The influence of wound geometry on the measurement of wound healing rates in clinical trials

Daniel R. Gorin, MD, Paul R. Cordts, MD, Wayne W. LaMorte, MD, PhD, MPH, and James O. Menzoian, MD, *Boston, Mass., and Honolulu, Hawaii*

Purpose: The comparison of wound healing rates in clinical trials presents a challenging problem. Wound healing typically has been expressed as a change in area over time or a percent change in area over time. These methods are inaccurate, however, when applied to wounds of varying size and shape. A relatively small amount of healing in a large wound will produce a greater change in area than in a smaller wound. Conversely, measurement of the percent change in area of a wound will tend to exaggerate the healing rates of smaller wounds. A method of calculating average linear healing of the wound edge toward the center of the wound has been proposed that should not be influenced by wound size: $D = \Delta A \div \overline{P}$, where D = linear healing, ΔA = change in area, and $\overline{P}$ = mean perimeter. The purpose of this study was to examine linear healing of the wound edge as a method of measuring wound healing in clinical trials.

Methods: We observed 39 patients with venous stasis ulcers. The area, perimeter, length, and width of each wound were calculated with computerized planimetry. Change in area per day and linear healing rate of the wound edge per day were calculated. Multiple linear regression analysis was used to explore factors that influence wound healing as measured by these methods.

Results: The change in area per day was significantly and independently influenced by initial area ($p < .0001$), perimeter ($p < .0001$), length ($p < .00055$), and width ($p < .0175$). Linear healing per day was not influenced by any geometric variable, including area, perimeter, length, width, and ratio of width to length.

Conclusion: Linear healing per day is a valid means of comparing wound healing rates in wounds of different dimensions. Linear healing per unit of time should be preferred to measurements of change in wound area to quantify wound healing rates in clinical trials. (J VASC SURG 1996;23:524-8.)

A variety of methods has been used to calculate wound healing rates in clinical trials. Most commonly a measure of the change in two-dimensional area of the wound is used and is expressed either as a raw number (cm^2) or as a percentage of initial wound area. These measurements are usually given per unit of time (such as area healed/week or % area healed/week). Less frequently, complete wound healing is used as an endpoint in wound healing studies. This is quantified either with the time until total healing of each wound or by calculating the percentage of wounds that healed during the study time. Fig. 1 shows the methods of comparing wound healing rates used in a random sample of 20 double-blind prospective trials on leg-ulcer healing published in the recent literature.

The use of total wound healing as an endpoint in clinical studies has several drawbacks. Wound healing is often a lengthy process; observing wounds until they completely heal is cumbersome and frequently takes an inordinate amount of time. In addition, the time a wound takes to heal may be largely dependent on its initial size. It seems intuitively obvious that a smaller wound will take less time to heal. The literature is inconclusive on this point. Stacy et al.[1] found no correlation between initial wound size and

From the Department of Surgery, Division of Vascular Surgery, Boston University School of Medicine; and the Department of Vascular Surgery, Tripler Army Medical Center, Honolulu (Dr. Cordts).

Presented at the Seventh Annual Meeting of the American Venous Forum, Fort Lauderdale, Fla., Feb. 23-25, 1995.

Reprint requests: James O. Menzoian, Department of Surgery, D-5, Boston University Medical Center, 88 East Newton St., Boston, MA 02118.

0741-5214/96/$5.00 + 0 **24/6/68963**

complete wound healing in a prospective trial of 99 leg ulcers. Skene et al.[2] in a study of 200 patients, however, found that a smaller initial wound area with shorter duration of ulceration and lack of deep vein involvement was a predictor of shorter healing time.

Calculations of wound healing rates on the basis of area are also inaccurate when wounds of differing size and shape are compared. Figs. 2A to 2C show calculations of the healing rates of two different-sized wounds by total area healed and by percentage of area healed. A relatively small amount of healing in a large wound will produce a great change in total area when compared with a small wound. Conversely, measurement of the percentage change in area will tend to exaggerate the healing of smaller wounds.

Because clinical trials invariably include wounds with a great variety of sizes and shapes, a technique for measuring wound healing that is independent of wound geometry is needed. Snowden[3] examined the relative contributions of wound contraction and epithelialization in the healing of experimental wounds. He found that both factors occurred perpendicular to the wound edge in a predictable linear fashion. The sum of these two factors is the total linear healing of the wound edge toward the center of the wound. The rate of linear healing provides a good description of the overall wound healing rate. Gilman[4] proposed a method of calculating the linear healing of the wound edge as a function of wound area and perimeter. Gilman's equation, $D = \Delta A/\bar{P}$, where D = linear healing, ΔA = change in area, and $\bar{P}$ = mean perimeter of initial and final wounds, calculates the average distance that the wound has healed from the initial wound edge to the center of the wound. Fig. 2D demonstrates the use of this equation to show that the two different-sized wounds discussed earlier actually heal at the same rate.

