Prediction of Healing for Postoperative Diabetic Foot Wounds Based on Early Wound Area Progression

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OBJECTIVE — To evaluate the probability of wound healing based on percentage of wound area reduction (PWAR) at 1 and 4 weeks in individuals with large, chronic, nonischemic diabetic foot wounds following partial foot amputation.

METHODS — Data from a 16-week randomized clinical trial (RCT) of 162 patients were analyzed to compare outcomes associated with negative-pressure wound therapy (NPWT) delivered through the V.A.C. Therapy System (Kinetic Concepts, San Antonio, TX) ($n = 77$) versus standard moist wound therapy (MWT) ($n = 85$). The 1- and 4-week regression models included 153 and 129 of the RCT patients, respectively.

RESULTS — Early changes in PWAR were predictive of final healing at 16 weeks. Specifically, wounds that reached ≥15% PWAR at 1 week or ≥60% PWAR at 4 weeks had a 68 and 77% (respectively) probability of healing vs. a 31 and 30% probability if these wound area reductions were not achieved. Patients receiving NPWT were 2.5 times more likely to achieve both a 15% PWAR at 1 week and a 60% area reduction at 1 month (odds ratios 2.51 and 2.49, respectively) compared with those receiving MWT.

CONCLUSION — Results of this study suggest that clinicians can calculate the PWAR of a wound as early as 1 week into treatment to predict the likelihood of healing at 16 weeks. This might also assist in identifying a rationale to reevaluate the wound and change wound therapies.

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Diabetic foot wounds result in substantial morbidity, reduced quality of life, and increased mortality in individuals with diabetes. To date, there are no universally accepted guidelines defining diabetic foot wound healing indicators, such as time course reduction in area or recommended therapies for nonresponders. Several studies have confirmed that intermediate wound reduction is a predictor of final healing in venous stasis, pressure, and neuropathic foot ulcerations (1–6). For instance, Sheehan et al. (1) reported that the percentage of change in wound area at 4 weeks post-therapy was a predictor of wound healing at 12 weeks in diabetic neuropathic foot ulcerations. They found that 58% of patients with a reduction in area greater than the 4-week sample median achieved final healing compared with only 9% who had a reduction in area below the 4-week median. In addition, wound area decreased by 82% at 4 weeks among those who healed compared with a 25% decrease at 4 weeks among those who did not heal. However, interpretation of these findings may be challenging because the amount of wound area reduction may vary by study, wound type, or wound characteristic (4).

The available literature on diabetic foot wounds begs a specific question: can early wound changes predict clinical outcomes in complex amputation wounds? As a means to track wound healing progress, Attinger (7) recommended that wound area should reduce by 10–15% per week. Sheehan et al. (1) used the sample median wound change at 4 weeks to determine whether small, superficial, neuropathic foot wounds were likely to heal. However, no studies to date have specifically assessed whether wound changes as early as 1 week and 1 month can be used to predict final healing in diabetic amputation wounds.

The primary objectives of this study were as follows: *1*) to determine whether changes in diabetic foot wound area after 1 and 4 weeks of treatment are predictive of final wound healing at 16 weeks and 2) to evaluate the effect of vacuum-assisted closure using negative-pressure wound therapy (NPWT) and moist wound therapy (MWT) on wound healing trajectories.

RESEARCH DESIGN AND METHODS

Data for this study were derived from a 16-week, prospective, multicenter, randomized clinical trial (RCT) that compared wound healing in diabetic partial foot amputees treated with either standard MWT or V.A.C. NPWT. Detailed results are published elsewhere (8). In brief, patients with wounds up to the transmetatarsal level with evidence of adequate perfusion were included. Adequate perfusion was defined as either transcutaneous oxygen measurements on the dorsum of the foot ≥30 mmHg or ankle brachial indexes ≥0.7 and ≤1.2, as well as toe pressure ≥30 mmHg. Of 162 enrolled patients, 77 received NPWT with dressing changes no less than three times weekly and 85 received MWT with dressing changes every day per Wound Ostomy and Continence Nurses Society guidelines. The study's primary objective was to determine whether NPWT was efficacious in treating nonischemic par-

