Surrogate End Points for the Treatment of Diabetic Neuropathic Foot Ulcers

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OBJECTIVE — The goal of this study was to determine whether surrogate markers based primarily on changes in the size of a wound can be used to correctly predict which individuals with diabetic neuropathic foot ulcers will heal after 12 or 20 weeks of care.

RESEARCH DESIGN AND METHODS — This is a retrospective cohort study using the Curative Health Services database. As many as 39,918 neuropathic wounds on 20,213 individuals with diabetes were evaluated. Seven surrogates based on changes in wound size were evaluated.

RESULTS — Surrogates measured after 2, 4, or 8 weeks of care and based on percentage change in area, log healing rate, and log area ratio discriminated well with respect to differentiating between those wounds that healed and those that did not heal by the 12th or 20th week of care. For example, after 4 weeks of care, the percentage change in area can be used to correctly discriminate 76% of the time between those that healed and those that did not by the 20th week of care.

CONCLUSIONS — The surrogate markers can be used in clinical trials such that shorter and smaller trials can be conducted with reasonable accuracy in order to determine which potential new therapeutics should be studied in larger, longer trials. In addition, the surrogates may also benefit clinicians when they are trying to decide whether a wound care therapy will ultimately be successful.

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Clinical trials of therapies for individual patients with diabetic neuropathic foot ulcers are limited by the prolonged time period needed to reach the ultimate outcome, a healed wound. In fact, randomized clinical trials usually follow subjects for between 12 and 20 weeks. As a result, the trials are very expensive and patients may be exposed to potentially nonefficacious experimental agents for prolonged periods of time. A valid surrogate marker of complete wound healing would minimize the number of subjects exposed to a potentially unsuccessful treatment and minimize the time required to develop a successful new treatment, thereby improving the efficiency with respect to cost and design needed to successfully screen potential therapeutic agents. Finally, a valid surrogate marker allows for the identification of patients who are not likely to heal by standard methods early in the patient's course of treatment, thereby expediting referral to specialty centers or expediting initiation of stepped treatment algorithms.

More than 10 years ago, the rate of healing for patients with diabetic foot ulcers was shown by Pecoraro et al. (1) to statistically differentiate between those patients who eventually healed and those who did not. Studies have also shown that for other chronic wounds, the percent change in the wound area over the initial 4 weeks of therapy, as well as the rate of healing over the initial 4 weeks of therapy, may predict who will ultimately heal (2–8). However, most of these studies were small and did not evaluate diabetic foot ulcers. Surrogate markers require extensive epidemiologic testing to ensure validity. Recent statements from the Food and Drug Administration have implied that in order for a surrogate marker to be acceptable in a wound healing trial, it must be shown to predict healing with adequate follow-up on a large sample of patients (9,10).

Prentice (11) defined a surrogate end point as "a response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true end point." Temple (12) defined a surrogate end point as "a laboratory measurement or a physical sign used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions or survives." It should be noted that a surrogate end point must not only correlate with a true and important clinical outcome, but should also capture the net effect of the treatment on the clinical outcome. Therefore, a valid surrogate end point is related to the outcome of interest and accurately reflects the effect of the treatment, exposure, or disease characteristics as they would affect the true outcome.

We hypothesize that individuals with wounds that have a faster healing rate or a greater absolute change, or those who achieve a greater percentage reduction in wound size, will be more likely to heal. The goal of this study is to determine whether these surrogates can correctly

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Abbreviations: CHS, Curative Health Services; ROC, receiver-operating characteristic.

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

predict which individuals with diabetic neuropathic foot ulcers will heal after 12 or 20 weeks of care.

RESEARCH DESIGN AND METHODS

— For nearly 15 years, Curative Health Services (CHS) has been directly involved in the care of individuals with chronic wounds and has maintained an administrative and patient record database (13–17). All subjects for this investigation were treated at a CHS center between 1988 and 2000. To avoid including subjects who were one-time specialty center consultations, any individual who was coded as a consult and did not have a second office visit or documentation of a surgical procedure within 6 weeks of the first office visit was excluded. Patients in these centers are primarily treated by frequent wound debridement, moist dressing, and off-loading the foot (15,18).

