Prognostic factors in the prediction of chronic wound healing by electrical stimulation

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Abstract—*The aim of the study is to determine the effects of wound, patient and treatment attributes on the wound healing rate and to propose a system for wound healing rate prediction. Predicting the wound healing rate from the initial wound, patient and treatment data collected in a database of 300 chronic wounds is not possible. After considering weekly follow-ups, it was determined that the best prognostic factors are weekly follow-ups of the wound healing process, which alone were found to predict accurately the wound healing rate after a minimum follow-up period of four weeks (at least five measurements of wound area). After combining the follow-ups with wound, patient and treatment attributes, the minimum follow-up period was reduced to two weeks (at least three measurements of wound area). After a follow-up period of two weeks, it was possible to predict the wound healing rate of an independent test set of chronic wounds with a relative squared error of 0.347, and after three weeks, with a relative squared error of 0.181 (using regression trees with linear equations in its leaves). Regression trees with a relative squared error close to 0 produce better prediction than with an error closer to 1. Results show that the type of treatment is just one of many prognostic factors. Arranged in order of decreasing prediction capability, prognostic factors are: wound size, patient's age, elapsed time from wound appearance to the beginning of the treatment, width-to-length ratio, location and type of treatment. The data collected support former findings that the biphasic- and direct-current stimulation contributes to faster healing of chronic wounds. The model of wound healing dynamics aids the prediction of chronic wound healing rate, and hence helps with the formulation of appropriate treatment decisions.*

Keywords—*Electric stimulation, Inductive learning, Predictors of wound healing*

Med. Biol. Eng. Comput., 2001, **39**, 542–550

1 Introduction

SKIN is a vital organ, in the sense that the loss of a substantial fraction of its mass immediately threatens the life of the individual. Such a loss can result suddenly, either from fire or mechanical accident. The loss of skin can occur in a chronic manner, as in skin ulcers.

In more than a decade of clinical use of electrical stimulation to accelerate chronic wound healing at the Institute of the Republic of Slovenia for Rehabilitation in Ljubljana, each patient and wound were registered, and the wound healing process was followed weekly. Until now, 266 patients with 390 chronic wounds have participated in the controlled study involving conventional conservative treatment, sham treatment and biphasic pulsed-current and direct-current electrical stimulation.

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Paper received 10 October 2000 and in final form 5 June 2001
MBEC online number: 20013597

Since first reports (JERČINOVIČ *et al.*, 1994) confirmed the positive effects of electrical stimulation, it has been in regular use at the Institute of the Republic of Slovenia for Rehabilitation in Ljubljana. Since then, more than 250 chronic wounds of different aetiologies have been treated by electrical stimulation, However, the dynamics of the wound healing process depends not only on the type of treatment, but also on the wound and patient attributes.

The aims of our study were to determine the effects of wound, patient and treatment attributes on the wound healing process and to propose a system for prediction of the wound healing rate.

Only a limited number of groups have investigated the wound and patient attributes that affect chronic wound healing. LYMAN *et al.* (1970) found a significant relationship between the wound healing rate and bacterial load. SKENE *et al.* (1992) found that the presence of graduated compression healing occurred more rapidly in patients with a smaller initial ulcer area, shorter duration of ulceration, younger age and when no deep-vein involvement was detected on photoplethysmography. The measurement of ulcer area was found to be the strongest predictor of ulcer healing. BIRKE *et al.* (1992) found that the time to complete wound closure is related to wound depth and

wound diameter. JOHNSON (1997) found four factors influencing vascular ulcer healing: the ankle/brachial pressure index, (ABpI) liposclerosis (hardening and induration of the skin of the lower limb), oedema and wound characteristics (exudation, granulation, ulcer area). None of the listed studies included treatment attributes.

At present, the quantity of data available permits us to employ statistical tools and artificial-intelligence methods for analysis of the healing process itself, as well as of the effects of different therapeutic modalities. In the first step of our analysis, we determined which wound and patient attributes play a dominant role in the wound healing process. Then we discussed the possibility of predicting the wound healing rate at the beginning of treatment, based on the initial wound, patient and treatment attributes. Finally, we discussed the possibility of enhancing the wound healing rate prediction accuracy by predicting the rate after a few weeks of wound healing follow-up.

