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A novel method of comparing the healing properties of two hydrogels in chronic leg ulcers

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Abstract

Skin ulcers on the legs have a chronic, relapsing course and are often a significant management challenge. Novel methods of measuring and comparing the effects of different treatments can be of assistance in addressing this situation. A clinical pilot study using original methods was undertaken to compare the healing properties of the alginate gel Flaminal® (test) and the hydrocolloid gel Intrasite® (control) on chronic leg ulcers. The study was performed over a period of 28 days with two parallel groups of 10 patients. Both the surface (acetate tracing and planimetry) and the volume (Jeltrate® mould impression and weighting) of each wound were measured at baseline and after 7, 14 and 28 days of treatment. On both parameters results were superior with the test product compared to the control, with volume reduction being the first parameter to change. Between groups, difference in wound volume reduction was detected as early as day 7 whereas difference in surface reduction was clearly apparent only at day 28. Correlation between wound surface and volume reductions was also better in the test group ($r = 0.843$ vs. 0.421) than in the control. In conclusion, this pilot study suggests that combining wound surface and volume evaluations allows a more precise analysis of the healing process in venous leg ulcers and that this method is able to detect very early differences in treatments even with limited sample size.

Introduction

Ulceration of the lower limb affects 1% of the adult population and 3.6% of people older than 65 years.[1] Leg ulcers are debilitating and painful, and healing has been shown to restore quality of life.[2,3]

The common causes of leg ulceration are venous insufficiency, peripheral arterial disease, diabetes, decubitus and infections mostly caused by a number of bacteria.[4] The aetiology of leg ulcers can be divided into lower extremity ischaemia (arterial, venous and arteriolar origin, as well as pressure and lymphatic origin), neuropathy and immunological causes, and cancer origins. Diabetes ulcer is a result of neuropathy and arteriolar factors. However, the precise sequence of events that leads to leg ulceration remains unclear.[5,6]

The primary objective of this study was to evaluate a novel method of assessment of the safety and efficacy of two topical treatments for leg ulcers.

Patients and methods

Clinical profile and design

The study enrolled 20 hospitalized patients (male and female) who qualified for inclusion in the study (mobile, age 40–70 years) and had chronic leg ulcers of venous origin, exudating, and evenly distributed in each group. All these patients were at rest in the hospital throughout the duration of the study. They were randomly assigned to 4-week treatment groups (measurements made at day 0, 7, 14 and 28). It was decided that a 4-week follow-up would make a clinically reliable surrogate endpoint.[7]

The medical ethics committee of the Medicine Faculty of Liège University, Belgium, approved the project, and patients gave their informed consent after being fully advised about the purpose and consequences of the study. The following data relating to each patient were collected:

consensus of diagnosis, sex, age, ulcer dimension, and volume at day 7, 14 and 28. The study was performed in two-armed parallel groups, open and randomized, in 4 weeks. Baseline assessments (ulcer dimensions, area, volume and clinical parameters) were made prior to the application of either treatment.

Treatments

Two topical treatments were compared for the purpose of the study: the hydrophilic gel Flaminal® (test) and the hydrocolloid gel Intrasite® (control).

Flaminal is composed of alginate polymers containing balanced proportions of guluronic and mannuronic acids as well as sodium and calcium ions. A new technology with enzymatic complexes (a combination of glucoseoxidase and lactoperoxidase) protects against microbial contamination. After wound debridement and cleaning with saline, a 3–5 mm layer of Flaminal was applied to the wound and secured with an overwrap. Flaminal can be left on the wound for 1 to 4 days as long as the gel remains intact, and depending on the type of wound and the amount of exudates produced.

Intrasite gel is an amorphous hydrogel that rehydrates necrotic tissue, facilitating autolytic debridement. It is able to loosen and absorb slough and exudates. Intrasite can also be used to provide an optimum moist-wound management environment during the later stages of wound closure. After wound debridement and cleaning with saline, a 5 mm layer of Intrasite was applied and covered with a secondary dressing of choice, depending on the wound stage. The frequency of changes depended on the clinical condition of the wound and the amount of exudates produced.

Patients were given no other treatments that could influence the wound healing process.

Surface measurement of the ulcer using acetate tracing

Acetate tracing Opsite Flexigrid® (Smith and Nephew Healthcare) sheets were used. Orientation N/S/E/W was drawn on the acetate tracing and the tracing was subjected to planimetry. The dimensions of the ulcer were assessed on the acetate tracings.

