

Evaluation of the efficiency of venous leg ulcer treatment with a membrane dressing

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Abstract

A quantitative method for the evaluation of ulcer healing has been developed. The method consists of calculating an ulcer healing efficiency ratio (f_z) interpreted as the second derivative of the regenerated ulcer area over time. The (f_z) value is in direct proportion to the acceleration of healing, and in inverse proportion to the initial ulcer area. In order to test this method, we measured the surface area that was delimited by the ulcer edge and the initial depth of the ulcer in three patient groups. The first and third groups were treated with a cellulose membrane and the second group—with Unna boot. The initial ulcer area was the same in groups 1 and 2, but in group 3, it was six times smaller. The greatest (f_z) value was obtained in group 3, the smallest—in group two. © 2003 IPPEM. Published by Elsevier Ltd. All rights reserved.

Keywords: Venous leg ulcers; Treatment; Cellulose membrane; Healing efficiency ratio

1. Introduction

Venous leg ulceration is a difficult clinical problem to treat. It occurs in around 1% of the adult population, and its incidence is five times higher among people over 60. The treatment of ulcers, involving regular application of dressings, is lengthy and costly [1-3]. Ulcer therapy involves a number of materials, including hydrogel, hydrocolloid, membrane (cellulose and collagen) and alginate dressings [1]. Usually, in order to assess the treatment efficiency, the ulcer area is planimetrically measured before and during treatment [4]. The healing of ulcers is dependent upon a whole series of risk factors including: initial ulcer area, patients age, gender, height, weight, mobility, wound location, wound exudate, the condition of the surrounding skin, etc. In carrying out comparative treatment studies, it is important to match all these risk factors to healing as much as possible, not just on initial ulcer area. Therefore, a comparative assessment of the efficiency of various dressings or modes of treatment is substantially difficult or, in fact, impossible.

The literature implies that the time (T) taken for ulcer to heal depends on a number of physical factors including initial ulcer surface area that is delineated by the ulcer edge (S_{po}), the initial ulcer depth (T_{po}), the location of the ulcers and keratinocyte and fibroblast migration rate [5]. This means that comparing the methods and materials used in ulcer treatment is difficult. In order to overcome this obstacle and express the results obtained for large and obstinate ulcers more objectively, we have developed a quantitative method for the assessment of ulcer healing efficiency. The method is based on an ulcer healing efficiency ratio (f_z) interpreted as temporal change of relative growth of regenerated area. In order to test this quantitative method of healing efficiency assessment, we have measured the area which is delineated by the ulcer edge, and the depth of ulcers.

2. Quantitative assessment of ulcer healing efficiency

Let us assume that the shank is approximately a cylinder. If bones, vessels, nerves and muscles are ignored,

Nomenclature/List of symbols

S_{p0}	initial ulcer surface area that is delineated by the ulcer edge
S_p	ulcer surface area that is delineated by the ulcer edge
S_{b0}	initial ulcer surface area
S_{bp}	ulcer surface
S_{bv}	surface area of the scar
l_{p0}	initial ulcer depth
l_p	ulcer depth
l_b	ulcer depth which is healing
V_7	ulcer healing rate
v_{7b}	initial speed of healing of the ulcer
v_{7b}	speed of scar formation
a	acceleration of healing
a	mean acceleration of healing
r_p	mean ulcer radius
t	time
f_0	the time in which the ulcer beginning to heal
t_k	the ulcer healing time
ξ_7	ulcer healing efficiency ratio
ξ_7	mean ulcer healing efficiency ratio

ulcers develop in the skin and in the connective tissue, which can be represented as a hollow cylinder. The ulcer itself may assume approximately the following shapes: paraboloid of revolution, spherical cap, cone of revolution, or truncated versions of the forms. Thus, ulcer related tissue deficiency may be approximately represented as a geometrical solid composed of two other solids (Fig. 1). The first is always a hollow cylinder, representing the vertical depth of the wall of the ulcer, and the other can be any of the shapes mentioned above. This means that the ulcer area is the internal surface of the solid which is cut out from the hollow cylinder and the 3D figure corresponding to the shape of the wound. Depending on the extent of the ulcer, this area may be roughly represented as the lateral surface of: paraboloid of revolution, spherical cap, cone of revolution, truncated paraboloid of revolution, truncated cone of revolution or spherical envelope.

