

Healing of Diabetic Neuropathic Foot Ulcers Receiving Standard Treatment

A meta-analysis

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OBJECTIVE — The aim of the study was to determine the percentage of individuals with neuropathic diabetic foot ulcers receiving good wound care who heal within a defined period of time.

RESEARCH DESIGN AND METHODS — We conducted a systematic review of the control groups of clinical trials that evaluated a treatment for diabetic neuropathic foot ulcers. The meta-analytic techniques used include an estimation of the weighted mean percentage healed by end point, an evaluation of the homogeneity of trials, and an estimate of the 95% CI of the grouped data. Grouped-data univariate and multivariate logistic regression was conducted to assess the impact of mean age, ulcer size, and duration on the percentage of ulcers healed at end point.

RESULTS — We found a total of 10 control groups meeting our criteria. Six control groups used 20 weeks as the end point for healing or nonhealing. For the six control arms with a 20-week end point, we found a weighted mean healing rate of 30.9% (95% CI 26.6–35.1). A similar analysis for the four 12-week arms found a mean healing rate of 24.2% (19.5–28.8). We failed to detect any statistically significant heterogeneity for either the 20-week or the 12-week trials.

CONCLUSIONS — After 20 weeks of good wound care, ~31% of diabetic neuropathic ulcers heal. Similarly, after 12 weeks of good care, ~24% of neuropathic ulcers attain complete healing. Further patient-level analyses are necessary to definitively determine the associations of age, wound size, and wound duration with likelihood of healing.

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Neuropathic foot ulcers are a serious complication of diabetes (1,2). At least 15% of people with diabetes will eventually develop a lower-extremity ulcer of some sort (3). Neuropathic foot ulcers arise in part as a result of impaired sensation in the lower extremity (4). By definition, these ulcers present within the context of arterial perfusion adequate for wound healing (5). Neuropathic foot ulcers generally

do not respond well to treatment, and several novel treatment modalities have been proposed over the past few years (1,6–8). Limbs with nonhealing neuropathic ulcers may eventually require amputation. Individuals with lower-limb amputations are at risk for developing concomitant medical ailments, report a diminished quality of life, and are more likely to die than other individuals with diabetes (9).

Patient compliance is critical to stopping ulcers from progressing to the state at which amputation is necessary. Being able to provide patients with a realistic estimate of their chances of healing within a set time period may increase the likelihood that they will comply with treatment (10). For health care providers, knowing that a wound will take several months to heal allows for a realistic allocation of financial and medical resources (2). Furthermore, this knowledge is particularly useful in developing clinical studies, where calculations of sample size are contingent upon knowing what percentage of ulcers may be healed by the study end point (11).

The purpose of this investigation was to determine the percentage of individuals with neuropathic ulcers receiving good wound care who heal within a set period of time. To that end, we conducted a systematic review of the control groups of randomized clinical trials that evaluated a treatment for neuropathic ulcers. The meta-analytic techniques (12) used include an estimation of the weighted mean percentage healed by end point, an evaluation of the homogeneity of the proportions healed in each trial, an estimate of the 95% CIs of the combined data, and an assessment of the effects of mean age, wound duration, and wound size on the percentage healed by the trial end point.

RESEARCH DESIGN AND METHODS

Data sources

We conducted a search on Medline using the search term “diab\$ and (ulcer\$ or wound\$) and (heal\$ or treat\$).” This search was not restricted by language or publication date, and it yielded 1,575 articles. We also searched CINAHL and Cochrane Reviews using the same search term. The results of all searches were evaluated manually. Leaders in the field and the appropriate individuals at selected pharmaceutical companies were also contacted to inquire about studies that may not have been published.

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

Study selection

We examined the control arms of these studies to estimate the likelihood of healing of neuropathic diabetic foot ulcers using a standard care regimen.

We used several strict inclusion and exclusion criteria in our analysis. All wounds had to be of neuropathic origin. Wounds were defined as neuropathic when they were present in an individual with adequate limb perfusion, which was determined by having a transcutaneous oxygen pressure >30 or an ankle-brachial index >0.7 (13). We included only the control arms from randomized controlled trials (i.e., nonexperimental studies were excluded), and trials must have reported the percentage of wounds healed after a set treatment duration (the study duration). We excluded studies whose control population explicitly included patients with infected wounds and those that did not include debridement as part of their standard protocol. We also included only those studies that explicitly instructed patients on the importance of avoiding weight bearing on the affected limb. Wound care was either saline moistened gauze or placebo gel and gauze.