Volume measurement of the ulcer using high algin impression material (Jeltrate® mould)

Before mixing the Jeltrate® (Dentsply Caulk International), the ulcer was gently cleaned with normal saline-moist gauze. The ulcer was filled with the Jeltrate and levelled to the corresponding anatomical surface. When it is set, the Jeltrate retains sufficient flexibility to be readily extracted from beneath the ulcer edges and it was rinsed after extraction. The mould was weighed on a digital scale and stored with disinfectant in an airtight, self-sealing, labelled plastic container.

Statistical assessment

Data were processed on UNISTAT 5.0. Surface area and volume were compared by using a two-way (time and treatment) analysis of variance (ANOVA). The method was similarly applied for surface and volume percentage regression as compared with baseline values. The Neuman–Keuls test was used for multiple comparisons. Results are presented as mean ± SD and with their 95% confidence interval (95% CI). As a complementary analysis, correlation coefficients between percentage volume and percentage surface regression were evaluated in both groups. *P*-values ≤ 0.05 (two-tailed) were considered significant.

Results

Baseline characteristics of patients

We investigated the efficiency of Flaminal and Intrasite regarding the volume and surface of the ulcer over a 4-week study. Of the 20 hospitalized patients in the two groups, 13 were female and seven male. Their ages ranged from 45 to 70 years, with a mean of 61 years. Known duration of the current ulcer ranged from 0.5 to 10 years (median 2.25 years) with no between-group difference ($P = 0.691$; Mann–Whitney *U*-test). Both groups were comparable at baseline for wound surface (20.9 ± 7.5 and 20.3 ± 7.6 cm^2 in control and test groups, respectively; $P = 0.826$) and volume (128.4 ± 55.2 and 124.7 ± 49.9 mm^3, respectively).

Ulcer surface evolution

In both groups, surface area decreased over time. The mean percentage decrease from baseline was only apparent at day 14 and was clearly significant in both groups at day 28 (Table 1 and fig. 1). Overall this decrease also differed significantly ($P < 0.01$) between groups. Between-group difference was similar at day 7 (mean percentage surface decrease: $-0.1 \pm 11.9\%$ and $+1.8 \pm 6.0\%$ in test and control groups, respectively; $P = 0.670$), reached significant threshold at day 14 ($-27.3 \pm 20.6\%$ vs. $-3.2 \pm 13.3\%$; $P < 0.01$) and increased by day 28 ($-61.2 \pm 26.2\%$ vs. $-19.4 \pm 24.3\%$; $P \leq 0.01$).

Ulcer volume evolution

Wound volumes also decreased significantly with time in both groups ($P < 0.01$) and this decrease was significantly

Table 1 Mean wound surface area and volume reduction

	Wound surface area (cm^2)/volume (mm^3)		Wound surface area/volume reduction (% reduction from D0)	
	Flaminal ***n*** **= 10**	**Intrasite** ***n*** **= 10**	**Flaminal** ***n*** **= 10**	**Intrasite** ***n*** **= 10**
Wound surface area reduction				
Day 0	20.3 ± 7.6 (14.8/25.8)	20.9 ± 7.5 (15.5/26.3)		
Day 7	19.7 ± 6.2 (15.3/24.1)	21.2 ± 7.5 (15.8/26.6)	–0.1 ± 11.9 (–8.6/8.5)	1.8 ± 6.0 (–2.5/6.0)
Day 14	14.4 ± 5.7 (10.3/18.5)	19.9 ± 7.2 (14.7/25.1)	–27.3 ± 20.6 (–42.1/–12.6)	–3.2 ± 13.3 (–12.7/6.3)
Day 28	7.6 ± 4.7 (4.3/10.9)	16.3 ± 6.8 (11.4/21.2)	–61.2 ± 26.2 (–80.0/–42.4)	–19.4 ± 24.3 (–36.7/–2.0)
Wound volume reduction				
Day 0	124.7 ± 49.9 (89.0/160.4)	128.4 ± 55.2 (88.9/167.9)		
Day 7	75.6 ± 38.8 (47.9/103.3)	119.1 ± 49.8 (83.5/154.7)	–37.9 ± 19.1 (–51.6/–24.3)	–5.8 ± 10.4 (–13.3/1.6)
Day 14	50.2 ± 20.8 (35.3/65.1)	97.1 ± 38.6 (69.5/124.7)	–55.5 ± 23.1 (–72.0/–38.9)	–20.9 ± 20.0 (–35.2/–6.6)
Day 28	22.5 ± 15.4 (11.5/33.5)	65.3 ± 28.5 (44.9/85.7)	–79.6 ± 16.8 (–91.6/–67.6)	–43.3 ± 26.8 (–62.4/–24.1)

Results expressed as mean ± SD.
95% confidence interval of mean value within parentheses.