The ulcer parameters, which may be directly measured are the surface area that is delineated by the ulcer edge (S_p) and the depth of the ulcer (l_p). Initially, $S_p = S_{p0}$ and $l_p = l_{p0}$. Although the ulcer edge is typically irregular, it may be nonetheless assumed that it is roughly a circle with the radius r_p . The ulcer area (S_{bp}) is larger than S_p , initially $S_b(f=0) = S_{b0}$, $S_p(f=0) = S_{p0}$ and $S_{bp} = S_{b0}$ if the ulcer area is small. These two values decrease over time during treatment. On the other hand, the area of the scar (S_{bv}), i.e. of the healed part of the

ulcer, as well as its depth (l_b) increases over time. These values are interrelated in accordance with the formulae

$$S_{b0} = S_{bz} + S_{bp} \tag{1}$$

$$l_{p0} = l_p + l_b \tag{2}$$

Because initially $S_{bz} = 0$ and $l_b = 0$, therefore $S_{bp} = S_{b0}$, and $l_p = l_{p0}$. On the other hand, when the ulcer is healed $S_{bp} = 0$ and $l_p = 0$, thus $S_{bz} = S_{b0}$ and $l_b = l_{p0}$.

In order to assess the ulcer healing efficiency, we suggest that it be represented by the following formula

$$\zeta_z = -\frac{1}{S_{b0}} \left(\frac{d^2 S_{bz}}{dt^2} \right) \tag{3}$$

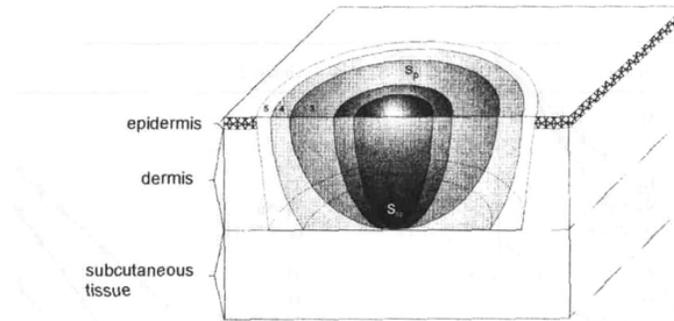
where: dS_{bz} is the increase in the scar tissue, and S_{b0} is the initial ulcer area. Let us assume that

$$a_z = \frac{d^2 S_{bz}}{dt^2} = \frac{dv_z}{dt} \tag{4}$$

is the indicator of wound healing acceleration representing a change of speed of the healed part of the ulcer, where,

$$v_z = \frac{dS_{bz}}{dt} \tag{5}$$

Considering formulae (4) and (5), it is seen that, if S_{bz} is constant over a period of time, then $v_z = 0$ and the



1. Paraboloid of revolution,
2. Truncated paraboloid of revolution,
3. Spherical cap,
4. Truncated cone of revolution,
5. Spherical envelope.

S_p ulcer surface area that is delineated by the ulcer edge

S_{bo} ulcer surface area

Fig. 1. The model of leg ulcer.

ulcer does not heal. If, in turn, S_{bz} increases in a linear manner, $v_z = \text{const}$, and $a_z = 0$. This means that the ulcer heals at a constant rate. The rate v_z and, consequently, acceleration a_z , depend primarily on the ulcer location and migration rate of the keratinocytes and fibroblasts [5], and therefore are dependent on the shape of the curve illustrating the relationship $S_{bz}(t)$. By substituting Eq. (4) in Eq. (3), we obtain