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Abbreviations: MWT, moist wound therapy; NPWT, negative-pressure wound therapy; PWAR, percentage of wound area reduction; RCT, randomized clinical trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Patient demographics*

	Total population	NPWT subjects	Control subjects
n	153	73	80
Age (years)	58.7 ± 12.8	56.8 ± 13.4	60.4 ± 12.2
Sex (male)	126 (82)	63 (86)	63 (79)
Ethnic origin			
Non-hispanic white	72 (47)	34 (46)	38 (48)
African American	26 (17)	10 (14)	16 (20)
Mexican American	51 (33)	27 (37)	24 (30)
Native American	4 (3)	2 (3)	2 (2)
BMI (kg/m^2)	31.0 ± 8.4	31.0 ± 7.9	30.9 ± 8.9
Baseline wound area (cm^2)	20.0 ± 20.0	21.6 ± 22.6	18.5 ± 17.4
Wound duration (months)	1.6 ± 5.2	1.2 ± 4.0	1.8 ± 6.0
Currently use alcohol	38 (25)	20 (27)	18 (23)
Currently use tobacco	14 (9)	4 (5)	10 (13)
Type 2 diabetes	139 (91)	65 (89)	74 (93)

Data are means ± SD or *n* (%).

tial foot amputation wounds to improve the proportion of wounds that healed.

Wound photographs were taken using a digital camera on days 0, 7, 14, 28, 42, 56, 84, and 112. In addition, a bilayered wound tracing was made for planimetric assessment. Healing was assessed by clinical examination and confirmed by independent, blinded wound evaluators. Area was determined from a computer program measurement of the acetate tracing (Canfield Scientific, Fairfield, NJ). Determination of healing was performed by the clinical investigator and confirmed by blinded reviewers from digital photos. In three instances, the blinded reviewer considered the wound healed when the clinical investigator did not. In each instance, the wounds were not considered healed.

Final healing was defined as 100% reepithelialization without drainage. The majority of wounds healed by secondary intention, and a minority (NPWT 15.6%, MWT 9.4%) had delayed primary surgical closure. In the later instances, healing was not defined as the time of surgery but, rather, after the sutures were removed, and the site met the definition of 100% reepithlialization without drainage. In this study, patient data from the RCT were included if the patient had complete wound measurements at baseline and weeks 1, 4, and 16. Patients who reached 100% wound closure by 4 weeks were excluded from the 4-week models.

Statistical analyses

Demographic data were compared using Wilcoxon's rank sum and χ^2 tests. The primary analyses for this study were conducted using hierarchical Bayesian models with noninformative prior distributions on model hyperparameters. The choice to use a Bayesian approach for modeling was made because Bayesian models yield inferences with a very straightforward probabilistic interpretation—unlike conventional CIs. Specifically, Bayesian methods condition on the data in hand and do not rely on hypothetical repeated samples. In this study, Bayesian logistic regression techniques were used to assess the relationship between the percentage of wound area reduction (PWAR) and final healing. Modeling was conducted first for the PWAR at 1 week and then again at 4 weeks. Posterior distributions were computed using Markov chain Monte Carlo methods implemented in the WINBUGS software system (9). This analysis used three parallel chains starting at overdispersed initial values with a burn-in sample of 10,000 and with subsequent combined iterations totaling 250,000. Convergence of the Markov chains was assessed using standard methods, and no difficulties were found.

