

A Multicenter Randomized Controlled Trial Comparing Treatment of Venous Leg Ulcers Using Mechanically Versus Electrically Powered Negative Pressure Wound Therapy

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Objective: This study compares two different negative pressure wound therapy (NPWT) modalities in the treatment of venous leg ulcers (VLUs), the ultraportable mechanically powered (MP) Smart Negative Pressure (SNaP[®]) Wound Care System to the electrically powered (EP) Vacuum-Assisted Closure (V.A.C.[®]) System.

Approach: Patients with VLUs from 13 centers participated in this prospective randomized controlled trial. Each subject was randomly assigned to treatment with either MP NPWT or EP NPWT and evaluated for 16 weeks or complete wound closure.

Results: Forty patients ($n = 19$ MP NPWT and $n = 21$ EP NPWT) completed the study. Primary endpoint analysis of wound size reduction found wounds in the MP NPWT group had significantly greater wound size reduction than those in the EP NPWT group at 4, 8, 12, and 16 weeks (p -value = 0.0039, 0.0086, 0.0002, and 0.0005, respectively). Kaplan–Meier analyses showed greater acceleration in complete wound closure in the MP NPWT group. At 30 days, 50% wound closure was achieved in 52.6% (10/19) of patients treated with MP NPWT and 23.8% (5/21) of patients treated with EP NPWT. At 90 days, complete wound closure was achieved in 57.9% (11/19) of patients treated with MP NPWT and 38.15% (8/21) of patients treated with EP NPWT.

Innovation: These data support the use of MP-NPWT for the treatment of VLUs.

Conclusions: In this group of venous ulcers, wounds treated with MP NPWT demonstrated greater improvement and a higher likelihood of complete wound closure than those treated with EP NPWT.



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INTRODUCTION

VENOUS LEG ULCERS (VLUs) constitute a significant healthcare problem due to impaired healing.^{1,2} VLUs usually result in substantial disability, reduced quality of life, and high economic costs.^{3–13} Effective treatment of VLUs involves the use of compression therapy to address

the underlying venous disease and adjuncts such as advanced cellular and acellular wound care matrices (e.g., Apligraf, Organogenesis, Inc, Canton, MA; Oasis, Cook Biotech, Inc, West Lafayette, IN). Negative pressure wound therapy (NPWT) has been shown to create a moist wound healing environment, drain exudate,

reduce tissue edema, mechanically stimulate the wound bed, and augment blood perfusion at the wound edge thereby enhancing angiogenesis and formation of granulation tissue to reduce healing time.¹⁴ The primary treatment goal of NPWT, the topical application of subatmospheric pressure to a wound bed through a specialized dressing is wound closure, with the secondary goals of reducing wound dimensions and improving the quality of the wound bed.¹⁵

NPWT is traditionally delivered by an electrically powered (EP) pump, such as the widely used Vacuum-Assisted Closure (V.A.C.[®]) Therapy System (K.C.I., San Antonio, TX), which was the first commercially available NPWT system and remains the most widely used and studied NPWT system on the market today. EP NPWT systems are usually larger in size and have the ability to provide varying therapy (continuous and intermittent), and thus they are best suited for treating larger, more complex wounds. However, EP NPWT systems have several disadvantages in the outpatient setting because of their weight and bulk, need for an electrical power source, difficult rental-based procurement process, high cost, and negative impact on patient mobility and quality of life. Since most venous ulcers are treated in the outpatient setting, this has resulted in limited use of NPWT on VLUs in general though significant evidence supports the benefit of NPWT for VLUSs healing.^{14–23}

Recently, a single use, mechanically powered (MP) NPWT system has been developed called the Smart Negative Pressure (SNaP[®]) Wound Care System (Spiracur, Inc., Sunnyvale, CA).²⁴ Instead of using an electric pump to generate negative pressure, the MP device utilizes specialized springs to generate a preset continuous subatmospheric pressure level to the wound bed. By eliminating the electric pump, this device helps solve many of the constraints associated with traditional NPWT use in the ambulatory setting. Previous studies have shown that negative pressure delivered by the MP NPWT device has characteristics similar to the EP NPWT system in both biomechanical testing and in an animal wound healing model.²⁵ Most recently, a study comparing MP NPWT-treated patients to modern treatment protocols for highly refractory lower extremity ulcers demonstrated time to healing improvements similar to studies using EP NPWT devices.¹⁹ Importantly, the MP NPWT system has indications from the FDA for the treatment of VLUs.