Although linear healing of the wound edge occurs in a constant linear fashion in experimental wounds, clinical wounds are much more complex. We applied Gilman's equation to a series of clinical wounds to determine whether the calculated linear healing was affected by the size or shape of the wound.

METHODS

We retrospectively reviewed the records of 39 patients with 49 ulcers treated at the surgical clinics of Boston University Medical Center Hospital and Boston City Hospital. All patients had lower-leg wounds that were believed by the vascular surgeon in charge to be caused by chronic venous insufficiency. Wound area was recorded at each clinic visit by tracing the perimeter of the wound on a clear plastic sheet. All tracings were done by a vascular nurse specialist or vascular surgeon. In patients with more than one wound, an index ulcer was selected; this wound was traced on each subsequent visit. Ten patients returned to the clinic with new ulcers after having been successfully treated for their initial ulcer. In these patients, both wounds were included in the study. All wounds were treated with Unna's boot (Dome-paste; Miles; Elkhart, Ind.) or Duoderm CGF HD (ConvaTec; Squibb; Princeton, N.J.) plus compression (Coban wrap; 3M; St. Paul). Patients were observed for 7 to 105 days (mean, 49.3 days) and had an average of 4.5 visits (range, 2 to 10), with an average of 12.3 days between visits (range, 6 to 51).

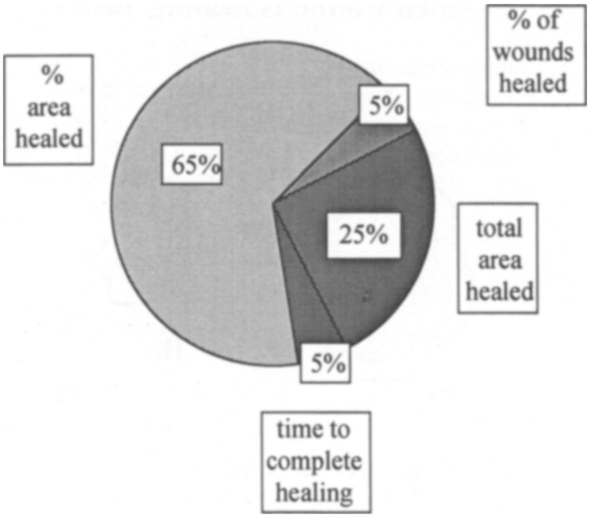

Fig. 1. Methods used to measure wound healing rates of chronic leg ulcers seen in random sampling of 20 prospective clinical trials reported in recent literature.

The wound tracings were entered into a computer with a digital scanner. The NIH Image program was then used to calculate the perimeter and area of each tracing planimetrically. In addition, a ratio of width to length (W/L) was calculated for each wound as a method of quantifying the shape of the wounds. A perfect circle has a W/L ratio of 1. The W/L decreases as the wound becomes more oblong.

Healing rates were calculated for each wound with two methods. First, the total area healed was determined by subtracting the final wound area from the initial wound area. This figure then was divided by the number of days that the patient had been observed, giving the total area healed per day ([initial area − final area]/days followed = area healed per day). Next the linear healing of the wound edge was

