make any statement on whether there is a difference in the wound healing or secondary outcomes. However, to evaluate a difference in NPWT-I and traditional NPWT-C (63% vs. 50%) with an alpha of 0.05 and a power of 80%, 180 subjects per treatment would have been required in each group. In addition, the study was performed at a single center, so cultural and cognitive bias of the surgeons that participated in the study may have influenced clinical and surgical decisions.^{13,21} All of the surgeons were podiatrists, and like many subspecialties, the culture of their training and the "rules of thumb" they were taught, bias their treatments. The study was performed at a hospital with a high volume of complex diabetic foot cases. The learning curve to understand simultaneous irrigation was probably faster compared to centers with lower volumes of complex foot infections.

This may be reflected in the high rate of limb salvage reported in this study (90%).

Selection bias is likely in this study. Parkland Hospital is a safety net hospital that serves a population that is often unfunded or under funded with difficulty accessing healthcare, ancillary medical services, and transportation. In addition, the hospital serves a large poor, minority population that is disproportionately Hispanic and African American compared to the general population in the United States. In addition, we considered that a higher number of patients in the NPWT-I group with chronic kidney disease and end stage renal disease may have biased the results ($p = 0.01$ and $p = 0.06$, respectively), because renal disease is associated with worse clinical outcomes, more frequent amputations and higher levels of amputations compared to patients with normal renal function. Overall 72.7% of patients with CKD healed. There was no difference among the three treatment arms ($p = 0.18$). In patients with ESRD, overall 60% healed. One patient did not heal in the NPWT-I and NPWT-C groups ($p = 0.17$). Based on these results, CKD and ESRD did not bias our study results because the rate of healing was the same as the study population as a whole.

CONCLUSION

We did not identify any differences in wounds that were surgically closed, proportion of wounds that healed, time to wound healing or postoperative complications in the three treatment arms. However, the sample size was small, so the data is not sufficiently robust to make any statement about the efficacy of the therapy on wound healing.

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Conflict of Interest: The authors do not have any relevant conflict of interest.

REFERENCES

1. Armstrong DG, Lavery LA. Negative pressure wound after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet* 2005; 366: 1704–10.
2. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care* 2008; 31: 631–6.
3. Saxena V, Hwang CW, Huang S, Eichbaum Q, Ingber D, Orgill DP. Vacuum-assisted closure: microdeformations of wounds and cell proliferation. *Plast Reconstr Surg* 2004; 114: 1086–96 discussion 97–8.
4. Davis KE, Moquin KJ, Lavery LA. The fluid dynamics of simultaneous irrigation with negative pressure wound therapy. *Int Wound J* 2016; 13: 469–74.
5. Davis KE, Lafontaine J, Bills J, Noble D, Wight-Carter M, Oni G, et al. The comparison of two negative-pressure wound therapy systems in a porcine model of wound healing. *Wound Repair Regen* 2013; 21: 740–5.
6. Kim PJ, Attinger CE, Steinberg JS, Evans KK, Powers KA, Hung RW, et al. The impact of negative-pressure wound therapy with instillation compared with standard negative-pressure wound therapy: a retrospective, historical, cohort, controlled study. *Plast Reconstr Surg* 2014; 133: 709–16.
7. Omar M, Gathen M, Liodakis E, Suero E, Krettek C, Zeckey C, et al. A comparative study of negative pressure wound therapy with and without instillation of saline on wound healing. 2016; 25: 475–8.
8. Gabriel A, Kahn K, Karmy-Jones RJE. Use of negative pressure wound therapy with automated, volumetric instillation for the treatment of extremity and trunk wounds: clinical outcomes and potential cost-effectiveness. *Eplasty* 2014; 14: 328–38.
9. DeFazio MV, Economides JM, Anghel EL, Mathis RK, Barbour JR, Attinger CE. Traction-assisted internal negative pressure wound therapy with bridging retention sutures to facilitate staged closure of high-risk wounds under tension. *Wounds* 2017; 29: 289–96.
10. Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. *Clin Infect Dis* 2007; 44: 562–5.
11. Lavery LA, Murdoch DP, Kim PJ, Fontaine JL, Thakral G, Davis KE. Negative pressure wound therapy with low pressure and gauze dressings to treat diabetic foot wounds. *J Diabetes Sci Technol* 2014; 8: 346–9.
12. Lavery LA, La Fontaine J, Thakral G, Kim PJ, Bhavan K, Davis KE. Randomized clinical trial to compare negative-pressure wound therapy approaches with low and high pressure, silicone-coated dressing, and polyurethane foam dressing. *Plast Reconstr Surg* 2014; 133: 722–6.
13. Douglas M. *The active voice: cultural bias*. London, Routledge, 1982.
14. Kim PJ, Attinger CE, Oliver N, Garwood C, Evans KK, Steinberg JS, et al. Comparison of outcomes for normal saline and an antiseptic solution for negative-pressure wound therapy with instillation. *Plast Reconstr Surg* 2015; 136: 657e–64e.
15. Gabriel A, Shores J, Heinrich C, Baqai W, Kalina S, Sogioka N, et al. Negative pressure wound therapy with instillation: a pilot study describing a new method for treating infected wounds. *Int Wound J* 2008; 5: 399–413.
16. Back DA, Scheuermann-Poley C, Willy C. Recommendations on negative pressure wound therapy with instillation and antimicrobial solutions - when, where and how to use: what does the evidence show? *Int Wound J* 2013; 10: 32–42.
17. Wukich DK, Ahn J, Raspovic KM, Gottschalk FA, La Fontaine J, Lavery LA. Comparison of transtibial amputations in diabetic patients with and without end-stage renal disease. *Foot Ankle Int* 2017; 38: 388–96.
18. Wukich DK, Crim BE, Frykberg RG, Rosario BL. Neuropathy and poorly controlled diabetes increase the rate of surgical site infection after foot and ankle surgery. *J Bone Joint Surg Am* 2014; 96: 832–9.
19. Wukich DK, Hobizal KB, Sambenedetto TL, Kirby K, Rosario BL. Outcomes of osteomyelitis in patients hospitalized with diabetic foot infections. *Foot Ankle Int* 2016; 37: 1285–91.
20. Armstrong DG, Lavery LA. Diabetic foot study C. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet* 2005; 366: 1704–10.
21. Biases C. In: Mills AJ, Durepos G, Wiebe E, editors *Encyclopedia of case study research*. SAGE Publications, 2010.