Prediction of healing for post-operative diabetic foot wounds based on early wound area progression

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Running Title: Foot Wound Healing

Received for publication 7 July 2007 and accepted in revised form 10 October 2007.
ABSTRACT

Objective: To evaluate the probability of wound healing based on percent wound area reduction (PWAR) at one week and 4 weeks in persons with large, chronic, non-ischemic 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 delivered through the VAC Therapy System (KCI USA San Antonio, TX) (NPWT) (n=77) versus standard moist wound therapy (MWT) (n=85). One 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 one week or ≥60% PWAR at four weeks had a 68% and 77% (respectively) probability of healing versus 31% and 30% (respectively) if these wound area reductions were not achieved. Patients receiving NPWT were 2.5 times more likely to achieve both a 15% PWAR at one week and 60% area reduction at one month (odds ratio = 2.51 and 2.49, respectively) compared to MWT.

Conclusion: Results of this study suggest that clinicians can calculate the PWAR of a wound as early as week one of treatment to predict the likelihood of healing at 16 weeks. This might also assist in identifying a rationale to re-evaluate the wound and change wound therapies.
Diabetic foot wounds result in substantial morbidity, reduced quality of life, and increased mortality in persons 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 non-responders. 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 and coworkers reported that the percent change in wound area at four weeks post-therapy was a predictor of wound healing at 12 weeks in diabetic neuropathic foot ulcerations (1). They found that 58% of patients with a reduction in area greater than the 4-week sample median achieved final healing, compared to only 9% who had a reduction in area below the 4-week median. In addition, wound area decreased by 82% at four weeks among those who healed, compared to a 25% decrease at four weeks among those who did not heal. However, interpretation of these findings may be challenging, as 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 recommended that wound area should reduce by 10-15% per week (7). Sheehan et al used the sample median wound change at four weeks to determine if small, superficial neuropathic foot wounds were likely to heal (1). However, no studies to date have specifically assessed whether wound changes as early as one week and one month could be used to predict final healing in diabetic amputation wounds.

The primary objectives of this study were (1) to determine whether changes in diabetic foot wound area after one and four 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 and moist wound therapy (MWT) on wound healing trajectories.

**RESEARCH DESIGN AND METHODS**

Data for this study were derived from a 16-week, prospective, multi-center randomized clinical trial (RCT) that compared wound healing in diabetic partial foot amputees treated with either standard moist wound therapy (MWT) or V.A.C.® NPWT (VAC 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 ≥ 30mmHg or ankle brachial indices ≥0.7 and ≤1.2, and 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 WOCN guidelines. The study’s primary objective was to determine whether NPWT was efficacious in treating non-ischemic partial 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 bi-layered wound tracing was made for planimetric assessment. Healing was assessed by clinical examination and confirmed by independent, blinded wound evaluators.
Foot Wound Healing

Area was determined from a computer program measurement of the acetate tracing (Canfield Scientific Fairfield, NJ, USA). Determination of “healing” was determined 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% re-epithelialization 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% re-epithelialization without drainage. In this present 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 rank sum and Chi-square tests. The primary analyses for this study were conducted using hierarchical Bayesian models with non-informative 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 confidence intervals. 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 percent of wound area reduction (PWAR) and final healing. Modeling was conducted first for the PWAR at 1-week and then again for the PWAR at 4-weeks. Posterior distributions were computed using Markov chain Monte Carlo (MCMC) methods implemented in the WINBUGS software system (9). This analysis used 3 parallel chains, starting at over-dispersed initial values with a burn-in sample of 10,000, and subsequent combined iterations totaling 250,000. Convergence of the Markov chains was assessed using standard methods and no difficulties were found.

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 VAC NPWT. Eighty-three percent were male and the median age was 60 years (range 24 - 83). Overall, 17% of the 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 Rank sum and Chi-square 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 four 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.

Percent reduction in wound area as a predictor of healing. The study results indicated that early changes in percent reduction in wound area were associated
with final wound healing at both time intervals. Specifically, the PWAR at one week was predictive of complete wound healing at 16 weeks (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 one 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 ROC curve is 0.724 which is considered acceptable discrimination. Wounds that reached 15% PWAR or more at one week had a 68% probability of healing versus 32% for those that did not reach 15% PWAR. (Figure 1)

Percent of Wound Area Reduction at four 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 four weeks, the likelihood of reaching final healing increased by 4%. In a frequentist model assessing the relationship between healing and PWAR at 4 week, the area under the ROC curve is 0.798 which is considered acceptable discrimination. Wounds that reached 60% PWAR or more at four weeks had a 77% probability of healing versus 30% for those that did not reach 60% PWAR (Figure 1).

Relationship between treatment modality and healing. Secondarily, we compared the association between the likelihood of healing and both PWAR and treatment modality. As depicted in Figure 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 one 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 one week to achieve the same 50% probability of healing by 16 weeks. The observed mean one-week PWAR change in the NPWT group was 18.9%, which was associated with a 60% probability of healing (Figure 2). In contrast, the observed mean one-week PWAR in the MWT group was only 9.9% which is associated with a much lower (39%) probability of healing by 16 weeks (Figure 2).