This study is a sub-analysis of a previously published prospective, multicenter, randomized controlled study of 132 patients with lower ex-

tremity wounds that included a large sample of VLUs.¹⁷ This study directly compares the MP NPWT system to the EP NPWT system for the treatment of venous ulcers. We hypothesized equivalent outcomes between the two NPWT systems in the treatment of venous ulcers in the lower extremity.

CLINICAL PROBLEM ADDRESSED

VLUs represent a significant challenge for wound care professionals due to their delayed healing and poor wound bed characteristics. NPWT has been shown to be effective in improving healing of VLUs, but traditional EP NPWT has been challenging to implement in the outpatient care setting.^{14–23} This study provides insight into the newer MP NPWT modality that allows for the practical treatment of these wounds in the outpatient setting.

MATERIALS AND METHODS

This was a multicenter, prospective, randomized controlled clinical trial designed to evaluate the relative impact on wound closure using a MP NPWT system (SNaP Wound Care System; Spiracur, Inc., Sunnyvale, CA) versus an EP NPWT system (V.A.C. Therapy System; KCI). This study was conducted in compliance with the 1975 Declaration of Helsinki and under presiding institutional review board approval. The study was registered at clinicaltrials.gov under number: NCT00951080. Subjects were recruited from 13 sites in the United States, with a mixture of physician offices, and private and academic wound care centers. Subjects were evaluated on a weekly basis to complete wound closure (defined as complete reepithelialization without drainage) or for up to 16 weeks of therapy. Dressing changes were performed following instructions recommended by manufacturer. For all enrolled subjects, debridement was performed in the wound care clinic as part of the normal standard of care (maximum 1×/week). Wound sizes were evaluated using wound tracings captured by the Visitrak wound measurement system (Smith & Nephew, Hull, England).

Inclusion criteria for the full study, included patients aged ≥ 18 years; lower extremity VLUs or diabetic ulcer with a surface area $< 100 \text{ cm}^2$ but larger than 1 cm^2 , and $< 10 \text{ cm}$ in widest diameter. Wounds were to have been present for > 30 days despite appropriate wound care prior to admission. Admission criteria also required adequate blood perfusion defined as transcutaneous oxygen measurements of the dorsum of the foot $> 30 \text{ mmHg}$, skin perfusion pressure $> 30 \text{ mmHg}$, or an ankle/

brachial index between 0.7 and 1.2. The wound was required to be in a location amenable to creation of an airtight seal using the provided dressings.

Exclusion criteria included active infection (redness, swelling, pain, and purulent exudate), untreated osteomyelitis, pregnancy, allergies to wound care products used in the study, etiologies of the wound that included malignancy, burn, collagen vascular disease, sickle cell, vasculopathy, or pyoderma gangrenosum. Further grounds for exclusion included a diagnosis of active Charcot arthropathy, wound location on toes or plantar surface of foot, end-stage renal disease requiring dialysis, active chemotherapy treatment, previous treatment with a NPWT device, growth factors, hyperbaric oxygen, or bioengineered tissue product within 30 days of enrollment. Patients were not enrolled if they exhibited greater than 30% wound surface area reduction in size at 1 week after the screening visit.

Randomization

Randomization was accomplished using blocks of numbers from Pocock.²⁶ Stratification was performed by treatment center. Sealed opaque envelopes contained the assigned treatment and patient identification number. Envelopes were sequentially numbered before clinical trial site distribution. At patient randomization, treatment was assigned on the basis of the next sequentially labeled envelope.

Blinding

Evaluation of the Visitrak tracing was performed in a blinded fashion. However, subject and investigator blinding could not be performed based on the differences in device appearance.

Statistical analysis

The sub-analysis of the venous ulcers mirrored the analysis of the overall intent to treat (ITT) population.¹⁷ VLU were defined as those patients who had a leg ulcer in the gaiter region with evidence of venous disease on physical exam and were not diabetic. Patient demographics and comorbidities were compared across device type using standard *t*-tests for continuous variables and Fisher's exact test for categorical variables. Percent wound reduction was measured at 4, 8, 12, and 16 weeks. If a wound was completely healed or a subject had discontinued prior to completion of 16 weeks, the last observation was carried forward for the intent-to-treat analysis. Wound reduction at each time point was compared between the two device groups using the nonparametric Wilcoxon Rank Sum test. This nonparametric test was used because a Shapiro–Wilk test indicated non-normality of the data at each time point. The comparison of percent wound reduction

was repeated using rank transformed data in a linear model to adjust for baseline wound areas.