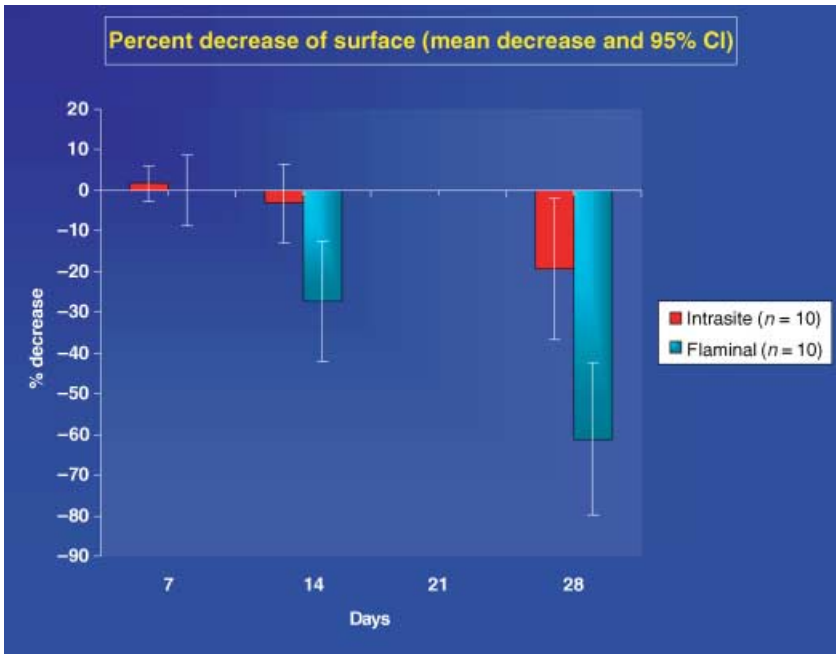


fig. 1 Percentage decrease of ulcer surface area for Flaminal and Intrasite as a function of days of treatment. A significant difference is observed at day 14 and at day 28 ($P < 0.01$).

higher in the test group than in the control group (Table 1 and fig. 2). However, the decrease profile was different from that observed for surface evolution. The between-group percentage volume decrease from baseline was already significant at day 7 (mean percentage volume decrease: −37.9 ± 19.1% and −5.8 ± 10.4% in test and control groups, respectively; $P < 0.001$), and had increased by day 14 (–55.5 ± 23.1% and –20.9 ± 20.0% respectively; $P < 0.001$) up to day 28 (–79.6 ± 16.8% vs. –43.3 ± 26.8%; $P = 0.002$).

Correlations between surface and volume reduction

Correlation between surface and volume reductions expressed as percentage decrease from baseline (fig. 3) is highly significant overall (Pearson's coefficient = 0.735; $P < 0.001$). However, this correlation is better in the test group (Pearson's coefficient = 0.843; $P < 0.001$) than in the control group (Pearson's coefficient = 0.421; $P = 0.020$).

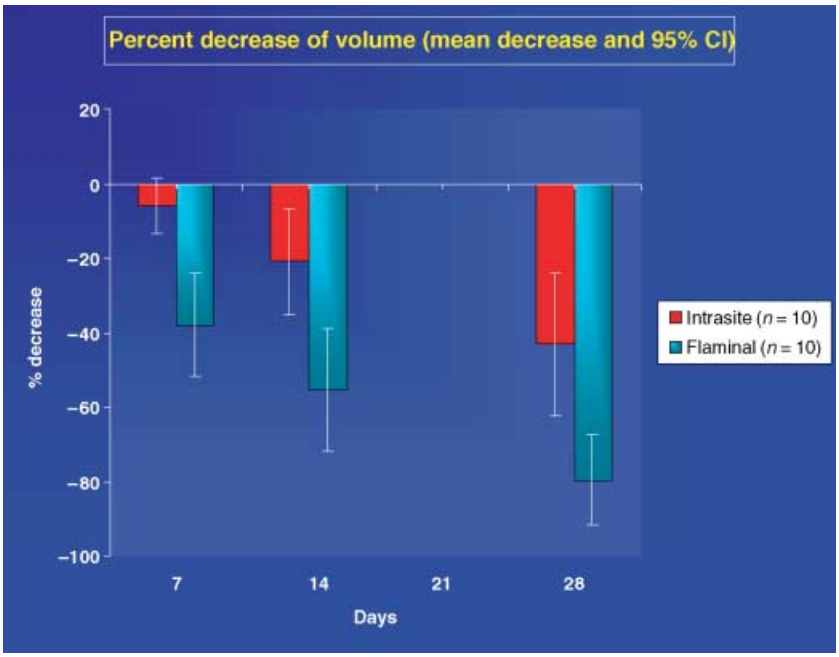


fig. 2 Percentage decrease of ulcer volume for Flaminal and Intrasite as a function of days of treatment. A significant difference is observed at day 7 ($P < 0.001$), day 14 ($P < 0.001$) and day 28 ($P < 0.01$).