2 Wound, patient and treatment data

During more than a decade of clinical use of electrical stimulation, data concerning patients, wounds and their treatment were collected. The Ethical Committee of the Republic of Slovenia approved the study, and every subject voluntarily acceded to this by signing the consent form. Altogether, 266 patients with 390 wounds have been recorded in our computer database to date. Unfortunately, many patient and wound data are missing, and not all wounds were followed up regularly or until complete wound closure, which is a relatively common problem with clinical trials. The wound case inclusion criteria (initial wound area larger than 1 cm^2 and at least four weeks or until the complete wound closure following the wound healing process) were fulfilled in 300 wound cases (214 patients).

At the beginning of our study in 1989, wounds were randomly assigned to four treatment groups: conservative treatment, sham treatment, biphasic-current stimulation and direct-current stimulation. Since Jerčinović *et al.* (1994) showed that stimulated wounds were healing significantly faster than conservatively or sham-treated wounds, it was not ethical to keep including patients in those groups. After KARBA *et al.* (1997) reported that electrical stimulation with direct current is effective only if the positive electrode is placed on the wound surface, which is an invasive method, only stimulation with biphasic current pulses was used. Therefore the group of patients stimulated with biphasic current pulses is larger than the other groups of patients.

For the evaluation of the efficacy of a particular treatment modality or for the evaluation of the influence of wound and patient attributes on wound healing, it is necessary to follow up the wound healing process periodically. It was demonstrated (CUKJATI *et al.*, 2001) that it is sufficient to follow up the wound area to determine wound healing process dynamics. Further, it was shown that wound shape can be approximated with an ellipse, and it is thus enough to follow up periodically mutually perpendicular diameters (largest wound diameter and diameter perpendicular to it) of the wound. From the measured diameters, the wound area, the perimeter and the width-to-length ratio were calculated. Therefore, to measure the wound extent, it is sufficient to take a measure of mutually perpendicular diameters, which are the easiest and the quickest measurements that can be performed at bedside (STEFANOVSKA *et al.*, 1993).

Wound depth measurement is invasive, because we have to insert our measuring device into the wound. Besides the disturbance to the wound, the depth can be underestimated because of the invisible edge at the bottom of the wound and degenerative tissue that fills up the wound. As an alternative measure of wound extent, grading systems were presented. We used the four-stage Shea grading system (SHEA, 1975). Wound depth and grade were collected only at the beginning of treatment.

Wounds were treated daily until complete wound closure. If the wound did not completely heal within the observation (in-patient) period, the patient continued his treatment at home, but follow-ups were discontinued, because the reliability of the home treatment was questionable. Among 300 wound cases, observation periods were until complete wound closure in 174 cases, and shorter in 126 cases. In these 126 cases, the time to complete wound closure was estimated from the wound area measurements obtained during the observation period (CUKJATI *et al.*, 2000; 2001). No significant difference between the actual time to complete wound closure and the estimated one (from four or more weeks of wound healing observation) was observed.

Because the time to complete wound closure was highly dependent on initial wound extent, a measure of the wound healing rate was defined as an average advance of the wound margin towards the wound centre, and it was calculated as the average wound radius (initial wound area divided by initial perimeter and multiplied by 2) divided by the time to complete wound closure. In Table 1, the wound, patient and treatment data collected in our computer database are listed. These data were selected to be the attributes of chronic wound description. All listed attributes, except wound extent, were collected at the beginning of wound treatment. In addition, wound extent was followed up weekly during the observation period or until complete wound closure. In further analysis, we divided listed attributes into wound, patient and treatment attributes.

