The American Journal of Surgery®

The American Journal of Surgery 188 (Suppl to July 2004) 73S–78S

Statistical analysis of wound-healing rates for pressure ulcers

Sylvan Wallenstein, Ph.D.[a,*], Harold Brem, M.D.[b]

[a]*Department of Biomathematical Sciences, 1 Gustave Levy Place, Box 1023, Mount Sinai School of Medicine, New York, New York 10029, USA*
[b]*Department of Surgery, Columbia University College of Physicians & Surgeons, New York, New York, USA*

Abstract

To establish a functional model for determining wound-healing rates to use in the evaluation of efficacy of wound therapies, a review was conducted of statistical analysis methods from past wound-healing studies. Because most wounds do not usually close within the period of observation, that is, 12 weeks, evaluating time to 100% closure is not practical. Thus, a new, practical model for statistical analysis was formulated. A Gompertz-like function was applied to wound-healing rates of pressure ulcers, in the context of repeated measures for a nonlinear model. Photographing the wounds weekly, tracing their area with planimetry, and applying this new statistical model allows for the calculation of the expected rate of healing as a function of time. This approach yields a model useful for identifying prognostic factors, evaluating treatments, and improving our understanding of the variables that affect the wound-healing process.

Several statistical methods for quantifying the rate of wound healing have been documented in wound-healing studies [1]. These methods can be used to identify prognostic factors that might be associated with changes in the rate of wound healing and are suggested for use in future studies of drug intervention to accelerate the rate of wound healing. Determination of wound-healing rates has been addressed in wound literature for a considerable time [2–4].

The importance of using wound-healing trajectory as an outcome has been established in acute wounds [5]. However, acute wound-closure rates are not easily compared with chronic wound closure rates. In this original report, statistical methods for estimating a healing rate of a specific type of chronic wound in a heterogeneous patient population are discussed. We focus on analyzing the normalized wound size, that is, $Y(t)$ = wound area (time t)/ wound area (baseline). $Y(t)$ has a lower bound of 0, which corresponds to a closed wound, with no upper bound (other than that forced by the human body). The value of $Y(t) = 1.0$ corresponds to no change, values between 0 and 1 correspond to improvement, and values >1 to deterioration.

To estimate healing rates, patients are followed periodically (eg, weekly). These measurement times are denoted as $t = 1$, $t = 2$, and so forth, and the corresponding normalized wound areas, $Y(1)$, $Y(2)$, and so forth, are viewed as a particular case of what statisticians call "repeat measurements." In the last 2 decades, there has been a huge increase in the statistical literature regarding analysis of repeat measurements. The problems that were overcome include unequal numbers of observations per patient and allowing for a decreased correlation between observations over time. Use of random effects or hierarchical models allow each of the subjects to have his or her own value for the rate of decline. Apparently, these methods of repeat measurements analysis are not commonly used in the context of wound healing.

Wound measurements have additional issues that require more consideration before these newer methods of repeat measurements analysis can be used. The problem of a wound-healing rate is different from that of other statistical applications in that within a "short" period many wounds will close, and ideally, after such an event, no further progress in terms of wound size is possible. The mirror image of this dilemma is that if the outcome is percent change in the wound size, some unusually large increases in wound size are also possible. Either event causes analytic difficulties and problems of unduly influential observations.

In this report, we focus on a Gompertz-like wound-healing model, which has been suggested in the wound literature as an appropriate method to model wound size against time.

* Corresponding author. Tel.: +1-212-241-1526; fax: +1-212-212-860-4630.

E-mail address: sylvan.wallenstein@mssm.edu

This work was supported in part by the United Spinal Association and by Grant No. DK059424 from the National Institutes of Health.

0002-9610/00/$ – see front matter
doi:10.1016/S0002-9610(03)00294-0

Methods

Use of wound size as an outcome

We suggest that wound size in addition to time to closure is a meaningful outcome and that this outcome is best analyzed by focusing on percent reduction in the wound area. We then use a single value to quantify the rate of wound healing for each patient. Different interventions could be evaluated by comparing these wound-healing rates.

