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Fifty percent area reduction after 4 weeks of treatment is a reliable indicator for healing—analysis of a single-center cohort of 704 diabetic patients☆

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Abstract

Introduction: The aim of the study was to investigate whether an area reduction greater than 50% within the first 4 weeks of treatment is associated with a higher long-term probability of healing. **Patients and Methods:** We treated diabetic foot ulcers according to a comprehensive interdisciplinary wound care protocol. Follow-up was documented through a special wound documentation system. Data were entered into SPSS for statistical analysis to calculate the probability of healing according to the Kaplan–Meier method. Results were expressed as median (minimum–maximum), and the percentage of area reduction (PA) was defined as $[(area_{4\ weeks}/area_{baseline})\times 100)/area_{baseline}$. Patients were divided into responders when PA reached at least 50% and nonresponders when PA was less than 50%. Healing was defined as PA=100%. **Results:** In total, 704 patients were included into the analysis. Median time of follow-up was 71 (2–365) days. Wound duration was 31 (1–4018) days, and the initial wound size was calculated to be 1.18 (0.1–99) cm^2. In 27.8%, there was a positive probing to bone; in 64.5%, both pedal pulses were not palpable. Major amputation rate was 2.8% and minor amputation rate was 10.2%. The overall probability of healing was 35% after 12 weeks, 41% after 16 weeks, and 73% after 1 year. The surrogate visit (4 weeks) was performed after a median of 27 (14–42) days without a difference between responders and nonresponders. There were 334 (47%) responders and 370 (53%) nonresponders. Responders had a significantly higher probability of healing compared with nonresponders (12 weeks: 52.3% vs. 18.4%, *P*=.0001; 16 weeks: 46.7% vs. 26.5%, *P*=.0001; 1 year: 82.5% vs. 64.9%, *P*=.0001). **Conclusions:** The calculation of the percentage of area reduction after 4 weeks of treatment is a valid tool to estimate the probability of healing. In clinical practice, a reevaluation of the treatment schedule is recommended for wounds that do not reach 50% area reduction within the first 4 weeks of therapy.

Keywords: Diabetic foot; Surrogate marker; Surgery

1. Introduction

The treatment of diabetic foot ulcers is usually performed in an interdisciplinary approach, which lead to a reduction in home visits and a reduction of the range local wound care products utilized (Gottrup, Holstein, Jorgensen, Lohmann, & Karlsmark, 2001; Risse, 2007). Such a comprehensive wound care protocol includes angiological and orthopedic as well as surgical aspects (Davey, Solomon, & Freeborn, 1994). In addition, subsequent documentation during follow-up is essential for checking the wound-healing process and the success of the treatment regimen. For this purpose, several subjective and wound-based parameters have been documented in the past (Knighton et al., 1986). However, the only objective parameters for healing are wound size and ultimately complete wound closure. Additionally, reduction of wound size during the course of treatment may be a good

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indicator for the healing response as well. This previous research raises the question of whether or not the reassessment of wound area may help to evaluate the efficacy of the current wound treatment in daily routine.

On the other hand, there is still discussion about the appropriate end points of clinical studies investigating diabetic foot ulcers. Thus far, randomized clinical trials have mostly evaluated clinical outcome, that is, healing rates after 12–24 weeks of care. In addition, secondary end points assessed after a shorter period of time have not been used very frequently. A statement by the US Food and Drug Administration implicated that such surrogate markers may be acceptable in a wound healing study if they have been previously evaluated in a large patient population and did indeed correlate significantly with healing rates after 12 or 16 weeks (FDA, 2001). Therefore, the incidence of complete wound closure and accelerated wound closure are the only accepted primary end points for wound healing studies thus far.