Similarly, from the 4-week model and as shown in Figure 3, patients treated with NPWT had greater probabilities of healing regardless of their PWAR at 4-weeks as compared to patients treated with MWT (Figure 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 while 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 (Figure 3). In contrast, the observed mean four week PWAR in the MWT group was 43% which was associated with a much lower (34%) probability of healing by 16 weeks (Figure 3).

Probability of achieving reduction in wound area and the impact of treatment modality. Persons receiving NPWT were approximately 2.5 times more likely to have a PWAR of 15% at one week compared to standard moist wound therapy (1-week OR = 2.51, 95% credible set = 1.25 to 4.59). NPWT patients who achieved a 15% reduction by Week 1 had a 57% probability
of healing. In comparison, MWT patients who experienced a 15% reduction in wound area at one week had a 41% probability of healing (Figure 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 the 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. Persons receiving NPWT were approximately 2.5 times more likely to have a PWAR of 60% at 4-weeks compared to standard moist wound therapy (4-week OR=2.49, 95% credible set = 1.18 to 4.73). Results of the 4-week analysis indicated that NPWT patients who achieved a 60% reduction by Week 4 had a 71% probability of healing. In comparison, MWT patients who experienced the same wound area reduction at four weeks had only a 51% probability of healing (Figure 3).

DISCUSSION

This study sought to assess whether early changes in wound progression status at one and four week time intervals were predictive of final healing at 16 weeks. In addition, negative pressure therapy was compared to moist wound care with regard to achieving targeted wound area reduction and the likelihood of complete wound healing. The results of this study suggest that clinicians could effectively use the "Percent Wound Area Reduction" 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 which decreased in area by at least 15% had a 68% probability of healing, almost a two-fold increase in likelihood of desired outcome. The odds ratios from our analysis of diabetic foot wounds indicated that there was a 3 to 4 percent increase in the likelihood of healing at 16 weeks for every additional percentage point reduction in wound area. While Sheehan et al. reported that percent wound area reduction (PWAR) at four weeks was highly predictive of healing when using the 4-week sample medians, the findings from this study suggest that PWAR at one week is also predictive of healing in diabetic foot wounds (1). Indeed, we found that including both 1-week and 4-week PWAR did not improve prediction compared to using the 4-week PWAR alone.

The secondary analyses in this study compared NPWT and moist wound therapy. The probability of healing was not solely dependent on percent wound area reduction, 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 one week or 60% wound area reduction at four weeks. These milestones are important because they were found to be most strongly associated with final healing and 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 to wounds treated with MWT. Furthermore, wounds treated with NPWT were more than twice as likely to heal by 16 weeks when compared to MWT.

There are several limitations to this study. First, data were utilized from a randomized controlled trial comparing NPWT and MWT Therapy on diabetic foot amputation.
Foot Wound Healing

wounds in particular and may not be
generalizable to other conditions. Secondly,
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. Thirdly, the
wounds in this study were complex.
Amputations wounds are larger and deeper
than the venous stasis, pressure and
neuropathic foot ulcers previously reported
in the medical literature (1-6).

Another limitations 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.

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 that are not likely to
respond to their current therapy. When
standard wound therapies such as off-
loading, 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.
REFERENCES

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Total Population (n = 153)</th>
<th>NPWT (n = 73)</th>
<th>Control (n = 80)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>58.7 (12.8)</td>
<td>56.8 (13.4)</td>
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<td>Sex (male)</td>
<td>126 (82%)</td>
<td>63 (86%)</td>
<td>63 (79%)</td>
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<tr>
<td>Ethnic origin</td>
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<td>Non-hispanic white</td>
<td>72 (47%)</td>
<td>34 (46%)</td>
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<tr>
<td>African-American</td>
<td>26 (17%)</td>
<td>10 (14%)</td>
<td>16 (20%)</td>
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<td>Mexican-American</td>
<td>51 (33%)</td>
<td>27 (37%)</td>
<td>24 (30%)</td>
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<td>Native American</td>
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<td>2 (3%)</td>
<td>2 (2%)</td>
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<td>Body-mass index (kg/m²)</td>
<td>31.0 (8.4)</td>
<td>31.0 (7.9)</td>
<td>30.9 (8.9)</td>
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<tr>
<td>Baseline Wound Area (cm²)</td>
<td>20.0 (20.0)</td>
<td>21.6 (22.6)</td>
<td>18.5 (17.4)</td>
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<tr>
<td>Wound Duration (months)</td>
<td>1.6 (5.2)</td>
<td>1.2 (4.0)</td>
<td>1.8 (6.0)</td>
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<td>Currently use alcohol</td>
<td>38 (25%)</td>
<td>20 (27%)</td>
<td>18 (23%)</td>
</tr>
<tr>
<td>Currently use tobacco</td>
<td>14 (9%)</td>
<td>4 (5%)</td>
<td>10 (13%)</td>
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<tr>
<td>Type 2 diabetes</td>
<td>139 (91%)</td>
<td>65 (89%)</td>
<td>74 (93%)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number of patients (%)
Figure 1. Probability of healing at 16 weeks based on percent wound area reduction (PWAR) at 1 and 4 weeks
**Figure 2.** Probability of healing by treatment and PWAR at 1-week
Figure 3. Probability of healing by treatment and PWAR at 4-weeks