$$\zeta_z = -\frac{1}{S_{bo}} \frac{dv_z}{dt} = -\frac{a_z}{S_{bo}} \quad (6)$$

The value of the ζ_z coefficient is in direct proportion to the acceleration of healing, and in inverse proportion to the initial ulcer area. This means that the greater the value of a_z and the smaller the value of S_{bo} , the greater the healing efficiency. From the formula, it follows that if $a_z = \text{const}$, the efficiency of healing is not time dependent. In order to introduce the value, we will consider a media of as, so as to bring it to the following form

$$\bar{\zeta}_z = \frac{1}{S_{bo}} \frac{dv_z}{dt} \Big|_{v_{zo}, t_0}^{v_{zk}, t_k} = \frac{1}{S_{bo}} \frac{\Delta \bar{v}_{zk}}{\Delta t_k} = \frac{\bar{a}_z}{S_{bo}} \quad (7)$$

where, $\Delta \bar{v}_{zk} = v_{zk} - v_{zo}$, $\Delta t_k = t_k - t_0$, v_{zk} and v_{zo} are the final and initial regeneration rates, respectively, t_k is the ulcer healing time, and t_0 is the time the ulcer starts to heal. Thus, we have obtained a method, which can be used to evaluate the usefulness of the modalities and materials used in ulcer treatment. We will test the

method below, presenting the relevant experimental and calculated results.

3. Materials and methods

3.1. Patients

The study included 93 patients with chronic venous leg ulcers (inclusion criteria) who were treated in the surgical outpatient clinic of the general surgery ward at the Silesian Medical University in Bytom between January 1999 and January 2001. The patients were divided into three groups, in accordance with the ulcer area and treatment modality. The patient's demographic and ulcer details are presented in Table 1. Each ulcer was diagnosed as venous ulcer, using Doppler sonography (Logiq 500, General Electric, USA). None of the patients suffered from diabetes mellitus or atherosclerosis of the lower limbs (exclusion criteria).

Ali patients had previously been treated with traditional methods such as hydrogel and hydrocolloid dressings.

The treatment methods, the plan and scope of treatment, inclusion of patients in the groups and other necessary procedures of a controlled clinical trial were reviewed, approved and adopted by the regional Scientific Research Commission in Katowice (Poland).

Table 1
Patient demographic data

Risk factor	Group 1	Group 2	Group 3
Number of patients	31	31	31
Sex			
Male	15	14	11
Female	16	17	20
Age (years)	50–53	51–56	52–60
Median and range	($x = 51.8$)	($x = 53.1$)	($x = 55.2$)
Ulcer location			
Left leg	17	15	18
Right leg	14	16	13
The initial ulcer area (cm ²)	18.6–26.12*	16.8–26.83*	4.68–5.98
Median and range	($x = 22.55$)	($x = 21.23$)	($x = 5.31$)
Duration of ulcers (months)	8–36	9–48	4–14
Median and range	($x = 21$)	($x = 23$)	($x = 6/12$)
Mobility			
Full	27	26	31
Limited	4	5	0
Body mass index (kg/cm ²)	20.0–40.8	19.4–36.8	14.2–20.1
Median and range	28.7*	26.5*	17.8

* $p < 0.005$: statistical significance compared with group 3.

3.2. Method

Patients from groups 1 and 3 were treated with the Nexfill® cellulose membrane by Fibrocel (Produtos Bioteχνologicos S.A., Brasil). Mean initial ulcer area (S_p) in patients from group 1 was around four times greater than the mean ulcer area S_p in patients from group 3. The Nexfill® membrane is a semitransparent porous membrane 50 μ m thick, made of microcellular cellulose synthesised by the Acetobacter bacteria; it is impermeable to bacteria and selectively permeable to isotonic saline [6]. The properties of the Nexfill® membrane had been discussed in our previous work [7–9], the Nexfill® membrane was applied around 1 cm beyond the ulcer edge, after the necrotic issue was removed and the wound was flushed with isotonic saline. The membrane was covered with gauze swabs, and then it was bandaged with elastic bandage. The dressing was moistened with isotonic saline, several times a day, to keep it moist at the times. The outer dressing was changed every day, and the Nexfill membrane was changed every 7 days, until the ulcer healed.