Ascertaining disease and outcome

We have previously published a validated algorithm that can be used to ascertain individuals with diabetic neuropathic foot ulcers in the CHS database (16,17). We conducted analyses of all the wounds listed for a patient in the CHS database and only the patient's primary wound. The primary wound is defined in the CHS database as the first wound or most severe wound evaluated during the patient's first session at a CHS center. The outcome for all subjects, a healed wound by the 12th or 20th week of care, was also determined using a previously validated algorithm (16,17).

Analysis

Surrogate formulas. Because a surrogate should be measured at a time period much sooner than the outcome, we evaluated surrogates that occurred at weeks 2, 4, and 8 for the 12th and 20th week care-healed outcome. Since exactly 4 weeks is not always what is meant when a patient is told to return in 4 weeks, our definition of 4, 6, and 8 weeks, respectively, varied by ±3 days. For example, 4 weeks meant that a patient had a return office visit and wound evaluation within 25–31 days after his or her initial visit. All the surrogates that we evaluated were based on changes in the size of the wound. We used the following seven formulas to generate our surrogates: *1*) absolute change in area: $Area_0 - Area_t$; 2) healing rate: $(Area_0 - Area_t)/t$; 3) area ratio: $Area_t/Area_0$; *4*) percentage change area: $[(Area_0 - Area_t)/Area_0] \times 100$; 5) log absolute change in area: $\ln(Area_0) - \ln(Area_t)$; *6*) log healing rate $[\ln(Area_0) - \ln(Area_t)]/t$; and 7) ratio of log areas: $\ln(Area_0)/\ln(Area_t)$.

$Area_t$ is the wound area at week 2, 4, or 8. $Area_0$ is the baseline wound area. However, it is important to note that in order for a surrogate to be calculated, a patient must have had data at that time point so that the calculation could be made. All wound areas are in millimeters squared and *t* was measured in days. If debridement was required, wounds were measured post debridement. All wound areas were determined by measuring and multiplying the largest length and largest width. The validity of this technique, as compared with computer-based, planimetry has been previously established (3). Natural logarithm transformation of wound area was performed due to our previous experience with the skewed distribution of this parameter (19,20). The accuracy of the database is maintained by CHS.

Descriptive analyses. Means with SDs and medians with 25th and 75th percentiles were used to describe all continuous variables. Comparisons were made between those who healed and those who did not heal by using a *t* test for normally distributed continuous variables and a rank-sum test for non–normally distributed continuous variables.

Surrogate discrimination and dichotomization. The ability of a test to differentiate between two individuals, one who healed and one who did not, was measured by the area under the receiver-operating characteristic (ROC) curve (21). ROC curves were generated for the candidate surrogate markers at weeks 2, 4, and 8 compared with the healed outcome at both the 12th and 20th week of care. The candidate surrogate markers with the best ROC curve areas were further investigated. A cut point for the candidate surrogate marker was generated such that it maximized the correct classification of the 12th or 20th week healed outcome. Correct classification is the probability that the surrogate result matches the outcome result. We used correct classification to define the surrogate because a surrogate should reflect the true outcome of a patient either healing or not healing. This is different from creating a cut point for a diagnostic test that often favors either sensitivity or specificity. We also estimated the sensitivity (the probability of testing positive if the outcome is truly present), specificity (the probability of testing negative if the outcome is truly absent), positive predictive value (the probability of having the outcome given a positive test), and negative predictive value (the probability of not having the outcome given a negative test) for the dichotomous surrogates.

Test validation and sensitivity analyses. To further explore the statistical characteristics of the surrogates, we investigated whether estimates of association of three wound characteristic were similar for the surrogate and healed 20-week outcome. These wound characteristics were the baseline wound grade, size, and duration. They have been evaluated in the past and shown to be important predictors of a healed wound (17,22). The association between these risk factors and the dichotomous surrogate was estimated as an odds ratio using logistic regression. Associations were also estimated using generalized estimating equations in order to better understand center- and person-based effects (for the all wound models). Variance estimates were not meaningfully different; therefore, only the fixed effects models are presented.

To further explore the robustness of our results, several sensitivity analyses were performed, including investigations of subjects who dropped out and those who were not available at weeks 4 and 6 for analysis. In addition, we estimated healing rates for those who received adjuvant therapies.