2.1 *Statistical methods*

Distribution of the wound healing rate or its transform was not normal; non-parametric statistical analysis was therefore employed. To determine differences in the distribution of quantitative attributes in groups formed by qualitative attributes, we used the Kruskal–Wallis one-way analysis of variance. If the difference was significant, we used a two-sample Kolmogorov–Smirnov test to compare mutually distributions of quantitative attributes at specific values of qualitative attributes. To test the

Table 1 Wound, patient, and treatment data collected in a database during more than a decade of using electrical stimulation at Institute of Republic of Slovenia for Rehabilitation

Wound data
length of wound
width of wound
depth
grade
date of wound appearance
date of treatment beginning
aetiology
location
Patient data
sex
date of birth
number of wounds
diagnosis
date of spinal cord injury
degree of spasticity
Treatment data
type of treatment
daily duration of treatment
duration of treatment

relationship of qualitative attributes, we used a chi-square test. To determine if two quantitative attributes are correlated, we used the Spearman correlation test.

2.2 *Wound attributes*

Wound extent was described by wound length, width, depth and grade. Wound depth was measured only in 43% of cases, and wound grade was determined in 94%. A positive correlation coefficient ($rs = 0.568$, $n = 128$) and a p value less than 0.001 show that the wound grade tends to increase with increasing wound depth and also tends to increase with increasing initial perimeter ($rs = 0.348$, $p < 0.001$, $n = 281$) and area ($rs = 0.292$, $p < 0.001$, $n = 281$) (rs = Spearman correlation coefficient, p = probability of being wrong in concluding that there is a true association between the variables, and n = number of cases).

Like wound grade, wound depth is also correlated to perimeter ($rs = 0.356$, $p < 0.001$, $n = 132$) and area ($rs = 0.306$, $p < 0.004$, $n = 132$). As wound depth was strongly correlated to wound grade, and wound depth values were often missing, depth was omitted from further analysis. Also, owing to the strong correlation between the initial wound area and perimeter ($rs = 0.969$, $p < 0.001$, $n = 300$), the perimeter was omitted from further analysis. No other correlations between wound extent attributes were found.

The time to complete wound closure is correlated to wound extent attributes, area ($rs = 0.428$, $p < 0.001$) and grade ($rs = 0.388$, $p < 0.001$). The wound healing rate is not correlated to initial area, perimeter or width-to-length ratio, but is moderately correlated to wound grade ($rs = -0.237$, $p < 0.001$, $n = 281$). Wounds of higher grade healed more slowly.

Other wound attributes collected were wound type, location, time elapsed from spinal cord injury to wound appearance (injury appear) and time elapsed from wound appearance to the beginning of treatment (appearstart). The latter was modestly correlated to wound grade ($rs = 0.181$, $p = 0.005$, $n = 243$), which can indicate that wounds should be treated as soon as they appear. Therefore it was also expected that the wound not appropriately treated for a long period would heal slowly (negative correlation coefficient when comparing appearstart with the wound healing rate) ($rs = -0.215$, $p < 0.001$, $n = 243$). A small initial wound area ($rs = -0.261$, $p < 0.001$, $n = 178$) of wounds that appeared a long time after spinal cord injury is probably a result of better patient self care.

Wounds on the trochanter healed significantly slower ($p < 0.030$) than wounds on other locations, between which no significant differences were found ($p < 0.060$) (Table 2). Locations did not differ with respect to grade ($p = 0.236$), but they differed with respect to area ($p < 0.001$), revealing significantly greater wounds on the trochanter and sacrum locations than on the gluteus or other locations (Table 2). Wounds on the trochanter, gluteus and sacrum were all pressure ulcers.

The major wound aetiology was pressure ulceration (82.7%). Other aetiologies were arterial ulceration (1.0%), neurotrophic ulceration (6.3%), traumatic ulceration (6.0%) and vascular ulceration (3.7%). The wound healing rate does not significantly differ ($p = 0.236$) for listed aetiologies although they were not randomly assigned into four treatment groups ($p = 0.001$).

2.3 *Patient attributes*

Recorded patient attributes were age, sex, total number of wounds, diagnosis and, in the case of a spinal cord injured patient, degree of spasticity. The number of patients is lower than the number of wounds, as one patient can have more than one wound. There were 154 patients with one wound, 45 patients with two wounds, three patients with nine wounds, four patients with three wounds, five patients with two wounds, and six patients with one wound included in the study. Because a patient with more than one wound can have his/her wounds at different ages, we presented age data for each wound case and not for each patient (Table 2). Patients with wounds on the sacrum or trochanter were significantly younger ($p < 0.010$) than patients with wounds on the gluteus or other locations. No significant difference in age was found between patients with wounds on the trochanter and sacrum ($p = 0.513$). As age was not correlated to the wound healing rate ($p = 0.541$), the slow wound healing of trochanter wounds cannot be a result of the patient's age.