Margolis et al. were the first to retrospectively investigate surrogate markers (in this case percentage change in wound area) after 4 weeks of treatment in a large multicenter patient cohort of diabetic foot ulcers and were able to show that they precisely discriminate between wounds that healed and wounds that did not heal by the 12th or 16th week of care (Margolis, Gelfand, Hoffstad, & Berlin, 2003). However, these data are questionable because this is a retrospective analysis of a large patient population and has been performed over 15 consecutive years with a high likelihood of changes in standard wound care and diagnostic procedures over this long time period. Recently, Sheehan et al. analyzed original data from the study of Promogran efficacy with respect to the surrogate marker 50% area reduction within 4 weeks of treatment and found that the percentage change in foot ulcer area after 4 weeks of observation is a robust predictor of healing at 12 weeks (Sheehan, Jones, Giurini, Caselli, & Veves, 2006). Here, treatment and documentation were performed prospectively within a short study period but in a highly selective patient population (Wagner Grade II ulcers). Therefore, this patient cohort is not representative of diabetic foot ulcer patients treated in daily clinical practice.

By reviewing these two studies, it is clear that there is no single-center study investigating a defined surrogate marker in a large patient cohort that reflects the situation in daily practice. Therefore, we evaluated the surrogate marker 50% area reduction after 4 weeks of standard care in a large single-center cohort of consecutive patients with diabetic foot ulcers.

2. Patients and methods

2.1. Patients

Over a period of 7 years, we prospectively documented 1000 patients with diabetic foot ulcers that were treated in our outpatient wound care center through a special wound documentation system (Coerper, Wicke, Pfeffer, Köveker, & Becker, 2004). Time of follow-up was 365 days or until healing or amputation if earlier. Patients that did not heal or have not been amputated were included in this analysis when follow-up was documented for at least 8 weeks. Patients with severe wound healing problems characterized by an increase in wound area of more than 1000% within the first 4 weeks of treatment were excluded. These limitations resulted in a cohort of 704 patients.

2.2. Wounds

All patients had diabetic foot ulcers located below the ankle and were assessed by a surgeon at the initial visit with the following components: wounds were graded by measuring wound depth with a sterile blunt probe, and the deepest tissue involved was documented (dermis as Grade 1, subcutaneous as Grade 2, fascia as Grade 3, muscle as Grade 4, and bone as Grade 5). We clinically defined ischemia by the absence of both pedal pulses.

In patients with multiple ulcers, the wound with the highest grading was selected for analysis. For wounds with identical grading, the larger wound was chosen. Healing was defined as complete epithelialization maintained for at least 4 weeks, minor amputation as toe or forefoot amputation, and major amputation as below- or above-knee amputation. Infection was defined as soft tissue infection by clinical signs such as swelling, redness, and purulent discharge.

2.3. Local wound therapy

Treatment in the wound care center was performed according to a comprehensive wound care protocol as previously described by an interdisciplinary team of a general and vascular surgeon, a radiologist, a diabetologist, an orthotist, and a specially trained wound care nurse (Coerper et al., 2004). Treatment was characterized by initial sharp debridement, advanced local surgical procedures such as limited bone resections, moist wound therapy, and adequate pressure off-loading. For toe ulcers, off-loading was achieved by half-shoes (Thanner, Höchstädt, Germany) while foot ulcers were off-loaded by individually modified handcrafted orthotic devices (Brillinger GmbH, Tübingen, Germany).

2.4. Wound documentation

Wound documentation was performed within a special wound documentation program as previously described (Coerper et al., 2004). A special software program was created on the basis of a commercially available database (Windows Data Access Objects). Hardware requirements were a personal computer, 64-MB RAM (>Pentium 200 processor), a digital photocamera (>2 million pixels), a port

Table 1
Baseline data of 704 patients

Sex	M: 489 (69.5%); F: 215 (30.5%)
Age	68 (26–94) years
No. of visits	6 (2–59)
Time of follow-up	71 (2–365) days
Patients hospitalized	444 (63%)
Wound history	31 (1–4018) days
Wound area	1.18 (0.1–99) cm^2
Positive probing to bone	196 (27.8%)
Ulcer location	Toe: 225 (32%); foot: 479 (68%)
Non-palpable peripheral pulses	454 (64.5%)
Recurrent ulcer	255 (36.2%)
Negative monofilament test	545 (77.4%)

for a Smart Media Card, and a digitizer pad (Wacom Germany) for planimetric measurements of ulcer area. At every patient presentation, the ulcer outline was traced on transparent paper (Opsite, Smith & Nephew Medical, Lohfelden, Germany) prior to debridement, and area was calculated in a blinded manner using a standardized computer system.