Patients from group 2 were treated with hydrocolloid Unna boot, which was applied to the ulcer after necrotic tissue was removed and the wound was flushed with isotonic saline. The dressing was changed every 7 days, until complete ulcer healing.

Prior to the treatment, as well as before each change of dressing, all the patients had the bacterial swab from the ulcers taken. At the same time, the area of the ulcers was measured. The procedure was as follows. First, homothetic congruent projection of the ulcer was plotted onto transparent foil, after which the planimetric

measurements of the wound were taken with the use of a digitiser Moutoh Kurta XGT-1218A3 (USA) [10,11]. Ulcer depth was measured by a precision mechanical micrometer. Measuring accuracy was 0.1 mm. The area and depth of any ulceration was measured three times, and the result was averaged. The ulcers were measured once a week, every week, until the wounds were healed completely. The mean ulcer radius was calculated from the ulcer area measurements, using the formula

$$r_p = \sqrt{S_p/\pi} \quad (8)$$

where: r_p and S_p are mean ulcer radius and ulcer surface area that is delineated by the ulcer edge, respectively.

It has been observed that in patients from groups 1 and 2, the deficit is roughly a cylinder of revolution, and in group 3—cone of revolution

$$S_{bp} = \pi r_p(2l_p + r_p) \quad (9)$$

$$S_{bp} = \pi r_p \sqrt{r_p^2 + l_p^2} \quad (10)$$

The obtained results were analysed by the Mann-Whitney U -test. A p -level of less than 0.005 was considered statistically significant.

4. Results

The measured results of mean ulcer depth (l_p) and mean ulcer area delineated by the ulcer edge (S_p) for patients in groups 1, 2 and 3 are graphically represented as lines 1, 2 and 3 in Figs. 2 and 3. The calculated results of mean ulcer radius (r_p), calculated from formula (8), are presented in Fig. 4.

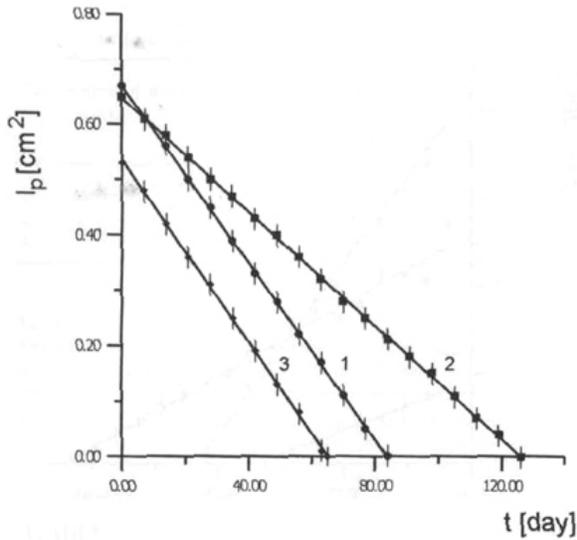


Fig. 2. The dependence of the depth of the ulceration (l_p) on the duration of ulceration (t) for the patients from group 1 (line 1), group 2 (line 2) and group 3 (line 3).

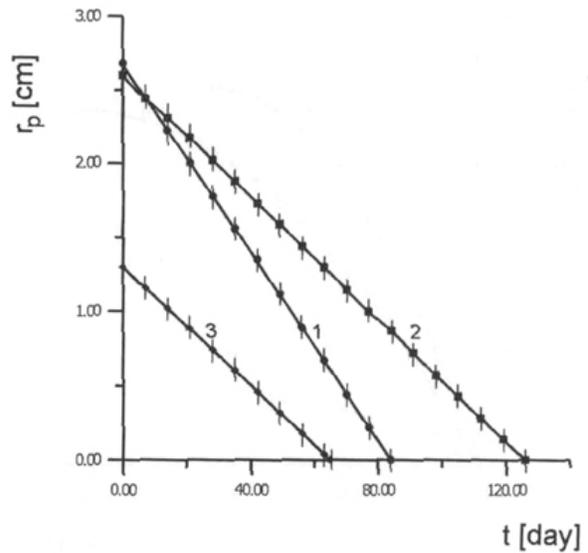


Fig. 4. The dependence of the average radius of ulceration (r_p) calculated on the basis of Eq. (8) on the duration of the ulceration (t) for the patients from group 1 (line 1), group 2 (line 2) and group 3 (line 3).