The most frequent diagnosis was spinal cord injury (71.7%). Trauma appeared in 11.3% of cases, diabetes mellitus appeared in 7.3%, geriatrics appeared in 3.3%, multiple sclerosis appeared in 3.0%, and venous diseases appeared in 3.0% of wound cases. Wounds of geriatric (healing rate = 0.271 mm per day) and traumatic (0.224 mm per day) patients were healing significantly faster ($p = 0.005$) than wounds of patients with another diagnosis: spinal cord injury (0.173 mm per day), vascular insufficiency (0.171 mm per day), diabetes mellitus (0.102 mm per day) and multiple sclerosis (0.138 mm per day).

In future, more data should be collected to determine whether the wounds of geriatric and traumatic patients are healing significantly faster than wounds of patients with another diagnosis, because there were almost no geriatric or traumatic patients with wounds on the trochanter, which were found to heal slowly. The relationship could also be otherwise, indicating that wounds located on the trochanter healed significantly slower than wounds on other locations, because there were no wounds of geriatric and traumatic patients on this location. Geriatric patients (age = 77 (72–88), $n = 77$), diabetes mellitus patients (68 (60–77), $n = 22$) and patients with venous diseases (63 (54–72), $n = 9$) were significantly ($p < 0.001$) older than those with spinal cord injury (36(26–51), $n = 215$), multiple sclerosis (41 (33–52), $n = 9$) or trauma (43 (25–74), $n = 34$). We found diagnosis strongly related to wound aetiology ($p < 0.001$).

2.4 *Treatment attributes*

Wounds were randomly assigned to four treatment groups. All patients received conservative treatment of their chronic wound (FEEDAR and KLOTH, 1990). The conservative treatment included initial selective debridement, the application of a new

Table 2 Medium healing rate, wound area and patient age with interquartile ranges at different wound locations

Location	*Trochanter*	*Sacrum*	*Gluteus*	*Other*	*p*
Healing rate, mm per day	0.115 (0.024–0.259) $n = 58$	0.223 (0.131–0.372) $n = 93$	0.234 (0.111–0.423) $n = 32$	0.176 (0.097–0.302) $n = 110$	0.030
Area, mm^2	1018 (382–2721) $n = 58$	1012 (511–2753) $n = 93$	684 (370–1249) $n = 32$	393 (231–648) $n = 110$	< 0.001
Age, years	35 (23–49) $n = 57$	37 (28–49) $n = 92$	57 (39–82) $n = 32$	51 (30–61) $n = 108$	< 0.010

Format of data is median (interquartile range). n is number of collected data

standard dressing to the chronic wound two or more times per day, as needed, and broad-spectrum antibiotics in cases of infection, which were rather rare. Fifty-four (18.0%) wounds received only conservative treatment. In addition to the conservation treatment, 23 (7.7%) wounds received sham treatment, where electrodes were applied to the intact skin on both sides of the wound for 2 h daily and connected to stimulators, in which, however, the power source was disconnected so that they delivered no current.

Two different modes of electrical stimulation were used: direct and biphasic current. Forty-two (14.0%) wounds were stimulated with direct current of 0.6 mA for 0.5 h 1 h, or 2 h daily. The positive stimulation electrode was placed over the wound surface, and the negative electrode was placed on the intact skin around the wound, or both electrodes were placed on the healthy skin at the wound edge across the wound, one of them being positive and the other negative. We have pooled different electrode placements in the direct-current stimulation group, in spite of the difference in effectiveness of direct-current stimulation (KARBA *et al.*, 1997). We did this for two reasons: in the literature, both electrode placements were shown to accelerate chronic wound healing; and, in this way, we kept an otherwise small direct-current stimulation group of wounds at the size that allowed us to perform statistical analysis. 181 (60.3%) wounds were stimulated with biphasic, charge-balanced current pulses (KARBA *et al.*, 1991) for 0.5 h, 1 h or 2 h daily, with electrodes placed on both sides of the wound. The pulse duration was 0.25ms, and there was a repetition rate of 40 Hz. The 4 s stimulation trains were rhythmically alternated with pauses of the same duration. The pulsed currents produce tetanic contraction of the stimulated tissue, which is kept at a minimum level (adjusted by the stimulation amplitude, usually at 15–25 mA) to prevent mechanical damage of the newly-formed tissue.