When a drug is being tested for efficacy in randomized placebo-controlled studies, the time to 100% closure in the control versus treatment group is an accepted indicator. This type of statistical analysis was used for the 3 US Food and Drug Administration (FDA)–approved treatments for diabetic foot ulcers (Regranex, Ortho-McNeil Pharmaceuticals, Raritan, NJ [6–8]; Apligraf, Organogenesis, Canton, MA [9,10]; and Dermagraft, Smith & Nephew, Hull, United Kingdom [11,12]). This method was also used in approving Apligraf for treatment of venous stasis ulcers [13–15]. However, for examining healing in other types of wounds, for example, the rate of healing of other chronic wounds (such as pressure ulcers), different analyses are required, because the time to 100% closure is not observed in many subjects.

Often, those who study wounds automatically focus on time to 100% closure. As simple as it sounds, methods for finding time to closure should be limited to when one is specifically trying to ascertain this. In the case of pressure ulcers and other types of wounds, an equally pertinent question is, What is the rate of healing? There are no drugs approved by the FDA based on efficacy for pressure ulcers; therefore, a fundamental, practical question is, What rate of closure should be expected for a pressure ulcer? A healing wound, as measured by decreased area, is one that eventually closes. Therefore, the clinical issue is what patients and a clinical staff should expect to be the rate of healing. Answering this question is important for 2 reasons: (1) to help guide clinical therapy or, specifically, when a change in a treatment regimen should be made, and (2) to evaluate new therapies.

Reasons for using wound area

The size of a wound can be either inferred or measured qualitatively. One example of the former is the histomorphologic scale. Although such a scale can be useful, it is not highly correlated with gross appearance of the scar, which limits its clinical validity and relevance [16].

If we base our outcome on physical measurement, we can choose among (1) volume, (2) area, or (3) 1-dimensional outcome, such as diameter or perimeter. Volume is not easily measured objectively, because use of gel or some other complex and nonreadily reproducible or practical method is needed to acquire an accurate measurement. Area is therefore the most relevant, objective, reproducible value for determining whether the wound is healing.

Analyzing the ratio of area to perimeter is another concept used to describe wound healing [17–20]. Investigation would be required to determine whether, in a particular data set, such an outcome would be useful. However, because we have not as yet measured the perimeter, these methods are not applicable.

How do we measure area?

The easiest, most direct method of documenting wounds is by area. Wounds are measured (length, width, and maximum depth) weekly. Our study used planimetry to calculate wound area. The planimetric computer programs currently available allow one to trace the perimeter of the wound image with a mouse and then compute the area the way in which one counted the squares on a grid transparency in the past [21]. This procedure works well, even for the most irregularly shaped wounds.

Currently, instruments for measuring the size of wounds show little variation in accuracy [1]. The highest precision of area and volume measurements can be obtained, thanks to the advent of recent technology, with digital videometry [22,23]. Nonetheless, use of planimetry has been shown to have good intrarater and interrater reliability. Planimetry is also more cost-effective and less cumbersome than the digital approach, thus making it a good choice for clinical practice [23].

Scaling the area

After we have selected a physical measurement, such as area, the rate of change can be evaluated on (1) original measurement scale, (2) transformation of original scale, and (3) percent of baseline (or nearly equivalently, percentage reduction).

Analyzing the area according to the original measurement scale, given its wide variability, is not universally appropriate. For example, a reduction of 2 cm^2/wk might be significant for a large wound and exceed the size of a small wound.

Transformations are often used in such cases. For example, the log transformation would allow one to evaluate percent change directly. However, this transformation is not applicable because of the presence of closed wounds that involve the undefined log(0). Adding a small constant circumvents the technical issue but leaves open the question of what constant to use. Moreover, transformations can be difficult to interpret.

We prefer to analyze the percent of baseline area, because it is easy to interpret and is easily interpretable for wounds of any size. Thus, the approach is consistent with Robson's observation [24], which considers the premise that wounds "are normalized by using a fractional decrease in wound size or percentage closure to be consistent with

the analysis of chronic wounds that vary greatly in size" [25]. However, we do not recommend prespecified end points, such as 50%, 75%, or 90% closure, but rather prefer to look directly at percentage differences, which by itself is a relevant clinical end point.