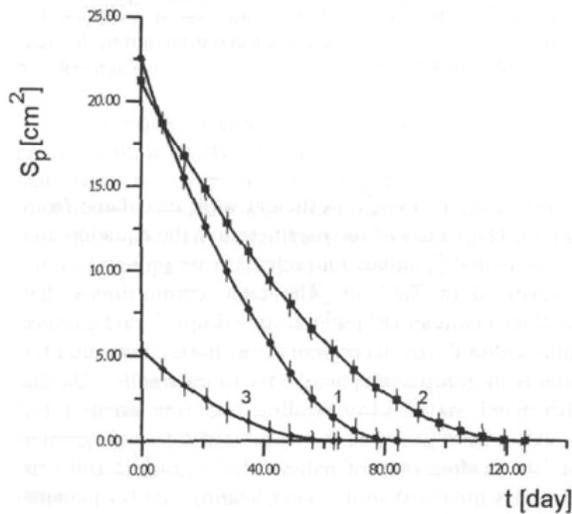


Fig. 3. The dependence of the surface of the contour of the ulceration (S_p) on the duration of ulceration (t) for the patients from group 1 (line 1), group 2 (line 2) and group 3 (line 3).

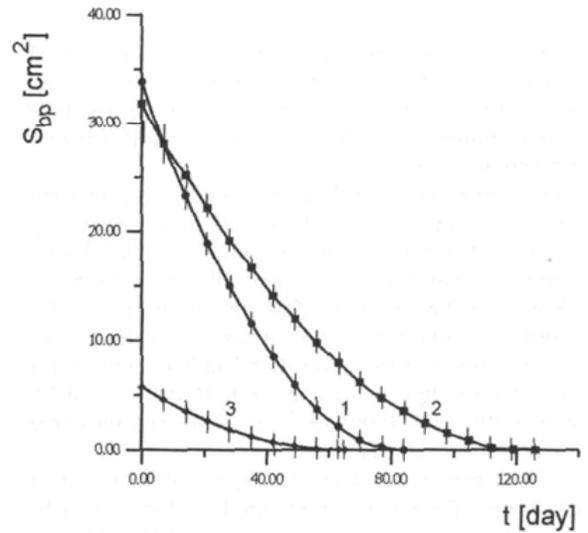


Fig. 5. The dependence of the surface of the ulceration (S_{bp}) calculated on the basis of Eqs. (9) and (10) on the duration of the ulceration (t) for the patients from group 1 (line 1), group 2 (line 2) and group 3 (line 3).

The mean ulcer areas (S_{bp}) calculated from formulae (9) and (10) and the mean scar areas (S_{bz}) calculated from formulae (1), (9) and (10) are illustrated by lines 1, 2 and 3 in Figs. 5 and 6, respectively.

Figs. 2 and 4 show that both the mean ulcer depth and the mean ulcer radius decrease over time in a linear fashion. The tangent of the inclination angle of the curves $l_p = f(t)$ calculated as $tg\alpha_b = (\Delta l_p / \Delta t)$ is: $tg\alpha_{11} = 0.008$ cm per 24 h (for curve 1), $tg\alpha_{12} = 0.005$ cm per 24 h (for curve 2) and $tg\alpha_{13} = 0.008$ cm per 24 h

(for curve 3). The tangent of the angle of inclination of the curves $r_p = f(t)$ calculated as $tg\alpha_b = (\Delta r_p / \Delta t)$ is: $tg\alpha_{r1} = 0.03$ cm per 24 h (for curve 1), $tg\alpha_{r2} = 0.02$ cm per 24 h (for curve 2) and $tg\alpha_{r3} = 0.02$ cm per 24 h (for curve 3).