Finally, a Kaplan–Meier and Life Table analysis were performed to compare the time (in days) to healing between the two device groups. Additionally, since these devices were used as a monotherapy, we also compared the surrogate marker of 50% wound closure rate at 30 days to allow us to predict the intended clinical endpoint of wound healing.^{27,28} The thirty-day timeframe is also important because this considered the cutoff point for evaluating the effectiveness of a therapy on wound progression in many studies. Primary healing analysis was performed on the Visitrak data and the reported wound closure outcomes. Statistical analyses were performed using SAS version 9.1.

Secondary outcome analysis

Serious adverse events, device-related adverse events, and complications were also collected and reported.

RESULTS

This analysis involved 40 patients ($n=19$ MP NPWT, $n=21$ EP NPWT) who completed the study with either healing or 16 weeks of therapy. Overall, the average age was 67 years and 52% of patients were women. Fifteen percent of patients were smokers and 12.5% had coexistent mild to moderate peripheral artery disease. There were no significant differences in the baseline demographics comparing the MP NPWT group to the EP NPWT group (Table 1).

Despite randomization, there were differences in the mean initial wound size (mean \pm SD: 4.85 ± 4.49 cm² for MP NPWT versus 11.60 ± 12.12 cm² for

Table 1. Pure venous leg ulcer comorbid demographics

Demographic	V.A.C. [®]	SNaP [®]	p-Value
Age (mean \pm SD, years)	66.8 \pm 18.1 (21)	67.5 \pm 14.8 (19)	0.9045
Male (%)	52.4% (11/21)	42.1% (8/19)	0.5450
Race (% white)	76.2% (16/21)	89.5% (17/19)	0.4124
Current smoker (%)	9.5% (2/21)	21.1% (4/19)	0.3976
Lower extremity edema (%)	76.2% (16/21)	68.4% (13/19)	0.7271
PAD (%)	14.3% (3/21)	10.5% (2/19)	1.0000
Peripheral neuropathy (%)	19.0% (4/21)	5.3% (1/19)	0.3451
COPD/asthma (%)	9.5% (2/21)	5.3% (1/19)	1.0000
Cardiac disease (%)	47.6% (10/21)	42.1% (8/19)	0.7605
Anticoagulated/coumadin (%)	33.3% (7/21)	36.8% (7/19)	1.0000
Immobility (%)	23.8% (5/21)	26.3% (5/19)	1.0000
Steroid use (%)	4.8% (1/21)	5.3% (1/19)	1.0000
Poor nutrition (%)	4.8% (1/21)	10.5% (2/19)	0.5962
Other comorbidity (%)	4.8% (1/21)	5.3% (1/19)	1.0000

PAD, peripheral artery disease; SNaP, Smart Negative Pressure; V.A.C., Vacuum-Assisted Closure.

EP NPWT). For all 40 patients treated with NPWT, 22.5% (9/40) of the wounds were closed at 8 weeks and 52.5% (21/40) were closed after 16 weeks of treatment. The average% decrease in wound area was 38.4% at 8 weeks and 49.5% at 16 weeks.

Comparison of VLU treatment with EP NPWT versus MP NPWT

The incidence of complete wound closure over time is represented for each group by Kaplan–Meier estimates in Fig. 1. Although there is a trend toward superior overall wound closure in the MP group, there was no significant difference ($p=0.3547$ without or with ($p=0.4656$) adjustment for baseline wound size) in the proportion of subjects that completely healed over time. Based on the surrogate endpoint of 50% wound closure, 52.63% (10/19) of MP NPWT subjects versus 23.8% (5/21) of EP NPWT subjects experienced 50% wound closure at 30 days; odds ratio was 3.56 with a 95% confidence interval (CI) of [0.923, 13.699]. Hence, EP NPWT treated patients were 3.5 times more likely not to have achieved 50% wound closure at 30 days. However, *ad hoc* analysis at 90 days showed that the proportion of MP NPWT patients healed was 57.9% (11/19) compared with 38.15 (8/21) for the EP NPWT (odds ratio estimate: 2.23 with a 95% CI of [0.63, 7.93]). Hence, at 90

days, patients treated with the EP NPWT device were twice more likely not to have healed than patients treated with the MP NPWT device.