Statistical analysis

To maximize information from the analyzed studies, the percentages of ulcers healed at 20 weeks and at 12 weeks were estimated using the weighted mean of the studies' results. CIs were estimated using the normal theory method for obtaining a CI for a binary parameter (11,12).

Random effects and fixed effects logistic regression models were used to evaluate the homogeneity assumption and to assess the impact of mean age, ulcer size, and wound duration on the percentage of ulcers healed at the 12- and 20-week end points. Ultimately, group logistic regression was reported to assess the impact of mean age, ulcer size, and duration on the percentage of ulcers healed at end point.

Statistical analyses were conducted using Stata for Windows 95 version 5.0 (Stata Corporation, College Station, TX).

RESULTS — Only nine studies met all our inclusion and exclusion criteria (1,6–8,14–18). Six of these studies were published (1,6–8,14,15), and three studies were unpublished Food and Drug Administration drug trials (16–18). One of the studies (17) included two control groups, one treated with saline gauze and one

Table 1—Summary of clinical trials included in the meta-analysis

Study	Trial duration (weeks)	Number of controls	Standard treatment	Percent healed at end point
Steed et al. (14)	20	6	Saline gauze covered with vaseline gauze; totally non-weight bearing	16.7
Richard et al. (6)	18	8	Saline and vaseline gauze; not given footwear	62.5
Steed et al. (15)	10	25	Saline gauze covered with vaseline gauze; given shoes and inserts	8
Steed et al. (8)	20	57	Placebo gel and wrapped; instructed on pressure relief	25
Gentzkow et al. (7)	12	13	Saline gauze; no footwear given	8
Dermagraft trial (16)	12	126	Saline gauze; received shoes with inserts	31.7
Wieman et al. (1)	20	127	Placebo gel and wrapped; off-loading weight	35
Becaplermin #3 (17)				
Placebo gel	20	70	Placebo gel and wrapped	36
Good wound care	20	68	Saline gauze	22
Becaplermin #4 (18)	20	122	Saline gauze	32

treated with placebo gel, and these two control groups were evaluated separately. The bulk of studies were excluded from our analysis because they were not randomized clinical trials; they failed to include an end point defined by percentage of wounds healed at the conclusion of the study; or they failed to establish that all wounds were of neuropathic origin.

We thus found a total of 10 cohorts meeting our criteria (Table 1). Six of these control groups used 20 weeks as the end point for healing or nonhealing. Two used 12 weeks, one study adopted 18 weeks, and one study used 10 weeks as an end point. We were able to determine the percentage healed at 12 weeks using data from two of the 20-week studies that included graphs of percentage healed by week (1,8), thus providing us with four 12-week studies for analysis. All studies presented their results as percentage of wounds healed before the conclusion of the study.

For the six cohorts with a 20-week cutoff, we found a weighted mean healing rate of 30.9% (95% CI 26.6–35.1%). A similar analysis for the four 12-week arms found a mean healing rate of 24.2% (19.5–28.8%) at 12 weeks. The assumption of homogeneity of proportion healed was not rejected for either the 20-week or the 12-week trials using fixed effects or random effects logistic regression models

(12). Although data for 10 and 18 weeks were too sparse to merit a full statistical analysis, it is worth noting that as would have been expected, there was a lower percentage healed at these times than at 20 weeks.

Because all logistic regression models showed similar estimates of covariate effect, for simplicity we are reporting the estimates from the single variable group logistic regression model. Wound duration affected the chance of nonhealing in the 12-week cohort (odds ratio per week = 0.97 [95% CI 0.94–0.99], $P < 0.05$). In other words, there was a 3% reduction in the odds of attaining complete healing by 12 weeks for each week of wound duration (i.e., the age of the wound as reported by the patient before entering the study). We found for the 12-week and 20-week cohort that mean age and wound size, and for the 20-week cohort wound duration, had no effect on healing (Table 2).