Area–time relations: previous approaches

In 1916, Carel and Hartmann [2] performed an extensive evaluation of wounds on men and on guinea pigs. They observed that the rate of cicatrization of a wound is greater at the beginning than at the end of the period of repair. Du Noüy [3] quantified this finding, suggesting a function predicting area of the wound based on time and square root of time that yielded results consistent with the experimental findings noted above.

Gorin et al [20] proposed a method that evaluated the rate of healing based on area but assumed a linear relation between wound size and time. A linear relation would ultimately predict negative wound sizes and therefore has rather restricted functionality.

Another possible model assumes that the normalized wound area decays in an exponential fashion. Formally, one assumes $Y_i(t)$—the normalized area for patient i at time t—decays with time t as $Y_i(t) = \exp(-t\beta_i)$.

We do not use this exponential model because of problems of modeling data for patients whose wounds increase in size. The exponential model postulates that either the wound will close or the wound size will increase to infinity, which is unrealistic.

A Gompertz model for area–time relation

Although the Gompertz distribution was originally proposed and still is primarily used to evaluate the length of life or survival in general [26], it has a history of also being used as a growth curve [27]. Hokanson et al [4] applied the model to healing of wounds, in a slightly different context than here.

As with the other area–time relations described above, we use a single value to capture differences in healing rates between patients. Our model accommodates those whose wounds heal completely, as well as those whose wounds fail to decline in the period of the study. We describe the changes in wound size by a single value, β. For a certain range of values (typically $\beta < 0$), the wound size ultimately declines to 0. The magnitude β determines how soon that wound will be near closure. For another range of values (typically $\beta > 0$), the wound size increases to an arbitrarily set ceiling, a doubling of size, in this particular model. In that case, β might be used to measure the increase at wound size at, for example, 1 month.

Our proposed model expresses the normalized area (percent of baseline) for patient i at time t as $Y_i(t) = \exp\{0.69[1 - \exp(-t\beta_i/0.69)]\} + \epsilon_i(t)$. Here, β_i is the quantity that summarizes a patient's improvement. The model has been constructed (with the repetition of the 0.69) so that β_i is the rate of closure, at least near time 0 and possibly over a considerable length of time. The equation $0.69 = \ln(2)$ implies the maximum percent change is 200%. Values slightly in excess of 200% can be ascribed to measurement error. We discuss below appropriate actions when increases well beyond 200% are noted in the data.

Figure 1 plots the Gompertz-like curve when β_i takes on values ± 0.1, ± 0.2, ± 0.5, ± 1.0, and where time varies from 1 to 8 weeks. The curve has 2 mirrorlike properties depending on whether β_i is, or is not, positive. When β_i is negative, the curve decreases in time, starting in a linear manner, and approaches an asymptote of 0. When β_i is positive, the curve increases in time, starting in a linear manner, and approaches an asymptote of 2. It is a mirror image of the case when β_i is negative. In this respect, our model differs from an exponential model, which would portray the wound size as increasing at a faster and faster rate over time.

Our proposed model has 2 random components of variability. The first source of variability concerns the different rates of healing in people relative to the mean healing rate and reflects the anticipated large differences in individual healing abilities. The second source of variability is a random error, $\epsilon_i(t)$, at each measurement point. These measurement random error terms are assumed to be independent from time to time and from person to person.

Results

A total of 45 consecutive hospitalized patients with stage II or III pressure ulcers were studied. They were selected from a larger subset and had 2 exclusions: (1) stage IV pressure ulcers, and (2) wounds with initial size <2.0 cm^2. These 2 groups were excluded because the variability in the clinical presentation, as well as progression of the wounds, is too great for this model to be applicable. Consent was obtained from every patient and the institutional review board approved the study. Standard protocols were used and no topical or systemic agents were being evaluated. The primary purpose of the study was to measure the rate of healing for pressure ulcers.