All statistical analyses were performed using Stata 7.0 (College Station, TX) for a PC.

RESULTS

— In total, there were 31,172 patients in the CHS database with a diabetic neuropathic foot ulcer. As expected, due to the natural scheduling variability in clinical practice, the total number of individuals who had wound measurements at a given office visit defined by our surrogates time points (i.e. weeks 2, 4, and 8) varied. Therefore, in the CHS database at 2 weeks, 39,918 wounds on 20,213 individuals were examined; at four weeks, 28,624 wounds were examined on 16,205 individuals; and at 8 weeks, 16,773 wounds were examined on 11,009 individuals. Finally, 6.5% of patients were lost to follow-up and 7.2% had an amputation before the

Table 1—*Patient characteristics and week 4 surrogate characteristics for those who healed and those who did not by the 20th week of care and who were evaluated at week 4*

Variable	Healed	Unhealed
Wounds	15,382 (53.7)	13,242 (46.3)
Age (years)	64 (54–73)	65 (54–74)
Wound size (mm^2)	133 (49–401)	255 (82–827)
Wound duration (months)	1 (0.5–3)	2 (0.75–5)
Log wound size (mean)	4.97 (0.012)	5.59 (0.014)
Log wound duration	0.36 ± 1.40	0.73 ± 0.01
Log rate	0.062 ± 0.0006	0.007 ± 0.0004*
Percent change	−0.016 ± 0.06*	−1.02 ± 0.25*
Ratio of log areas	0.64 ± 0.004*	0.99 ± 0.003*

Data are *n* (%), median (25th–75th percentile), or mean ± SD unless otherwise indicated.

20th week of care. For the purpose of our primary analyses, these individuals were coded as not having healed. This is consistent with the intention-to-treat analysis of a clinical trial.

In total, 53.7% of all wounds healed and 50.7% of the primary wounds healed (Table 1). By the 12th week of care, 41.9% of all wounds had healed and 37.1% of the primary wounds had healed. Cumulatively, by weeks 2, 4, and 8 of care, 3.6, 7.4, and 13.3% (n = 1,148, 2,311, and 4,134) of wounds had healed, respectively. Cumulatively, by weeks 2, 4, and 8 of care, 2.3, 3.7, and 4.1% (n = 860, 1,145, and 1,272) of patients had dropped out, respectively. Cumulatively, by weeks 2, 4, and 8 of care, 1.4, 2.4, and 3.9 (n = 429, 751, and 1,222) of patients had had an amputation, respectively. Those who healed at baseline had smaller wounds of shorter duration than those who did not heal (all P values <0.001). With respect to our surrogates, patients who healed had a larger log wound rate, a higher percent change, and a smaller log ratio at all surrogate time points (Table 1).

The surrogates percentage change in area, log healing rate, and log area ratio discriminated well at all time points with respect to differentiating between those wounds that healed and those that did not heal by the 12th or 20th week of care (Table 2). Their ability to discriminate did not vary, regardless of whether the analysis included only the primary wound (i.e., the first diabetic neuropathic wound coded by CHS) or all of a patient's wounds (Table 2). The surrogates absolute change in area, healing rate, and area ratio poorly discriminated at all time points with respect to differentiating between those that healed and those that did not heal by the 12th or 20th week of care, as demonstrated by an ROC curve <0.60 (data not shown).

The surrogates were dichotomized at a point that optimized the ability of the surrogate to correctly classify a wound as healed or unhealed by the 20th week of care. The cut points and test characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, and correct classification) are listed in Table 3. About 69% of the time, the dichotomous 4-week percent change surrogate correctly classified a wound as healed by the 20th week of care. Since percent correct classification is dependent on the prevalence of the outcome, it is important to note that within the expected range of wound healing in most clinical trials (i.e., 20–60%), our estimated correct classification could vary from 77 to 67%. Second, our rates are very conservative in that all patients who dropped out were coded as not healed and patients who healed before the surrogate time were dropped from analysis. The ability of the surrogate to correctly classify a patient's outcome improves if these criteria are relaxed. For example, if patients who healed before the 4th week of care were included as healed for the 4-week percent change dichotomous surrogate (i.e., since they healed, they must have achieved the surrogate cut point at some point before healing), then the surrogate would have correctly classified patients 73% of the time.