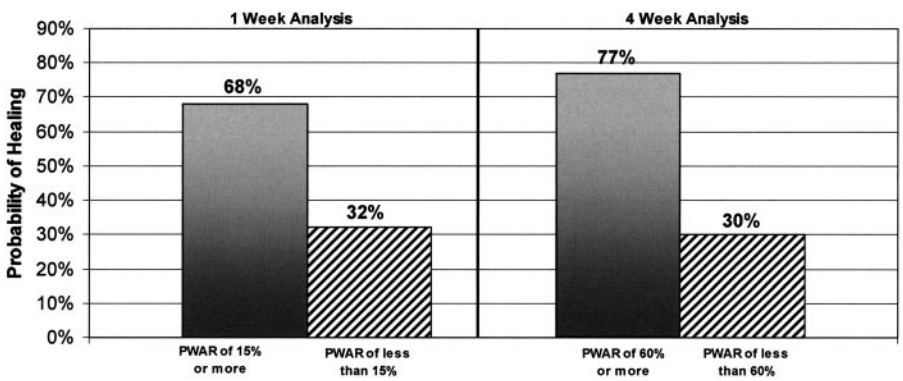

Figure 1—*Probability of healing at 16 weeks based on PWAR at 1 and 4 weeks.*

RESULTS — Of the 162 patients in the RCT study with baseline wound measurements, a total of 153 patients had complete wound measurements at their 1-week visit. Of these 153 patients, 80 (52%) were in the control group, i.e., received MWT, and 73 (48%) received V.A.C. NPWT. Eighty-three percent were male, and the median age was 60 years (range 24–83). Overall, 17% of patients were reported to be African American, 47% Caucasian, 33% Hispanic, and 3% Native American. There were no statistically significant differences in demographic or baseline variables between the NPWT and MWT study groups ($P > 0.05$) using Wilcoxon's rank sum and χ^2 tests (Table 1).

The 4-week analysis included 129 of the 162 RCT patients; 18 patients were missing 4-week wound measurements, and another 15 patients had already reached 100% closure at 4 weeks and were excluded from the analysis. Of the 129 patients, 72 (55.8%) were in the control group and 57 (44.2%) in the NPWT group.

Percentage of reduction in wound area as a predictor of healing

The study results indicated that early changes in PWAR were associated with final wound healing at both time intervals. Specifically, the PWAR at 1 week was predictive of complete wound healing at 16 weeks (odds ratio [OR] 1.03 [95% credible set 1.01–1.04]), meaning that for every additional percentage point in the reduction of wound area from baseline at 1 week, the likelihood of reaching final healing increased by 3%. In a frequentist model assessing the relationship between healing and PWAR at 1 week, the area under the receiver operating characteristics curve was 0.724, which is considered

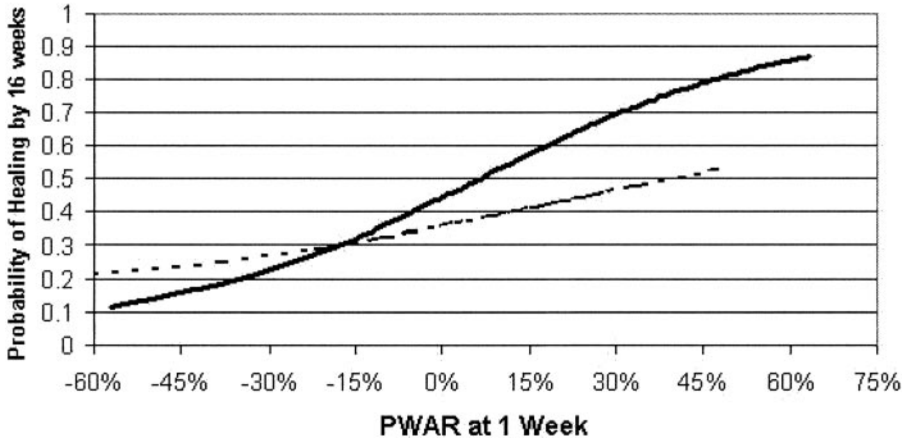

Figure 2—*Probability of healing by treatment and PWAR at 1 week. —, NPWT; ----, MWT.*

acceptable discrimination. Wounds that reached ≥15% PWAR at 1 week had a 68% probability of healing vs. 32% for those that did not reach 15% PWAR (Fig. 1).

PWAR at 4 weeks was predictive of complete wound healing at 16 weeks (OR 1.04 [95% credible set 1.02–1.05]), meaning that for every additional percentage point in the reduction of wound area from baseline at 4 weeks, the likelihood of reaching final healing increased by 4%. In a frequentist model assessing the relationship between healing and PWAR at 4 weeks, the area under the receiver operating characteristics curve was 0.798, which is considered acceptable discrimination. Wounds that reached ≥60% PWAR at 4 weeks had a 77% probability of healing vs. 30% for those that did not reach 60% PWAR (Fig. 1).