The characteristics $S_p = f(t)$, $S_{bp} = f(t)$ and $S_{bz} = f(t)$ represented as lines 1, 2 and 3 in Figs. 3, 5 and 6 demonstrate that the mean ulcer area (S_{bp}) for all three groups

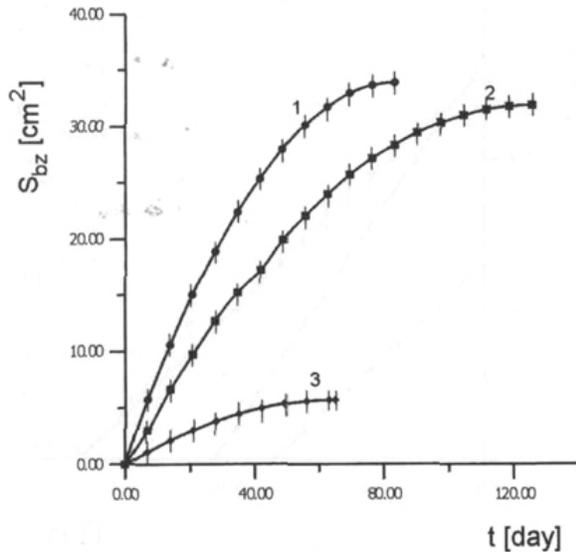


Fig. 6. The dependence of the cured surface of the ulceration (S_{bz}) calculated on the basis of the Eqs. (1), (9) and (10) on the duration of the ulceration (t) for the patients from group 1 (line 1), group 2 (line 2) and group 3 (line 3).

of patients decreases over time in a roughly exponential manner, i.e. like the function e^{-kt} , where k is a constant, and t is time. The mean scar area (S_{bz}) for all three groups of patients increases over time in accordance with the function $(1 - e^{-kt})$.

Fig. 7 represents the characteristics $v_z = f(t)$ calculated from Eq. (5). Line 1 was obtained for patients in group 1, line 2—for patients in group 2, and line 3—for patients in group 3. These characteristics indicate that v_z decreases roughly in a linear fashion with time. The figure shows that the tangent of the angle of inclination of the lines tangential to curves 1, 2 and 3 is greatest for curve 1 and is $tg\alpha_1 = (\Delta v_z / \Delta t) = 0.01 \text{ cm}^2 \text{ per } 24 \text{ h}^2$. For curve 2 $tg\alpha_2 = 0.004 \text{ cm}^2 \text{ per } 24 \text{ h}^2$, and for curve 3 $tg\alpha_3 = 0.003 \text{ cm}^2 \text{ per } 24 \text{ h}^2$.

Table 2 presents a map of temporal distribution of ulcer healing for patients in groups 1–3. The table indicates that first healing in group 1 occurred after 14 days of therapy. The greatest number of healings was obtained after 63 days, and the last healing occurred after 91 days of therapy. Among patients in group 2, the first healing was only obtained after 56 days of therapy. The greatest number of healings was obtained after 91 days of therapy, and the last healing occurred after 126 days of therapy. Among the patients in group 3, the first healing occurred after 14 days of therapy, the greatest number of healings occurred after 49 days of therapy, and the last after 65 days of therapy. Mean ulcer healing time for patients in group 1 was 59.6 days, for patients in group 2—91.2 days, and for patients in group 3—32.6 days.