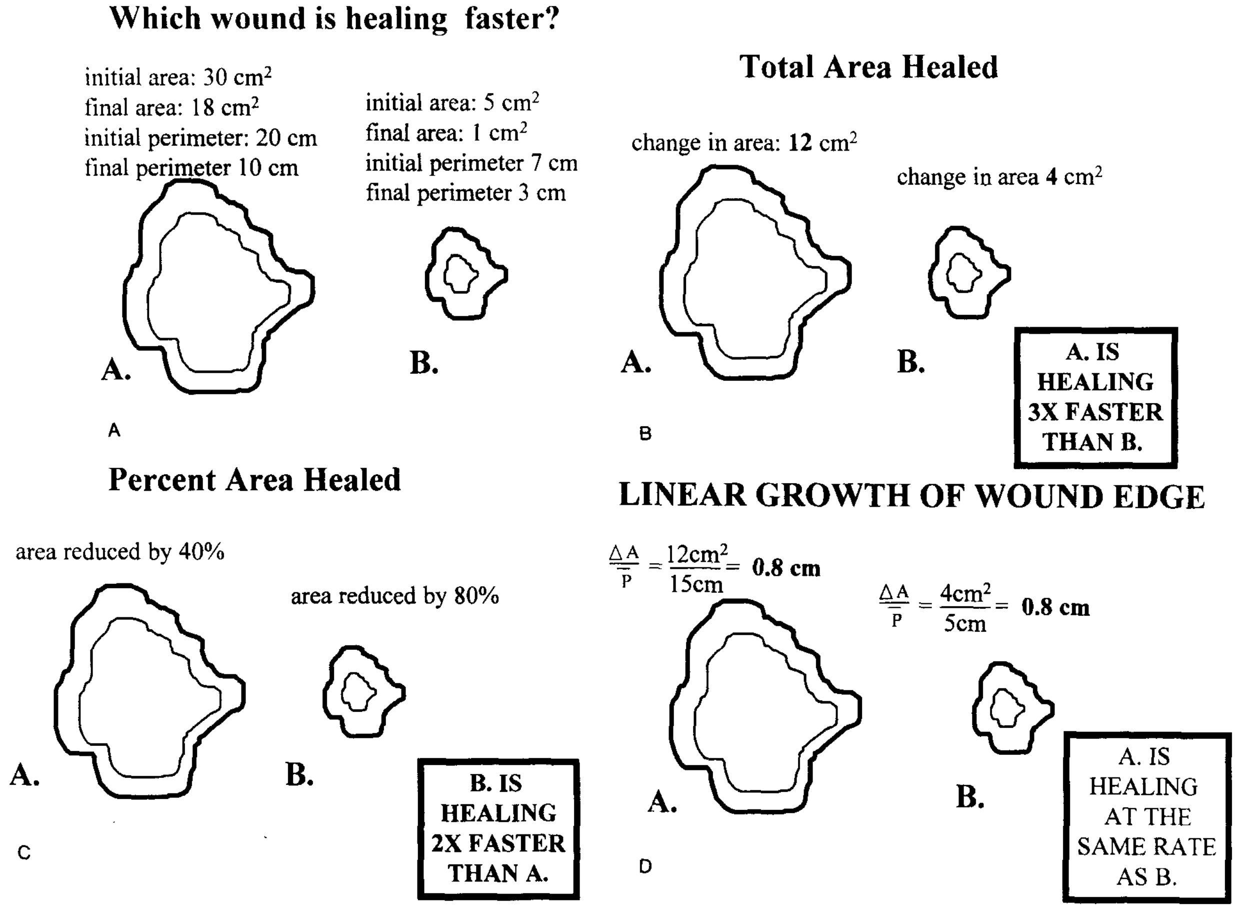

Fig. 2. **A,** Relative healing rates of two wounds pictured above vary depending on how rates are calculated. **B,** Healing rates expressed as change in total area; wound A appears to be healing at three times the rate of wound B. **C,** Healing rates expressed as percentage change in area; wound B appears to be healing twice as fast as wound A. **D,** Healing rates expressed as linear healing of wound edge; wound A and wound B are healing at the same rate.

calculated with Gilman's equation. This figure was also divided by the number of days observed to derive the linear healing of the wound edge per day.

All data were analyzed by Statistical Analysis System software licensed to Boston University.

RESULTS

Forty-nine wounds in 39 patients were included in the study. The wound characteristics are listed in Table I. The wide distribution of area, perimeter, and W/L is typical of a clinic population. Fourteen wounds healed completely. Eleven wounds enlarged and therefore had a negative healing rate. The mean area healed per day for the total population was 0.128 cm^2/day. The linear healing of the wound edge per day was 0.011 cm/day. Healing rates for the total group, the wounds with positive healing rates during the study, and the wounds observed >28 days are listed in Table II.

Regression analysis was used to examine the effect of wound area, perimeter, and W/L on the calculated wound healing rates. When healing was calculated as area healed per day, healing rates strongly correlated with the initial wound area (r = 0.80; $p < .0001$) and perimeter (r = 0.85; $p < .0001$). When healing was expressed as linear healing of the wound edge, however, no correlation with initial wound area (r = 0.18), perimeter (r = 0.26), or W/L (r = − 0.02) was found.

The mode of treatment (Duoderm vs Unna's boot) was known for all patients. Information on other risk factors, including sex, age, general health condition, skin condition, and the presence or absence of various other complications was available

Table I. Characteristics of ulcers at initial presentation

	Mean ± SD	*Range*
Area (cm^2)	10.47 ± 20.8	0.09 to 116.2
Perimeter (cm)	12.73 ± 11.6	1.63 to 60.8
Width/length ratio	0.58 ± 0.20	0.16 to 0.98

Table II. Wound healing rates

		Linear growth/day (cm)		*Area healed/day (cm^2)*	
	n	*Mean ± SD*	*Range*	*Mean ± SD*	*Range*
Total	49	0.011 ± 0.015	−.024 to .056	0.128 ± 0.333	−.738 to 1.74
Wounds with positive healing rate	38	0.016 ± 0.013	.001 to .056	0.200 ± 0.325	.001 to 1.74
Wounds observed >28days*	37	0.010 ± 0.011	−.012 to .050	0.100 ± 0.154	−.100 to .734

*Or until fully healed.

for many patients. Univariate analysis of these factors failed to demonstrate a correlation with wound healing rates when calculated by either area healed per day or linear healing per day. Multivariate analysis of these factors and the initial wound area and perimeter was also performed. The relationships between wound geometry and the calculated wound healing rates remained unchanged, with initial area and perimeter still strongly correlating with area healed per day. No other associated factor was shown to correlate with healing rates in the multivariate analysis.