Relationship between treatment modality and healing

Second, we compared the association between the likelihood of healing and both PWAR and treatment modality. As depicted in Fig. 2, the association between PWAR and the probability of healing was different between treatment groups in the 1-week model. Based on the model results, wounds treated with NPWT needed to achieve a 7% reduction in wound area at 1 week to achieve a 50% probability of healing by 16 weeks. In comparison, a patient treated with MWT needed to achieve a 37.5% reduction in wound area at 1 week to achieve the same 50% probability of healing by 16 weeks. The observed mean 1-week PWAR change in the NPWT group was 18.9%, which was associated with a 60% probability of healing (Fig. 2). In contrast, the observed mean 1-week PWAR in the MWT group was only 9.9%, which is associated with a much lower (39%) probability of healing by 16 weeks (Fig. 2).

Similarly, from the 4-week model and as shown in Fig. 3, patients treated with NPWT had greater probabilities of healing regardless of their PWAR at 4 weeks compared with patients treated with MWT (Fig. 3). Based on the model results, wounds treated with NPWT needed to achieve a 30% PWAR at 4 weeks to achieve 50% probability of healing by 16 weeks, whereas wounds treated with MWT needed to achieve a 59% PWAR at 4 weeks to reach the same 50% probability of healing by 16 weeks. The observed mean 4-week PWAR change in the NPWT group was 46%, which was associated with a 60% probability of healing based on the time point used in the evaluation (Fig. 3). In contrast, the observed mean 4-week PWAR in the MWT group was 43%, which was associated with a much lower probability of healing (34%) by 16 weeks (Fig. 3).

Probability of achieving reduction in wound area and the impact of treatment modality

Individuals receiving NPWT were ~2.5 times more likely to have a PWAR of 15% at 1 week compared with those receiving standard WMT (1-week OR 2.51 [95% credible set 1.25–4.59]). NPWT patients who achieved a 15% reduction at 1 week had a 57% probability of healing. In comparison, MWT patients who experienced a 15% reduction in wound area at 1 week had a 41% probability of healing (Fig. 2).

The PWAR at 4 weeks was skewed, as shown by the median values, which were 59% for NPWT and 47% for MWT. Thus, while it looks like there was little difference between treatment groups at 4 weeks in terms of PWAR, there was a significant difference between treatment groups in the frequency of achieving the goal of 60% PWAR at 4 weeks, as shown by the following logistic regression model results. Individuals receiving NPWT were ~2.5 times more likely to have a PWAR of 60% at 4 weeks compared with those receiving standard MWT (4-week OR 2.49 [95% credible set 1.18–4.73]). Results of the 4-week analysis indicated that NPWT patients who achieved a 60% reduction at 4 weeks had a 71% probability of healing. In comparison, MWT patients who experienced the same wound area reduction at 4 weeks had only a 51% probability of healing (Fig. 3).

CONCLUSIONS— This study sought to assess whether early changes in wound progression status at 1- and 4-week time intervals were predictive of final healing at 16 weeks. In addition, negative-pressure therapy was compared with moist wound care with regard to achieving targeted

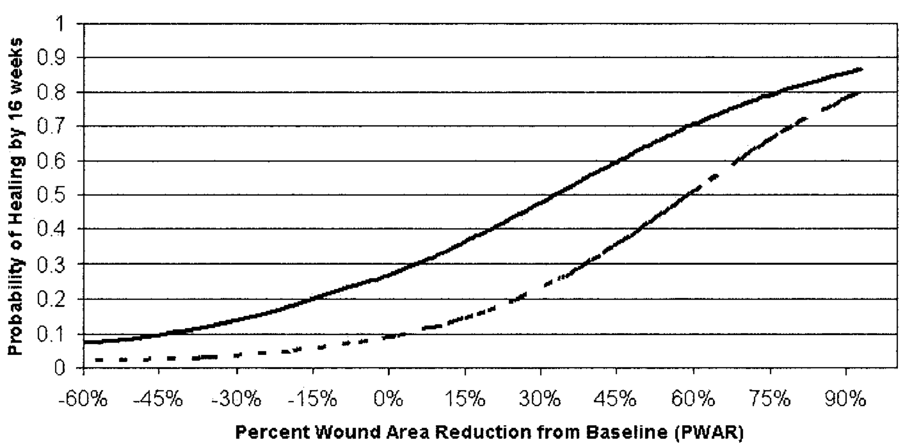

Figure 3—*Probability of healing by treatment and PWAR at 4 weeks. —, NPWT; ----, MWT.*