Examination of Figure 2 indicates that many wounds show excellent improvement but that some heal slowly, waver around initial size, or increase in size, but never dramatically so. Before applying our model, we examined whether there were any wounds that more than doubled in wound size area at any time. As indicated (Fig. 2), we found only 1 such case, a transient increase at weeks 3 and 4 to 2.2 and 2.0, which was preceded and followed by values in the 1.5 to 2.0 range. Thus, we thought that the model could be fit to the observed data so that we could get an overall rate of decline and have the potential then to determine which baseline characteristics are associated with faster rather than slower healing.

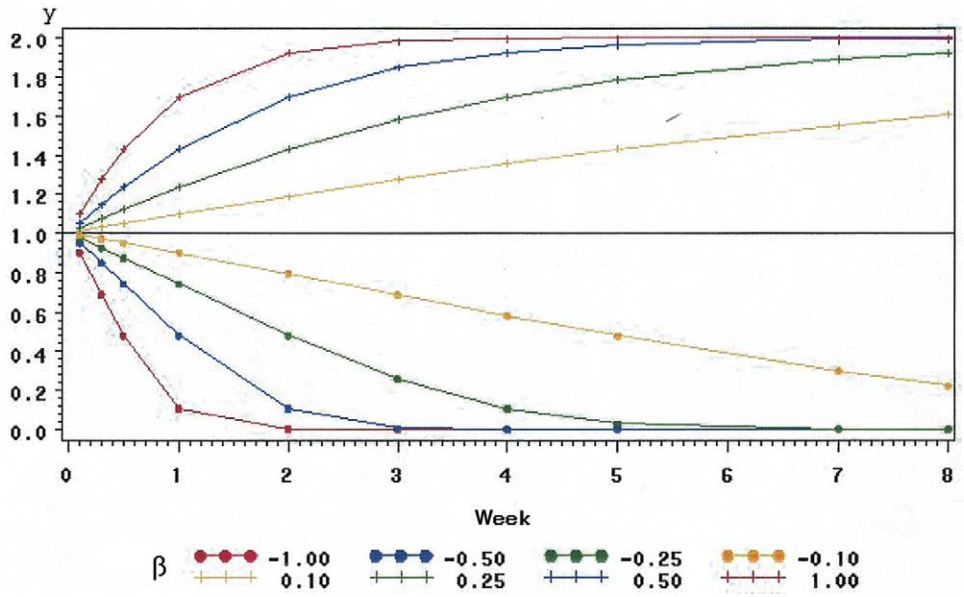

Fig. 1. The idealized Gompertz curve for 8 different values of β. Each joined figure plots normalized wound size against time.

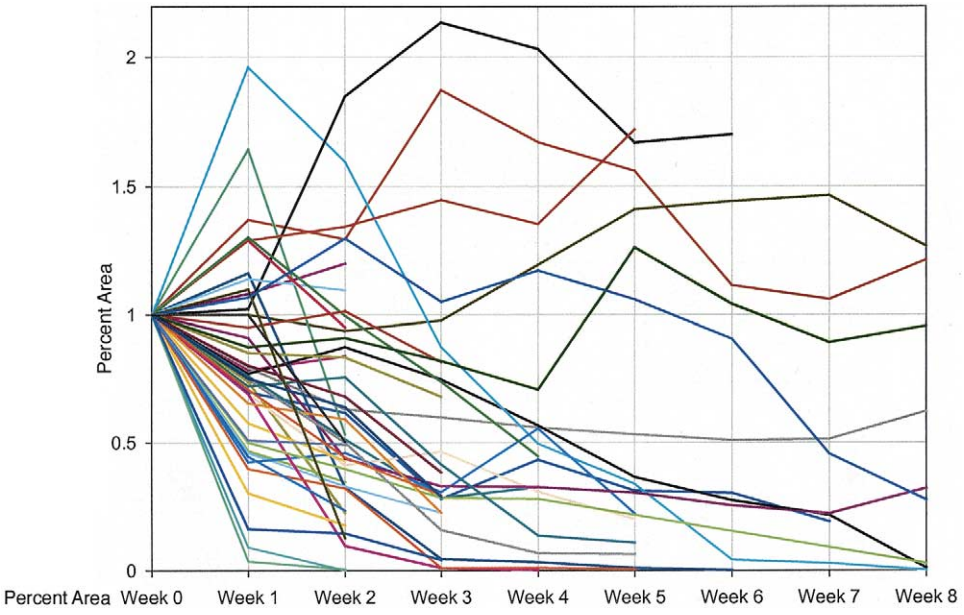

Fig. 2. The normalized wound sizes (ratios of observed areas to baseline areas) against time for each patient in the study.