DISCUSSION

The healing of chronic wounds is enormously complicated. The variety of methods used in their treatment are a testimony to the difficult clinical problem they present. Because of the many factors that affect wound healing, randomized trials are essential to objectively evaluate the efficacy of treatments. By their very nature, clinical trials invariably include wounds with a great variety of sizes and shapes. It is imperative that a method of comparing healing rates that is independent of wound geometry be used. Unfortunately, the most commonly used methods of quantifying wound healing are those that measure changes in wound area. As we have shown, the change in the area of a wound (ΔA) depends strongly on the wound's initial area and perimeter. If the treated group in a clinical trial has a greater mean wound area than the control group, it would falsely appear that the treated wounds are healing more rapidly. The treatment studied would then erroneously be assumed to be effective. Conversely, if the treated group has a smaller initial wound area than the control group, a real effect on wound healing might be masked.

The effect of the initial wound size on the calculation of wound healing when it is expressed as the area healed per unit of time was predicted by Gilman.[4] Cordts et al.[5] found that ΔA of venous ulcers correlated both with the initial wound area and, more strongly, with the initial perimeter of the wound. Margolis et al.[6] also found that ΔA of healing venous ulcers was strongly influenced by the initial wound area. Our data corroborate these findings.

When wound healing is calculated as linear healing of the wound edge, we found no correlation with the size (area, perimeter) or shape (W/L) of the initial wound—linear healing of the wound edge is independent of initial wound geometry. This independence makes linear healing an ideal method of measuring wound healing in clinical trials. We are aware of only two other studies in which the linear healing of clinical wounds was calculated. Pecoraro et al.[7] used linear healing to quantify the wound healing rates of diabetic foot ulcers. They found a mean healing rate of 0.0064 cm/day (0.064 mm/day). Margolis et al.[6] found a mean healing rate of 0.0093 cm/day (0.065 cm/wk) in a group of venous ulcers.

Our healing rate for the entire group was 0.011 cm/day, a rate that is similar to that seen by Margolis and colleagues. We saw great variation in healing rates, however, even when wounds with negative healing were excluded. This observation underscores that many factors affect wound healing rates, even in patients treated in the same institution.

CONCLUSION

We found that the calculation of the linear healing of the wound edge with the equation $D = \Delta A/\bar{P}$ provided a measurement of the rate of wound healing that is independent of the initial wound size or shape. In contrast, wound healing rates quantified by the change in area of the wound were strongly biased by the initial wound size and perimeter. The linear healing of the wound edge is an ideal method of measuring wound healing. It should be used in preference to measurements of change in wound area to compare wound healing rates in clinical trials.

Statistical analysis was performed by Wayne W. LaMorte, MD, PhD, MPH.

REFERENCES

1. Stacey MC, Burnand KG, Layer GT, Pattison M, Browse NL. Measurement of the healing of venous ulcers. Aust N Z J Surg 1991;61:844-8.
2. Skene AI, Smith JM, Dore CJ, Charlett A, Lewis JD. Venous leg ulcers: a prognostic index to predict time to healing. BMJ 1992;305:1119-21.
3. Snowden JM. Wound closure: an analysis of the relative contributions of contraction and epithelialization. J Surg Res 1984;37:453-63.
4. Gilman TH. Parameter for measurement of wound closure. Wounds 1990;3:95-101.
5. Cordts PR, Hanrahan LM, Rodriguez AA, Woodson J, LaMorte WW, Menzoian JO. A prospective, randomized trial of Unna's boot versus Duoderm CGF hydroactive dressing plus compression in the management of venous leg ulcers. J VASC SURG 1992;15:480-6.
6. Margolis DJ, Gross EA, Wood CR, Lazarus GS. Planimetric rate of healing in venous ulcers of the leg treated with pressure bandage and hydrocolloid dressing. J Am Acad Dermatol 1993;28:418-21.
7. Pecoraro RE, Ahroni JH, Boyko EJ, Stensel VL. Chronology and determinants of tissue repair in diabetic lower extremity ulcers. Diabetes 1991;40:1305-13.

Submitted March 17, 1995; accepted August 29, 1995.