wound area reduction and the likelihood of complete wound healing. The results of this study suggest that clinicians could effectively use PWAR as early as 1 week to predict wound healing. This is a simple tool that can be easily applied in clinical practice to monitor the effectiveness of therapy in the earliest stages of treatment. Wounds that decreased in area by at least 15% had a 68% probability of healing, almost a twofold increase in likelihood of desired outcome. The ORs from our analysis of diabetic foot wounds indicated that there was a 3–4% increase in the likelihood of healing at 16 weeks for every additional percentage point reduction in wound area. While Sheehan et al. (1) reported that PWAR at 4 weeks was highly predictive of healing when using the 4-week sample medians, the findings from this study suggest that PWAR at 1 week is also predictive of healing in diabetic foot wounds. Indeed, we found that including both 1- and 4-week PWAR did not improve prediction compared with using the 4-week PWAR alone.

The secondary analyses in this study compared NPWT and MWT. The probability of healing was not solely dependent on PWAR but also on treatment modality. Early wound changes predict healing, and treatment choice impacts the ability to obtain early wound progression. Wounds receiving NPWT had a greater probability of achieving a target of 15% wound area reduction at 1 week or 60% wound area reduction at 4 weeks. These milestones are important because they were found to be most strongly associated with final healing and because they have been found to be indicative of final healing in other studies. The results of this study demonstrated that wounds treated with NPWT were more than twice as likely to achieve the target PWAR compared with wounds treated with MWT. Furthermore, wounds treated with NPWT were more than twice as likely to heal by 16 weeks compared with those treated with MWT.

There are several limitations to this study. First, data were utilized from a randomized controlled trial comparing NPWT and MWT on diabetic foot amputation wounds in particular and may not be generalizable to other conditions. Second, as is inherent with RCTs, similar healing rates may or may not be seen in community settings. Subjects in the RCT were excluded if they had peripheral vascular disease, Charcot arthropathy, poor glucose control, or infection. These are factors that have been linked to delayed healing and poor clinical outcomes, so results in the general wound population may differ from those reported in this trial. Third, the wounds in this study were complex. Amputation wounds are larger and deeper than the venous stasis, pressure, and neuropathic foot ulcers previously reported in the medical literature (1–6).

Another limitation was our inability to evaluate the three-dimensional nature of wound healing. We did not include depth as a factor in the PWAR assessment. In this and other studies (1–6), two-dimensional evaluation tools were used primarily because the techniques are easy to use, inexpensive, and have good repeatability. Evaluating the depth of irregular wounds is challenging. The techniques are time consuming and have not been used extensively in clinical trials. We may have underestimated the severity of some wounds by not including depth or by evaluating area rather than wound volume. However, even considering the inherent limitations, the technique seems to offer a valuable tool to monitor the progress of pressure, venous stasis, and diabetic foot wounds.

Early aggressive intervention has been shown to be beneficial and cost-effective in many settings. The goal of diabetic foot wound care is not only to achieve the final end point of complete healing but also to achieve this goal as quickly as possible. Wounds that do not heal in a timely fashion are more likely to become infected, require subsequent hospitalizations, and increase overall costs (1). Attinger et al. (7) have suggested that NPWT be used as a means to effectively speed the wound healing process. New products such as NPWT delivered through the V.A.C. Therapy System (Kinetic Concepts, Inc.) have been shown to be efficacious in managing diabetic foot wounds (8,10,11) but may be reserved until other treatments have failed. The findings from this study support the use of aggressive care in diabetic foot amputation wounds to increase the likelihood of complete healing.

Data from this study and others suggest that poor responses in wound area progression in the first weeks with standard therapy can be easily evaluated and used to identify wounds that are less likely to heal. This practical and inexpensive evaluation approach could improve patient outcomes by identifying subjects who are not likely to respond to their current therapy. When standard wound therapies such as offloading, infection control, and debridement are provided and PWAR assessments indicate lack of progression, clinicians might consider using advanced wound therapies early in the treatment cycle, although specific studies are required to demonstrate the effectiveness of such therapies.

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