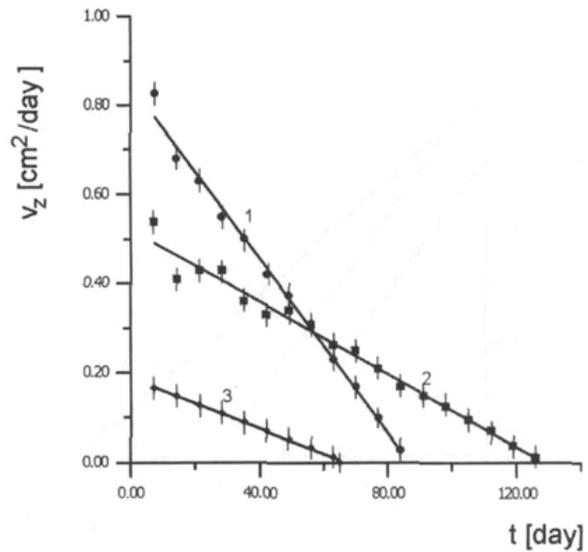


Fig. 7. The dependence of the speed of healing of the ulceration (v_z) calculated on the basis of the Eq. (5) on the duration of the ulceration (t) for the patients from group 1 (line 1), group 2 (line 2) and group 3 (line 3). (1) Paraboloid of revolution, (2) truncated paraboloid of revolution, (3) spherical cap, (4) truncated cone of revolution, (5) spherical envelope. S_p ulcer surface area that is delineated by the ulcer edge, S_{bp} ulcer surface area.

The values of the ξ_z coefficient were calculated from Eq. (7). The values of the parameters in the equation and the calculated ξ_z values for patients from groups 1–3 are summarised in Table 3. The table demonstrates that initial ulcer areas for patients in groups 1 and 2 were equal within the measurement error. Initial ulcer area for patients in group 3 was nearly six times smaller. On the other hand, initial ulcer healing rate was greatest for patients within group 1; it was around 1.5 times greater than the healing rate for patients from group 2 and was five times greater than the ulcer healing rate for patients from group 3. Ulcer healing time was shortest for patients from group 3 and was around 1.3 times shorter than the healing time for patients from group 1, and 1.9 times shorter than the healing time for patients from group 2. The ulcer regeneration efficiency ratios calculated from the parameters above indicate that the value of ξ_z for patients from group 3 is 1.6 times greater than the equivalent for group 1 and 3.6 times greater for patients from group 2. This means that the greatest ulcer healing efficiency was among patients from group 3, and the lowest—patients from group 2. A comparison of the results summarised in Table 2 indicates that the better therapeutic results were obtained using the *Bioprocess*® membrane dressing.

Table 2
The map of the timetable of ulceration healing for the patients from groups 1–3

The number of the group	The time of the ulceration healing (days)																		
	7	14	21	28	35	42	49	56	63	65	70	77	84	91	98	105	112	119	126
1		1		1		4		7	12			4		2					
2								4			6			10			8		3
3		1		3		8	10	6	2	1									

Table 3
The values of the initial surface of the ulceration (S_{bo}), of the initial speed (v_{zo}) and final (v_{zk}) of the ulceration healing, of the initial time (t_o) and the final (t_k) and the coefficient of the effectiveness of ulceration healing (ζ_s) for the patients from groups 1–3

Parameter	The number of the group		
	Group 1	Group 2	Group 3
S_{bo} (cm ²)	33.83 ± 4.06	31.84 ± 3.82	5.73 ± 0.63
v_{zo} (cm ² day ⁻¹)	0.827 ± 0.107	0.54 ± 0.094	0.166 ± 0.020
v_{zk} (cm ² day ⁻¹)	0.030 ± 0.008	0.013 ± 0.004	0.001 ± 0.001
t_o (day)	7 ± 0.125	7 ± 0.125	7 ± 0.125
t_k (day)	84 ± 0.125	126 ± 0.125	65 ± 0.125
ζ_s (day ⁻²)	3.17 ± 0.79 × 10 ⁻⁴	1.37 ± 0.50 × 10 ⁻⁴	4.99 ± 1.16 × 10 ⁻⁴

5. Discussion

The treatment of venous leg ulcers is a difficult clinical problem. It involves the application of many different materials, including the following types of dressings: hydrogel, hydrocolloid, membrane (synthetic and biological) and alginate. The material should have the following properties [1,12]: good wound adhesion, water vapour permeability, flexibility, durability; it should provide a barrier to bacteria; it should not cause antigen reactions; it should be hemostatic, should be easy to apply and remove, and cheap to produce. Polymer synthetic membranes used in the treatment of poorly healing wounds are typically made of polyurethane, cellulose and silicone [1,13]. Synthetic membranes adhere well to the wound, are thin, transparent, permeable to water vapour and gases but impermeable to fluids and bacteria. When used in patients with leg ulcers, they can lead to healing [9,3].