The currents were applied across the wounds by a pair of self-adhesive skin electrodes* attached to the healthy skin at the edge of the wound. In the direct stimulation group, where the positive stimulation electrode was placed over the wound surface, the wound surface was covered with sterile gauze, soaked in physiological solution, on top of which a conducting rubber electrode was applied. This assured uniform current distribution throughout the entire wound area. Four self-adhesive electrodes were attached to the intact skin around the wound, representing the ring-shaped negative electrode.

Treatment attributes were the type of treatment and the daily duration of electrical stimulation. Plotting the percentage of healed wounds against the time elapsed from the beginning of the treatment (Fig. 1) revealed differences between the four treatment groups.

Electrically stimulated wounds healed at a higher rate and greater extent than other wounds. Over 90% of electrically stimulated wounds healed within 60 weeks, whereas only 70% of sham treated wounds and 72% of conservatively treated wounds healed within the same period. The wound healing rate revealed a significant difference between the four treatment groups. Results of the Kolmogorov–Smirnov two-sample non-parametric test, comparing treatment modalities (p-values), are presented in Table 3. It was found that wounds treated with biphasic-current stimulation healed significantly faster than conservatively or sham treated wounds. No significant difference was found in the healing rates between wounds treated with direct current and wounds treated with biphasic-current pulses. The difference in the healing rates between the direct-current and the conservative or sham treatment was considerable, in favour of the direct current, although it was not significant. Conservatively or sham-treated wounds healed at the same rate.

* Encore Plus, Axelgaard Manufacturing Co. Ltd.

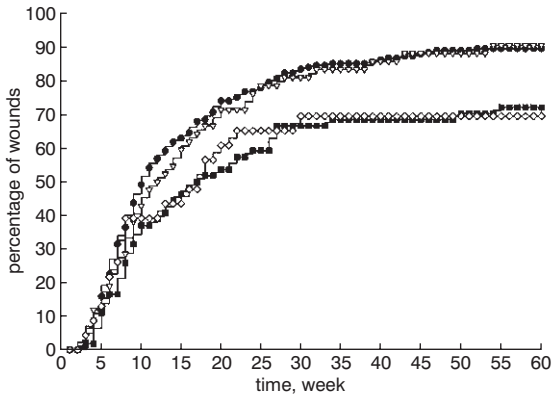

Fig. 1 *Percentage of healed wounds against time elapsed from beginning of treatment for four treatment modalities: (–●–) biphasic-current stimulation; (–▽–) direct-current stimulation; (–■–) conservative treatment. (–◇–) sham treatment*

Although wounds were randomly assigned into four listed treatment groups, some differences in attribute distribution between the groups were found. Table 4 presents the results of attribute comparisons between treatment groups. There was no statistically significant difference ($p = 0.631$) in the time to complete wound closure (when non-healing wounds are not considered) between treatment modalities. The time elapsed from spinal cord injury to wound appearance was significantly shorter ($p < 0.001$) in the conservatively treated and direct-current stimulated groups of patients than in the sham-treated and biphasic-current stimulated groups of patients. It is not correlated to the wound healing rate or any other attribute.