2.5. Statistics

Data were entered into an SPSS database (SPSS 13.0, Chicago, IL) for statistical analysis to calculate probability of healing by the Kaplan–Meier method. Responders and nonresponders were compared with respect to parameters that have previously been associated with delayed healing (positive probing to bone, non-palpable peripheral pulses, multiple ulcers and ulcer location) by χ^2 test. In addition, baseline characteristics between both groups were compared by Mann–Whitney U test or χ^2 test when appropriate. $P<.05$ was considered significant. Results are expressed as median (minimum–maximum). Percent change of area was defined as:

$$[(\text{area}_{4\text{ weeks}} - \text{area}_{\text{baseline}}) \times 100)]/\text{area}_{\text{baseline}}.$$

The surrogate end point 50% area reduction after a period of 4 weeks of treatment was defined as at least −50% change within the surrogate measurement period. According to this calculation, patients were divided into groups achieving 50% area reduction (responder) or not (nonresponder). The probability of healing after 12, 16, and 52 weeks was compared between those two subpopulations by Kaplan–Meier method.

Table 2
Characteristics in both groups (N=704 patients)

	Responder	Nonresponder	P
Time of follow-up (days)	44 (2–365)	99 (14–365)	.0001
Visits (n)	5 (2–59)	6 (2–58)	.0001
Wound size (cm^2)	1 (0.1–99)	1.43 (0.1–64)	.79
Wound duration (days)	30 (2–2275)	38 (1–4018)	.25
Age (years)	67 (29–93)	69 (26–94)	.19
Positive probing to bone	22.2%	33.0%	.001
Non-palpable pulses	55.4%	72.7%	.0001
Soft tissue Infection	30.2%	40.3%	.002
Multiple ulcers	34.7%	46.2%	.0001
Toe ulcers	38.3%	26.2%	.0001

3. Results

In total, 704 patients were included into the analysis. The median time of follow up was 71 (2–365) days, with a median number of 6 (2–59) visits. The diabetic foot ulcers were characterized by a median wound duration of