Three risk factors known to be associated with an ulcer healing by the 20th week of care had similar associations with the 4-week percent change surrogate. Using logistic regression, initial log wound area was associated with a wound healing by the 20th week by an odds ratio of 0.78 (95% CI 0.77–0.80) and with the percent dichotomous surrogate by an odds ratio of 0.90 (0.88–0.91). Log wound duration was associated with a wound healing by the 20th week of care by an odds ratio of 0.83 (0.81–0.84) and with the dichotomous percent surrogate by an odds ratio of 0.87 (0.86–0.89). Using logistic regression, initial wound grade, as defined by a CHS grade of 2 or <2 vs. >2, was associated with a wound healing by the 20th week by an odds ratio of 0.50 (0.48–0.53) and with the percent dichotomous surrogate by an odds ratio of 0.54 (0.52–0.58).

Finally, our results were very robust to change. Sensitivity analyses revealed that those who dropped out after the 4th week of care had wound area percent

Table 2—*The ROC curve area for surrogate end points measured after 2, 4, or 8 weeks for a 12- or 20-week healed outcome*

			ROC curve		
Surrogate	Wound	End point	Week 2	Week 4	Week 8
Log rate	Primary	Week 12	0.73	0.78	0.85
Percent change	Primary	Week 12	0.73	0.79	0.85
Ratio of log areas	Primary	Week 12	0.74	0.79	0.86
Log rate	All	Week 12	0.75	0.79	0.85
Percent change	All	Week 12	0.75	0.80	0.86
Ratio of log areas	All	Week 12	0.76	0.80	0.86
Log rate	Primary	Week 20	0.69	0.73	0.77
Percent change	Primary	Week 20	0.69	0.73	0.77
Ratio of log areas	Primary	Week 20	0.69	0.73	0.78
Log rate	All	Week 20	0.72	0.76	0.78
Percent change	All	Week 20	0.72	0.76	0.78
Ratio of log areas	All	Week 20	0.72	0.76	0.79

Table 3—*Correct classification maximized dichotomous surrogate end points at 4 weeks for a 20-week healed outcome*

Surrogate	Wound	Cut point	Sensitivity	Specificity	Correct classification (%)
Log rate	All	0.033	68.2	71.1	69.5
Log rate	Primary	0.044	58.4	79.0	68.6
Percent change	All	0.61	68.2	71.2	69.6
Percent change	Primary	0.71	58.5	79.0	68.6
Ratio of log areas	All	1.23	68.8	71.9	70.2
Ratio of log areas	Primary	1.34	59.0	79.6	69.2

changes similar to those who did not heal, thereby justifying our assumption to include these individuals with those who did not heal. In an attempt to capture those who did not have a week 4 visit, we estimated percent changes at weeks 3 and 5. The percent changes for those who healed and those who did not heal were similar to our reported week 4 percent changes. The week 4 percent changes for those who ultimately received an adjuvant, such as platelet releasate, were similar to those who did not heal. This was expected based on our previous work and the actual timing of the administration of platelet releasate, which often did not commence until week 12 (17,19). As a result, the 20-week trial of adjuvant care does not occur until 32 weeks after CHS registration (17). Finally, as would have been expected from previous studies, our results did not vary significantly from center to center (17,19).