The percent decrease in wound area as measured from Visitrak tracings was compared for those subjects randomized to either treatment with the MP NPWT System or the EP NPWT System. The Shapiro–Wilk test indicated significant variation from a normal distribution ($p<0.0001$) in the data for each interval and as such, the primary endpoint was evaluated using nonparametric methods. A Wilcoxon–Rank Sum Test was conducted and the results indicated that the MP NPWT-treated subjects experienced significantly greater percent wound closure than EP NPWT-treated subjects at 4, 8, 12, and 16 weeks (p -value=0.0039, 0.0086, 0.0002, and 0.0005, respectively). The mean percent decrease in wound area is provided along with the results from the Wilcoxon Sum Rank Test in Table 2. To evaluate how patients responded if they completed the prescribed treatment, the data were analyzed based on those subjects who completed the entire study protocol (either healed or had follow-up data through 16 weeks of treatment). Given the difference in baseline wound size between the treatment groups, covariate analysis was performed to see whether wound size affected the statistical significance. We found the

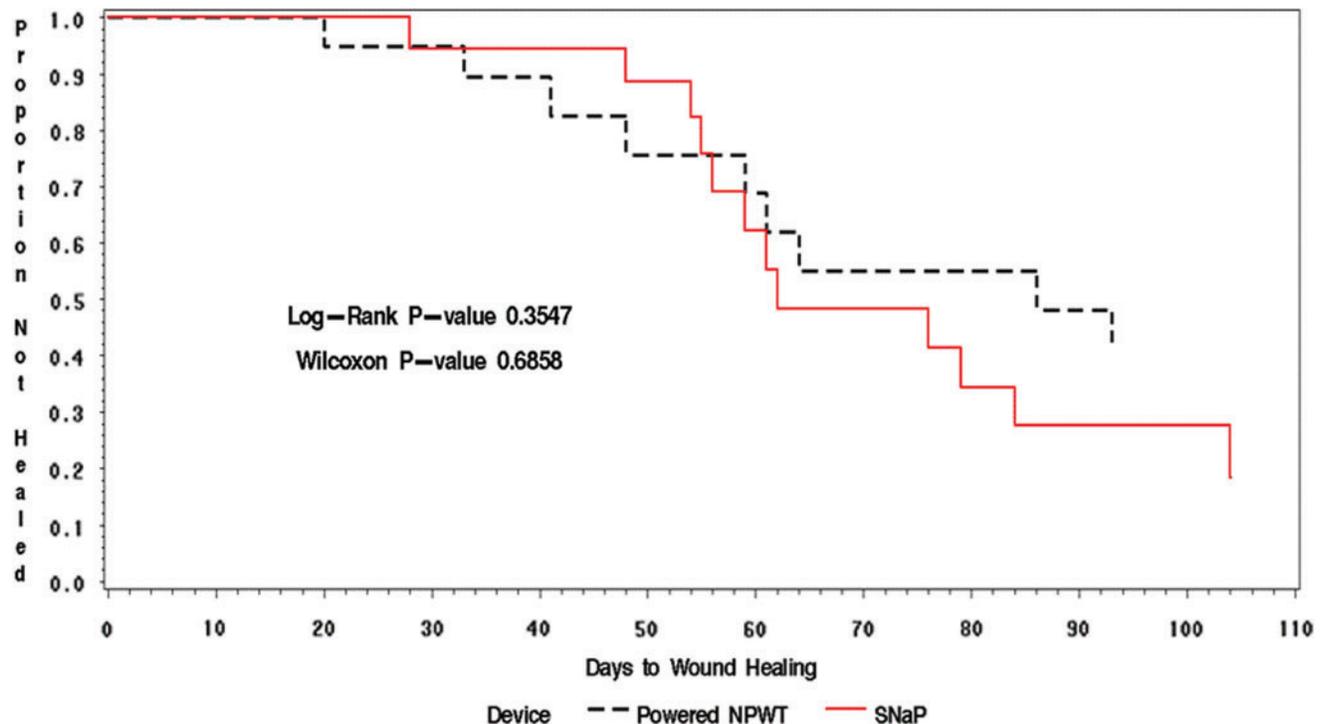


Figure 1. Kaplan–Meier graph showing time to healing; NPWT (SNaP[®] System and V.A.C.[®] Therapy System) effective at treating venous leg ulcers. NPWT, negative pressure wound therapy; SNaP, Smart Negative Pressure; V.A.C., Vacuum-Assisted Closure. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