CONCLUSIONS — Using group-level or study-level data, we found that 24.2% of diabetic neuropathic ulcers heal after 12 weeks of good treatment and that a total of 30.9% of ulcers heal after 20 weeks of good wound care. The percentage of wounds healed by 12 weeks may be affected by wound duration, but our group-level data suggest that wound duration, area, and size

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Table 2—Odds ratios as estimated by single-variable grouped logistic regression with 95% CIs of covariates that were available in all of the studies that might have affected an individual's odds of healing at either 12 or 20 weeks

Covariate	12 weeks	20 weeks
Age (years)	1.20 (0.79–1.82)	1.13 (0.69–1.84)
Wound size (cm ²)	0.90 (0.78–1.04)	0.93 (0.82–1.04)
Wound duration (weeks)	0.97 (0.94–0.99)	0.98 (0.96–1.01)

do not significantly affect the percentage of wounds healed at 20 weeks. The studies used for the analysis were control arms of randomized clinical trials evaluating the treatment of diabetic insensate foot ulcers. In fact, the percentage-healed data are similar (i.e., homogeneous) across the trials. This is itself interesting, as it suggests that there may be a relatively standardized rate of healing of diabetic foot ulcers when treated with good wound care.

The percentage healed at 12 weeks may be wound duration dependent, because according to logistic regression techniques, the mean ulcer duration is a risk factor for nonhealing by 12 weeks. That is, ulcers of longer duration were associated with a lower percentage healed at 12 weeks. This effect was not seen at 20 weeks. It is possible that by 20 weeks the effect of wound duration on percentage of ulcers healed is obviated by the longer treatment period. No other trends were found, but future "patient-level" analyses might be helpful to conclusively determine the impact of wound area, duration, and patient age on percentage healed at 12 and 20 weeks.

One important application of the results of this study is in clinical trial design (11). Determining the necessary sample size for a trial requires the investigator both to estimate the baseline rate of healing with placebo and to postulate the effects of the drug being investigated. Knowing the baseline healing rate with placebo helps to determine how many patients need to be enrolled in a study (11). For example, let us say that we wish to test a novel treatment that is postulated to heal 40% of diabetic neuropathic ulcers at 20 weeks. We want our sample to have a significance level (α) of 0.05 and a power ($1-\beta$) of 80%. We may then use a formula or computer program to find the sample size needed to compare two binomial proportions in a clinical trial setting (11). If we assumed (incorrectly) that 20% heal by 20 weeks with standard treatment, then we would calculate that 82

people are needed in each group to detect the improvement to 40%. If we know that baseline healing is 31% at 20 weeks, however, then we can calculate that 443 people are needed in each group to adequately assess the effect of the novel treatment. Therefore, an underestimation of baseline healing rates would lead to the development of underpowered clinical trials. Similarly, an overestimation of baseline healing rates would lead to trials that enroll large numbers of patients unnecessarily. Knowing the percentage of wounds healed with good wound care alone therefore has important implications for the design and execution of clinical trials, and knowledge of such baseline data may allow for the development of more powerful and cost-effective clinical trials in the future.

There are several potential limitations to this study. First, as with all meta-analyses, the quality of the data is only as good as the validity of the data collection and reporting of the individual studies. Second, because the unit of analysis was the study group, the power to detect the influence of a risk factor (e.g., wound size or wound duration) on the failure of a patient to heal was limited by both the unit of analysis (e.g., the study group) and the scope of publication (e.g., risk factors and end points reported in all studies). These limitations may have affected the quality of the estimates reported in our study. If full access to all of these studies were available, then an analysis of patient-level data would help to evaluate this limitation. Still, the lack of heterogeneity between all the studies included in this meta-analysis suggests that despite the almost infinite number of variables that are associated with wound healing, the percentage healed at 12 and 20 weeks remained relatively constant across all the studies. Finally, patients choosing to enroll and health care providers choosing to participate in randomized clinical trials may not be the same as the general population. This limitation could affect the generalizability of our study. However, to our

knowledge, this is the first meta-analysis that has evaluated the expected results of treatment of insensate diabetic foot ulcers, and the results in our study appear to be homogenous among the studies evaluated.

In summary, ~30% of individuals with a neuropathic diabetic foot ulcer will heal within 20 weeks of commencing good care. This benchmark allows health care providers to provide patients with a realistic assessment of their chances of healing and provides information useful in clinical trial design. Still, these data are compiled from studies where wound-care specialists treated patients. It may also establish for regulatory agencies and managed care corporations a benchmark for what percentage of wounds should be healed within a set time period. Although these data should be largely generalizable, particularly because they are internally homogenous, it is possible that the patient population of these studies does not mirror that seen in many practices. Future patient-level analyses, multicenter prospective cohort studies, and population studies are necessary to provide more detailed information to better assess the impact of patient age, wound area, wound duration, and other risk factors on the percentage of wounds healed at 20 weeks.

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