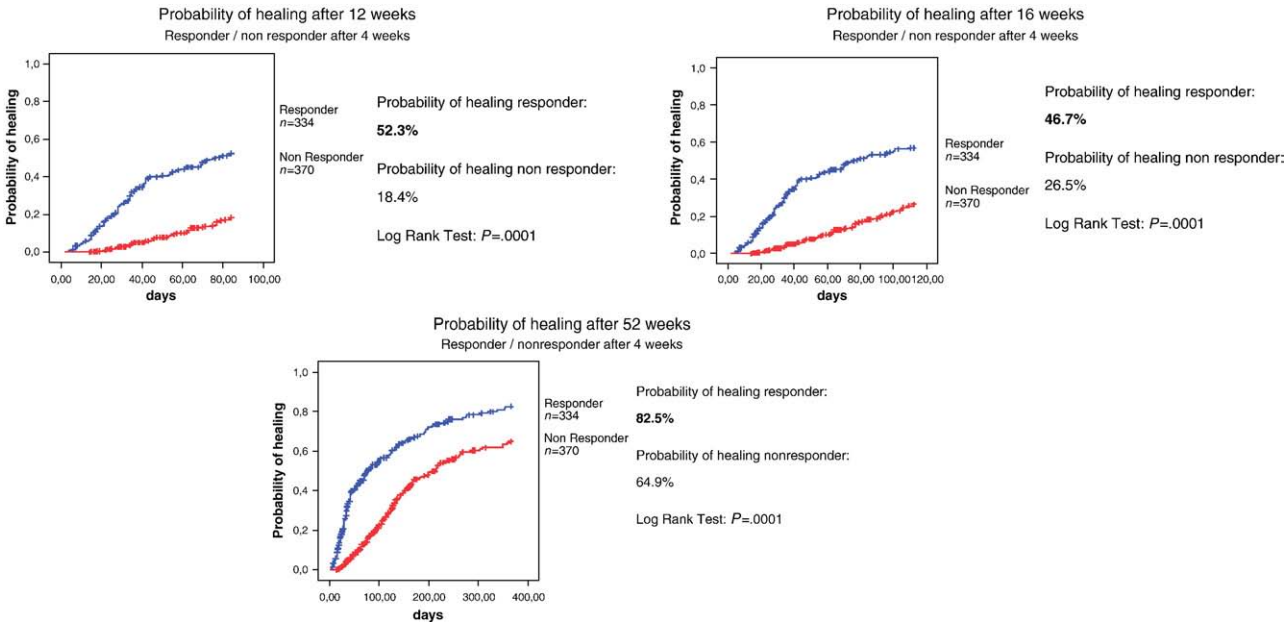

Fig. 1. Probability of healing in responders compared with nonresponders.

Table 3
Subgroup analysis for probability of healing excluding patients with nonpalpable peripheral pulses, ulcers with positive probing to bone or soft tissue infection, and patients with multiple ulcers

	All n=95	Responder n=63	Nonresponder n=32	P
12 weeks	58.0%	75.0%	23.0%	.0001
16 weeks	71.0%	84.0%	44.0%	.0001
52 weeks	91.0%	99.0%	76.0%	.0001

31 (1–4018) days, a median initial wound area of 1.18 (0.1–99) cm^2, and positive probing to bone in 196 cases (27.8%). In 454 patients (64.5%), pedal pulses were not palpable and 255 ulcers (36.2%) were recurrent ulcers. The baseline characteristics are listed in Table 1.

The major amputation rate was 2.8%, and minor amputations were performed in 10.2%. A major surgical wound debridement was performed on each wound at least once. Overall probability of healing was calculated to be 13% after 4 weeks, 35% after 12 weeks, 41% after 16 weeks, and 73% after a treatment period of 1 year. There were 334 responders (47%) achieving a 50% area reduction within 4 weeks and 370 nonresponders (53%). The surrogate visit was performed after a median of 27 (14–42) days. There was no significant difference in the time of surrogate measurement between the two groups: 26 (14–42) vs. 28 (14–42) days (P=.179).

According to the surrogate "50% area reduction within 4 weeks of treatment," we calculated the probability of healing in these two groups and found a highly significant difference. Probability of healing was higher in responders compared with nonresponders (Fig. 1).

Additionally, we calculated differences for important characteristics of wound healing in these two groups. Due to the higher probability of healing in the responder's group, we found a shorter time of follow-up [44 (2–365) vs. 99 (14–365) days; P=.0001] and fewer visits [5 (2–59) vs. 6 (2–58); P=.0001] as well. The responders group had a significantly lower incidence of positive probe to bone testing (22.2% vs. 33%; P=.001), a lower incidence of nonpalpable pulses (55.4% vs. 72%; P=.0001), less soft tissue infections (30.2% vs. 40.3%; P=.003), and less patients with multiple ulcers (34.7% vs. 46.2%; P=.0001) (Table 2).

Since the studied patient population represents a heterogeneous cohort, we performed a subgroup analysis excluding patients with nonpalpable pedal pulses, ulcers with positive probe to bone testing or soft tissue infection, and patients with multiple ulcers. These limitations created a subpopulation of 95 patients. Dividing this subpopulation into responders and nonresponders, responders still revealed a significantly higher probability of healing after 12, 16, and 52 weeks of treatment (Table 3).