Table 2. Venous leg ulcers—wound size reduction

	V.A.C. Mean (%) (SD), n = 21	SNaP Mean (%) (SD), n = 19	Impact of Baseline Wound Size Difference (p-Value)	p-Value ^a (Unadjusted for Baseline Wound Size)	p-Value ^a (Adjusted for Baseline Wound Size)
4 weeks	−9.87 (±106.04)	−35.35 (±69.23)	0.1606	0.0039 ^b	0.0346 ^b
8 weeks	−30.20 (±116.49)	−47.46 (±110.99)	0.0419 ^b	0.0086 ^b	0.0803
12 weeks	−30.20 (±118.26)	−56.29 (±112.89)	0.0559	0.0002 ^b	0.0079 ^b
16 weeks	−42.00 (±119.20)	−57.80 (±113.00)	0.0470 ^b	0.0005 ^b	0.0082 ^b

^ap-Values generated using Monte Carlo simulation.

^bStatistically significant (* $p < 0.05$).

difference in baseline wound size statistically impacted the wound size reduction results at 8 and 12 weeks (p -value = 0.0419 and 0.0470, respectively). After adjusting for baseline wound size, significant differences in the percentage of wound closure between groups was maintained at 4, 12, and 16 weeks (p -value = 0.0346, 0.0079, and 0.0082, respectively), as shown in Table 2.

Adverse events and incidence of infection

Device-related adverse events and complications such as infection were similar between treatment groups (Table 3) and was consistent with the larger population previously reported.¹⁷

DISCUSSION

NPWT is a well-characterized method of therapy for chronic nonhealing ulcers.^{29–31} Though there is significant reason for the potential benefits of NPWT for the treatment of VLU, there is only one venous ulcer-specific randomized controlled trial (RCT) utilizing NPWT.²³ However, several other RCTs that include VLU patients have demonstrated superior healing with NPWT.^{15–17,23,32–34} In addition to RCT data, there have been a number of retrospective comparison studies and case series that have demonstrated excellent results using NPWT for the treatment of refractory venous ulcers.^{14,19} Vuerstaek *et al.* reported a randomized study of NPWT for the treatment of venous ulcers enrolling 60 patients. In their study, they concluded that compared to conventional wound care, EP NPWT should be considered the treatment of choice for chronic leg ulcers owing to its significant advantage in time to complete

wound healing (29 days vs. 45 days for EP NPWT and conventional therapy, respectively, $p = 0.0001$), and especially time to wound bed preparation (7 days vs. 17 days for EP NPWT and conventional therapy, respectively, $p = 0.05$), and lower cost (\$3,881 vs. \$5,452 for EP NPWT and conventional therapy, respectively, $p = 0.001$).²³ In a retrospective analysis, Yao *et al.* showed that patients treated with NPWT healed faster even when they had significantly greater comorbidities, and that early intervention with NPWT demonstrated better healing.¹⁴ Using real world data, they found that venous ulcers treated with NPWT were 6.31 times more likely to heal than those ulcers treated with conventional therapy.

In this article we present a subgroup analysis of a previously reported prospective randomized study comparing MP NPWT to EP NPWT. Overall, NPWT as a monotherapy was able to heal 52.5% of VLUs at 16 weeks of treatment. However, the data demonstrated that wound size reduction was significantly faster in the MP NPWT group compared with the EP NPWT group and that there was a trend toward overall greater healing in the MP NPWT group. In addition, *ad hoc* analysis at 90 days showed that patients treated with the EP NPWT device were twice as likely to not have healed compared with patients treated with the MP NPWT device. The difference seen between the two devices at 30 days was greater than at 90 days most likely due to diminishing effects of NPWT as a monotherapy treatment to closure.