CONCLUSIONS — The results of this study show, with reasonable accuracy, that several surrogate end points exist, such that by the 4th or 8th week of care, we can predict which individuals with a neuropathic diabetic foot ulcer will heal by the 12th or 20th week of care. It seems reasonable to argue that for wound healing trials of either 12 or 20 weeks' duration, a surrogate end point measured by the 4th week of care maximizes the accuracy of the prediction and minimizes the expense of the trial. For this reason, we ultimately concentrated our analyses on a surrogate measured by the 4th week of care. In addition, we also concentrated our analyses on the surrogate we call "percent change," because this surrogate is the easiest to calculate. This surrogate end point at week 4 of care had an ROC curve area between 0.73 and 0.80, depending on whether all wounds were analyzed or just the primary wound and whether the ultimate end point was healed by 12 or 20 weeks of care. To simplify, an ROC curve area of 0.73 means that 73% of the time by the 4th week of care a randomly chosen patient who healed will have a larger percent change than one who did not heal. If this end point is dichotomized, then we can correctly classify a patient at the 4th week of care as either healed or not healed by the 20th week of care ~69% of the time. These findings are based on analyses using the CHS database, which is to our knowledge the largest wound care database. This database should be generalizable in that it includes data from as many as 150 wound care centers throughout the U.S. While we cannot guarantee that our results generalize to all clinical trials and all clinical situations, the sheer size and diversity of this study sample is such that the likelihood of generalizabilty is greater than for any previous publication on a diabetic foot ulcer surrogate that we could identify. Finally, to demonstrate that the surrogates follow the dictates of many who have published on this topic, we used regression models to demonstrate that risk factors for diabetic neuropathic wound healing, such as wound grade, wound duration, and wound size, were also important risk factors for the dichotomized surrogate markers (17,22,23).

The surrogates are important to both clinicians and clinical investigators. As stated above, for clinical trials, especially if the goal of the study is an early determination of the efficacy of a new treatment (i.e., a phase II study), an investigator can now use a 4-week surrogate end point instead of the more traditional 12- or 20-week outcome. This change in the duration of a trial is important in that it will increase the efficiency of screening a new wound care product and will decrease the length of time that a subject is exposed to a potentially unhelpful new agent. Second, it may be beneficial to clinicians in that very soon after starting a treatment, a clinician may be able to predict which patient will have a beneficial outcome. Finally, it is important to note that we maximized our dichotomous surrogates using correct classification. We did this because in a clinical trial, it is important to determine both who will and who will not heal. It is possible in clinical practice that the penalty for misclassifying a patient as healed or unhealed is not the same. For these situations, it might be necessary to recalibrate the dichotomous surrogates based on either the positive or negative predictive value.

As with every cohort study, there are many potential limitations to the validity of this study. Most importantly, the correct classification for the surrogate markers was not 100%. Therefore, by week 4, we are not able to fully predict who will heal by the 12th or 20th week of receiving standard care for a neuropathic diabetic foot ulcer. Unfortunately, at this time, we know of no other surrogate that has better statistical properties or that has been tested in as large and diverse a dataset. In addition, most other accepted surrogates (e.g., blood pressure measurement, cholesterol measurement, HIV viral load) have statistical characteristics that are far worse than what we report in this study (24,25). Another potential limitation is that we did not account for the depth of a wound or the shape of a wound. However, measurements of depth increase the "end-user complexity" of the surrogate, and it is likely that our log transformation compensates for irregular wound shapes (3). While some argue about what clinical and statistical characteristics should be present in a surrogate, it is hard to dispute our surrogates because they all naturally occur as a wound improves (11,12). In fact, some might argue that our surrogates are really intermediate end points (12). It should be noted that our surrogates have not been validated in a population different from the one from which they were derived. However, as stated above, there is no larger and more diverse a database for chronic wounds than the one we used. Finally, CHS health care providers follow specific patient treatment algorithms. While it is unlikely that all providers use

exactly the same standard therapies and methods to off-load a patient's wound, our inability to find important center-based effects implies that center variation has minimal effect on the likelihood of a wound healing and on our surrogate measures (17,19).

In conclusion, we have demonstrated in a large diverse patient population that the percentage change in area, log healing rate, and ratio of log areas at the 4th week of care can all be used as surrogate markers of complete wound healing for 12 or 20 weeks of care for a patient receiving standard therapy for neuropathic foot ulcer in a CHS wound care center. The size and breadth of the CHS population suggest that these results will generalize to the greater population of patients with a diabetic neuropathic foot ulcer. The surrogate markers that we report can be easily applied by clinicians because the surrogate percent change requires minimal mathematical computation and the measurement of the wound is part of routine clinical care. Correctly classifying patients with neuropathic diabetic foot ulcers into those who will heal or not heal by the 4th week of care has important implications when studying new wound healing therapeutics and for those health care providers managing diabetic neuropathic foot ulcers with standard therapy.

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