Discussion

Only recently have FDA-approved therapies been approved to accelerate healing. Our model allows one to conduct the next step, that of evaluating the effects of different characteristics or interventions on wound size. This model would be suitable for randomized and nonrandomized clinical trials and has the ultimate purpose of assessing the effect of various interventions.

Our proposed model implies that, ignoring measurement error, a wound would at most double in size. Wounds that show a slightly greater increase than doubling in size do not cause any particular problems, because the values >2 are ascribed to measurement error. As noted in the Appendix, if there are a few values much larger than 2.3, the model can be used after truncating these values to 2.3. One would then describe the percentage of times that wounds that more than doubled in size were noted and possibly examine, formally or informally, whether such changes were related to any covariates of interest. If truncation were applied, one would reinterpret average changes and effects of covariates in light of a ceiling on the increase. Alternatively, as described in the Appendix, one can change the "ceiling" in the model.

Our proposed model implies that ignoring random vari-

ability, a wound will either decrease continuously in size until it is healed or, alternatively, increase continuously in size until it reaches a ceiling. However, as noted in Fig. 2, it is not required that individual data exhibit such a pattern. Our model could not suggest a pattern of increases followed by decreases (or vice versa). Plotting differences between observed and predicted values would visually suggest such a pattern.

In practice, debridement presents a difficulty for any model, because it causes a wound to increase in size before contraction. Thus, data collection would stop before debridement, or possibly debridement could be added as a time-varying covariate. Other potential interventions, such as evaluation of antibiotics, nutrition regimens, and multiple topicals could be handled similarly.

It is also important to acknowledge that in any statistical analyses of healing that no single drug or intervention alone will heal a wound. Growth factors, cellular therapies, bed surfaces, age, diabetes mellitus, and other contributing factors may have a significant impact on healing a chronic wound but even when addressed will not result in 100% healing.

Conclusion

Our new statistical model provides a relevant method to detect prognostic factors and evaluate interventions in the context of wound healing. Positive features include (1) a single variable with a physical interpretation that summarizes data from an individual patient, (2) a model that works well for wounds that close, and (3) a model that is not overly influenced by wounds that deteriorate. This statistical model is useful to study which interventions can contribute to faster healing of wounds.

Appendix

In our proposed Gompertz model, ceilings other than 2.0 could be used by changing the 0.69 in the model to c, which would result in a ceiling of $C = e^c$. Ideally, it would be preferable to eliminate any such ceiling and replace the Gompertz function in our model by a function that has a noninfinite upper bound that is a function of the value of β. We have not been able to construct such a model that also has the other features we have incorporated. Alternatively, we obviously could let the model choose C, which presumably would be near the observed maximum, but prefer not to do so. As suggested in the text, if the Gompertz model is used with values higher than the ceiling + 1.5s, where s is an estimate of ϵ, then these large values should be truncated and the results interpreted in light of truncation. In the text, we assumed that with our model, this truncation level was 2.3.

Software to estimate the parameters of the model is evolving rapidly. We used PROC NLMIXED of SAS (Statistical Analysis System, version 8; SAS Institute, Inc, Cary, NC) [28] to analyze the data set. Slight changes in various computational options can be helpful in the convergence of the procedure. In this particular run, we used the default options with addition of a METHOD = FIRO option, which approximates the integral of the likelihood over the random effects using the first-order method of Beal and Sheiner [29]. The actual statements used in SAS were:

```
proc nlmixed data=notstage4 method=firo;
  parms b=−0.1 sb=0.1 s2=0.2;
  beta=b+bran;
  pred=exp(log(2.0) * (1−exp (−β*week/log(2.0))));
  model ratio ~ normal (pred,s2);
  random bran~normal (0, sb) subject=id;run;
```

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