Despite randomization, there was a difference in the baseline median wound size between the two groups studied, with the EP NPWT group being larger on average. This was likely due to the relatively small number of patients in each group and the wide range of wound sizes eligible for enrollment (1–100 cm²). To adjust for this baseline wound size, covariate analysis was performed and the difference in percent wound closure remained significant. This indicates that wound size does not completely account for the difference in results observed between the two types of NPWT. One would expect to see noninferiority between the MP NPWT-treated and the EP NPWT-treated subjects in this VLU subset

Table 3. Patients with device-related adverse events

Adverse Event	VAC (n = 21)	SNaP (n = 19)	p-Value ^a
Infection	9.5% (2)	5.3% (1)	1.000
Maceration	14.3% (3)	15.8% (3)	1.000
Allergic reaction to dressing	14.3% (3)	5.3% (1)	0.607
Pain	14.3% (3)	5.3% (1)	0.607
Blisters	9.5% (2)	15.8% (3)	0.654
Other	9.5% (2)	10.5% (2)	1.000

^aFisher's exact test.

given that both systems have been shown to provide similar NPWT therapy²⁵ with similar clinical outcomes.^{16,17} The main weakness of this study is the relatively small sample size leading to the variability in baseline wound sizes. The findings require confirmation in a study with larger sample size of VLU patients.

Although it is unclear why there might be differences in the response of wounds to varying types of NPWT, a number of factors might be involved. First, of the two devices used in this comparison, the MP NPWT System is more compact, lightweight, and does not require battery power or recharging for operation. Overall, this increased portability may enhance patient adherence resulting in more effective hours per day receiving NPWT therapy. Previous study results have shown that the MP NPWT system offers significantly better quality of life advantages over the EP NPWT system such as less detrimental impact on daily activities, overall higher mobility level, improved sleep, reduced noise level, and better levels of comfort in social situations, in addition to overall wearability.¹⁷ These factors can significantly affect a patient's psychological well-being and may have effects on compliance and overall outcomes.^{10,35-38} It also stands to reason that the compact nature of the MP NPWT device may yield a relatively higher activity level than the heavier EP NPWT device resulting in increased calf muscle pump activation and reduction in venous pressures in the affected limb.

Second, the two systems use different wound interface materials, with the MP NPWT device employing a gauze interface while the EP NPWT device used a foam interface. Preclinical study results suggest that gauze dressings may be more effective for smaller and shallower wounds or in painful ulcers.^{14,39,40} VLUs are typically more superficial than other types of chronic wounds extending only through the dermis into the subcutaneous tissue. Foam interfaces appear to be particularly useful to stimulate granulation tissue formation to fill wounds, but the venous ulcer may require more epithelial migration and coverage rather than wound granulation.

Third, the fact that all MP NPWT dressing changes were performed by a clinician at a wound care center may have enabled the MP NPWT-treated patients to have more consistent care compared to the EP NPWT-treated patients, whose dressings were performed at home by visiting nurses. This may have been particularly important in the routine application of compression therapy, which is the primary treatment for the underlying venous insufficiency.⁴¹

KEY FINDINGS

- NPWT combined with compression therapy resulted in healing of refractory chronic VLUs.
- MP clinic applied NPWT may be superior to EP home applied NPWT for the treatment of VLUs in terms of speed of wound healing and wound closure.

Finally, additional design features of the MP NPWT system may have also played a role. Its hydrocolloid dressing may protect periwound skin, reducing maceration or other adverse effects of NPWT on the periwound area. Overall compatibility of the MP NPWT system and compression therapy may have impacted the healing response of the VLUs as well. Further study in a larger sample size may be necessary to evaluate risk factors contributing to healing in patients with VLUs treated with NPWT.

INNOVATION

VLUs represent a major challenge in wound healing. NPWT appears to be an effective method of treatment for patients with VLUs. Compared to subjects treated with the EP NPWT system, those subjects treated with the MP NPWT system experienced significantly faster wound healing. This information may be useful in selecting NPWT for treatment of refractory VLUs. Additional study in a larger patient cohort would allow identification of specific VLU patient criteria associated with good outcomes using NPWT.

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Dr. Marston is a scientific consultant for Spiracur, Inc. Dr. Armstrong is a scientific consultant for Spiracur, Inc. Dr. Reyzelman is a scientific consultant for KCI. Dr. Kirsner is a scientific consultant for KCI. No ghostwriter was used for the preparation of this article.

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Abbreviations and Acronyms

- EP = electrically powered
 MP = mechanically powered
 NPWT = negative pressure wound therapy
 RCT = randomized controlled trial
 SNaP[®] = Smart Negative Pressure
 V.A.C.[®] = Vacuum-Assisted Closure
 VLU = venous leg ulcer