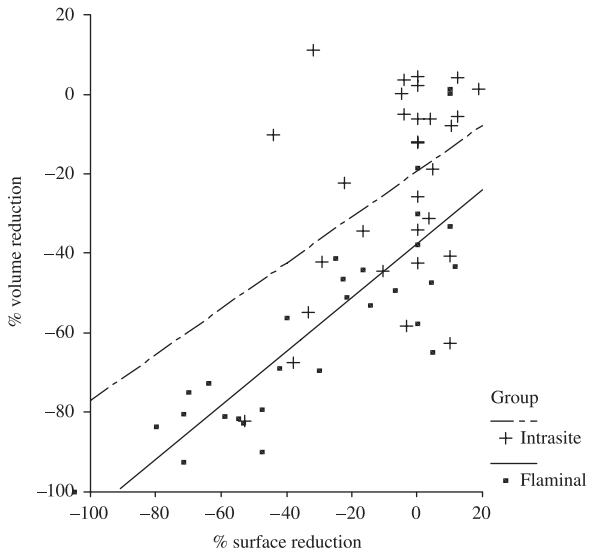


fig. 3 Flaminal and Intrasite correlation coefficients between surface area and volume percentage reduction.

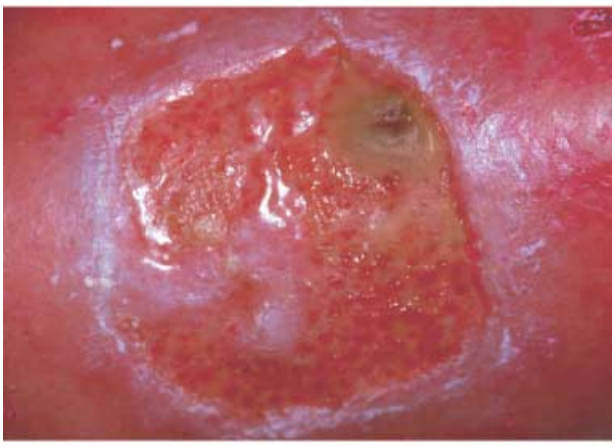
Discussion

The evaluation of therapies for venous leg ulcers is challenged by the prolonged observation period necessary to reach complete healing, clearly the most relevant clinical outcome for comparing therapeutic strategies. The observation period may be at least 12 weeks, or 24 weeks at the best. This delay is not practical during hospitalization to help in detecting early evaluations of new therapeutic strategies. Therefore, attempts have been made to define acceptable surrogate endpoints to complete healing. Numerous studies have shown that ulcer surface reduction at 4 weeks is appropriately predictive of complete healing at 12 or 20 weeks and can be regarded as an acceptable surrogate endpoint to healing.[7–10] However, because of the relatively high variance of surface area measurements, using this endpoint requires the inclusion of a substantially high number of patients to reach appropriate statistical power.[10]

In this context our study has compared a new topical treatment based on an alginate polymer with enzymatic complexes protecting against microbial contamination (Flaminal) with a usual strategy based on the use of an amorphous hydrogel (Intrasite) over 4 weeks in the treatment of venous leg ulcers. Two surrogate endpoints were used: planimetric and wound volume reductions measured at day 7, 14 and 28. One of our purposes in this early pilot study was to evaluate whether volume reduction measurement was able to provide additional information to wound surface reduction and to highlight potential clinical interest of a new treatment. These parameters evaluate two different aspects of the wound healing process: the volume of the ulcer decreases due to the action of fibroblasts and endothelial cells making the granulation tissue until the moment when it is possible for keratinocytes to start to migrate and induce a reduction of the surface (fig. 4).

This study reveals that wound volume reduction is a more sensitive parameter than wound surface reduction, and significant changes can be detected as early as day 7 even

a



b

fig. 4 (a) Photograph of a chronic ulcer before (day 0) treatment. (b) Photograph of ulcer after 28 days of treatment with Flaminal.

with a limited number of patients (fig. 1). However, although changes in wound surface differed significantly at day 14, this difference was clinically relevant only at day 28.

Furthermore, whereas wound surface and volume reductions are significantly correlated overall, the correlation coefficient is different between groups. It is indeed largely better with Flaminal. In this latter group pairs of values are more dispersed, suggesting some heterogeneity in the rate of wound closure.

In conclusion, we have shown in this study that a novel and enhanced method of measuring and comparing the effects of different treatments can be of assistance in determining, even on a limited sample size, the healing properties of substances such as Flaminal and Intrasite gel used in the treatment of venous leg ulcers, and provide more focused and accurate statistical results.

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