4. Discussion

Therapy of diabetic foot ulcers should be evaluated individually in every patient by some form of documentation system in order to recognize success or failure (Deutschle et al., 1998). There is a debate as to which parameter during the course of treatment can precisely indicate whether the ulcer will heal or not. Such surrogate parameters have been evaluated in only two clinical studies thus far, but the results of these two studies are not transferable to daily practice because of several limitations (Margolis et al., 2003; Sheehan, 2006). The study by Margolis et al. was a retrospective analysis that has been performed over a long time period with a high likelihood of changes in standard wound care. Similarly, the study by Sheehan et al. represented an analysis of a selected patient population out of a prospective, controlled multicenter trial not reflecting daily routine by excluding ischemic, and infected ulcers. However, with our large single-center analysis, we were able to show that the surrogate end point parameter 50% area reduction within 4 weeks of treatment is capable of predicting the probability of healing after 12, 16, or 52 weeks in a large patient cohort, reflecting daily practice. In our analysis, the probability of healing was significantly decreased for ulcers that did not reach 50% area reduction after 4 weeks of treatment.

It has been shown that ischemic wounds (Apelqvist, Larsson, & Agardh, 1992) have a significantly lower healing rate and a higher risk for amputation. Similarly, wound infection has an impact and is very likely to delay the healing process (Lipsky et al., 2006). Even though there are published guidelines available (Lipsky et al., 2006; IDF, 2005), the management of osteomyelitis in the diabetic foot may substantially vary. Especially the question whether or not the early removal of infected bone is essential is still under discussion. Thus, there are wound-based parameters that have an influence on the healing of diabetic foot ulcers (Beckert, Witte, Wicke, Königsrainer, & Coerper, 2006; Margolis, Allen-Taylor, Hofstad, & Berlin, 2002; Margolis, Kantor, Santanna, Strom, & Berlin, 2000). Therefore, we evaluated these known factors in our patient population that might be responsible for the delay in the nonresponder group. Indeed, these parameters were detected more frequently in the nonresponder group. In a next step, we performed a subgroup analysis excluding patients with nonpalpable pulses, soft tissue infection, positive probing to bone, or toe ulcerations. However, even in this subpopulation, we found significantly different probabilities for healing after 12, 16, or 52 weeks of care. Since the evaluation of non-wound-based impact factors has not been the focus of this study, we did not include parameters such as end-stage renal disease, glycemic control or foot deformities even though they have also been shown to influence healing (Game, Chipchase, Hubbard, Burden, & Jeffcoate, 2007).

Inappropriate use of off-loading devices, untreated wound infection, and noncompliance are common reasons for nonhealing of chronic wounds. From a clinical point of view, it is essential to detect signs of nonhealing as early as possible. With this background, we believe that reevaluation

of the wound after 4 weeks of treatment is a suitable tool for routine checking on therapeutic strategy and for identifying patients with "problematic wounds." If a wound does not reach a 50% area reduction within 4 weeks of adequate local therapy, diagnostic procedures should be intensified and the treatment regimen has to be modified. This should be taken into consideration in any protocol for the treatment of diabetic foot ulcers (American Diabetes Association, 2007).

On the other hand, in a multidisciplinary network for patients with diabetic foot ulcers, one could recommend that general practitioners initiate the treatment of uncomplicated diabetic foot ulcers and refer patients with wounds that do not reach 50% area reduction after 4 weeks of care to specialized centers, to guarantee an intensive and innovative new diagnostic and therapeutic regimen.

Taking into consideration the published data of surrogate markers and the results of our investigation, we believe that 50% area reduction within 4 weeks of treatment might be a reliable primary end point for clinical studies. This surrogate marker helps to categorize patients as healers and nonhealers in both inhomogeneous and well-defined patient populations. This new end point marker could help to simplify and likely increase the frequency of clinical studies in wound healing since it shortens the study period and lowers study expenses.

5. Conclusion

This report of a large single-center patient population shows that the surrogate end point marker 50% area reduction after a treatment period of 4 weeks is a feasible parameter for assessing the healing response independent of the treated patient population. This new measure might have a strong impact on the treatment outcome in daily practice. Based on our findings, local wound care protocols should be reassessed in every wound that fails to reach 50% area reduction within 4 weeks of treatment. In addition, this new marker could be used as a primary study end point.

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