In our current study, as in the previous work [9], we used a cellulose membrane Nexfill® of selective properties. Owing to these properties, excess tissue fluid migrates to the outside of the ulcer. Bacteria do not penetrate into the wound through the membrane. On the other hand, the membrane lets in isotonic and hypertonic solutions from the outside. This maintains a proper microenvironment in the ulcer, necessary for correct healing. This is illustrated by the ulcer healing rates (v_z).

The data in Fig. 6 indicate that the value of v_z for an average ulcer with an initial area of $S_{bo} = 33.83$ cm², treated with a Nexfill® membrane dressing, is

between 0.03 and 0.83 cm²/day. The first healing in this group occurred as early as within 2 weeks, and the last healing occurring after 13 weeks of therapy. The value of v_z for an average ulcer of an initial area, $S_{bo} = 5.73$ cm², treated with Nexfill® membrane dressing is between 0.001 and 0.17 cm²/day. The first healing occurred as in group 1, as early as within 2 weeks, but the last healing occurred after 9 weeks of therapy. When the ulcer was treated with hydrocolloid Unna boot, the value of v_s was between 0.01 and 0.54 cm²/day. In this case, the first healing was only obtained after 8 weeks, and the last—after 18 weeks of therapy. The above indicates that ulcer healing rate is much greater for larger ulcer areas. For patients in groups 1 and 3, the ratio of their initial ulcer areas is 6:1, and the ratio of maximum ulcer healing rates is 5:1.

We have not found any results in the literature which we would compare our v_s values against. The reason is that we differentiate between ulcer area S_{bo} and the area of the part of the ulcer that is surrounded by the edge S_p . For large ulcers, the difference between the two areas is significant. For example, in our cases, the difference between S_{bo} and S_{po} for patients from group 1 is 11.28 cm², for patients from group 2—10.61 cm², and for patients from group 3—0.42 cm². This means that only in the case of a relatively small ulcer area is it justified to assume that $S_{bo} = S_{po}$. If we calculate the v_z values, by substituting AS_{bz} for $A5_{pz}$ in Eq. (5), then, for example, the initial value of the factor for patients from group 1 will change from $v_{zb} = 0.83$ cm²/day (range 0.68–0.91 cm²/day) to $v_{zp} = 0.55$ cm²/day (range 0.37–

0.72 cm²/day), for patients from group 2—from $v_{zb} = 0.54$ cm²/day (range 0.32–0.90 cm²/day) to $v_{zp} = 0.36$ cm²/day (range 0.21–0.53 cm²/day), and for patients from group 3—from $v_{zb} = 0.17$ cm²/day (range 0.11–0.20 cm²/day) to $v_{zp} = 0.16$ cm²/day (range 0.12–0.19 cm²/day). This means that it is only justified to assume that $v_{zb} = v_{zp}$ in the last case. If, therefore, we consider the v_{zp} values, our results are comparable with the literature [4,14–16].

Expression (7), introduced in this work, is of significance to the evaluation of ulcer healing efficiency. The ξ_z coefficient, which has the meaning of an efficiency coefficient, enables us to compare ulcer healing processes with different initial area, different healing rate growths, and different healing times. The formula is correct for a case where v_z is a linear time dependent function. If $v_z = \text{const}$, it is enough to use expression (5) to evaluate healing efficiency. If, on the other hand, v_z is a nonlinear time function [9], then expression (7) should include the formula

$$\Delta \bar{v}_{zk} = \sum_{r=1}^k \Delta v_{zr} \quad (11)$$

where k —number of measurements, e.g. for group 1, $k = 14$.

6. Conclusions

1. The application of *Nexfill*® cellulose membrane in the treatment of venous leg ulcers yields better therapeutic results than a hydrocolloid dressing.
2. The healing rate is greater for larger ulcers than for smaller ulcers.
3. The ulcer healing efficiency coefficient is useful for the evaluation of the efficiency of venous leg ulcer healing.

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