Wounds were also not randomly assigned to treatment groups, regarding location, aetiology and diagnosis. Wounds on the sacrum (32%) and trochanter (33%) were significantly ($p = 0.026$) more often included in the conservatively or sham-treated groups than wounds on the gluteus (13%) and other locations (17%). Wounds on the trochanter and sacrum were healing significantly ($p = 0.048$) faster when treated with biphasic-current pulses. A electrically stimulated wounds healed faster than conservatively or sham-treated wounds, this can reveal why wounds on the trochanter and sacrum healed slower than wounds on other locations. Only pressure ulcers were conservatively ($n = 54$) or sham treated ($n = 23$). Thirty-five pressure ulcers, three neurotrophic ulcers and three traumatic ulcers were treated with direct-current pulses, and 136 pressure ulcers, 16 neurotrophic ulcers, 15 traumatic ulcers, 11 vascular ulcers and three arterial ulcers were treated with biphasic-current pulses. The healing rates of wounds treated with biphasic electric current with respect to wound aetiology did not differ significantly ($p = 0.129$). We concluded that the wound healing rate is not dependent on wound aetiology.

When considering the healing rates obtained with the 2 h daily wound treatment, biphasic current-stimulated wounds healed significantly ($p = 0.018$) faster (0.166 mm per day (0.097–0.328)) than sham-treated wounds (0.162 mm per day

Table 3 Effects of four treatment modalities on wound healing rate (p-values of Kolmogorov–Smirnov two-sample test)

	AC	DC	CO	SH
AC	1.000			
DC	0.365	1.000		
CO	0.031	0.085	1.000	
SH	0.008	0.056	0.607	1.000

AC = biphasic-current stimulation; DC = direct-current stimulation; CO = conservative treatment; and SH = sham treatment

Table 4 Baseline wound and patient attributes for each treatment group. Distributions of acquired attributes presented for each treatment group were compared, and p-values were calculated

	Total $n=300$	AC $n=181$	DC $n=42$	CO $n=54$	SH $n=23$	p
Age*, years	$n=297$	$n=178$	$n=42$	$n=54$	$n=23$	0.053
	41(28–59)	43(30–62)	43(25–59)	39(23–51)	37(23–57)	
Injury appear*, months	$n=178$	$n=94$	$n=27$	$n=42$	$n=15$	<0.001
	5(2–38)	11(3–69)	3(1–4)	3(1–10)	6(4–24)	
Appear start*, weeks	$n=243$	$n=150$	$n=33$	$n=44$	$n=16$	0.247
	8(3–18)	7(3–17)	6(4–12)	13(4–22)	8(2–14)	
Area*, mm	$n=300$	$n=181$	$n=42$	$n=54$	$n=23$	0.359
	634(308–1871)	566(283–1539)	660(346–2108)	797(432–2160)	661(289–1180)	
Perimeter*, mm	$n=300$	$n=181$	$n=42$	$n=54$	$n=23$	0.296
	95(68–161)	92(64–160)	104(73–165)	108(77–166)	91(64–127)	
Ratio*	$n=300$	$n=181$	$n=42$	$n=54$	$n=23$	0.983
	0.71(0.55–0.83)	0.71(0.54–0.81)	0.71(0.50–0.90)	0.69(0.57–0.86)	0.70(0.52–0.82)	
Depth*, mm	$n=132$	$n=79$	$n=17$	$n=28$	$n=8$	0.251
	4.5(2–15)	4(2–10)	15(4–20)	4(1–16)	5(3–9)	
Number of wounds*	2(1–3)	2(1–2)	1(1–2)	2(1–3)	2(1–2)	0.071
Grade†, *n*%						0.254
I	24(8.0)	10(5.5)	3(7.1)	9(16.7)	2(8.7)	
II	138(46.0)	92(50.8)	13(31.0)	23(42.6)	10(43.5)	
III	87(29.0)	52(28.7)	17(40.5)	11(20.4)	7(30.4)	
IV	32(10.7)	19(10.5)	4(9.5)	6(11.1)	3(13.0)	
Location‡, *n*%						0.012
trochanter	58(19.3)	34(18.8)	5(11.9)	13(24.1)	6(26.1)	
sacrum	93(31.0)	44(24.3)	19(45.2)	22(40.7)	8(34.8)	
gluteus	32(10.7)	21(11.6)	7(16.7)	3(5.5)	1(4.3)	
other**	110(36.7)	80(44.2)	11(26.2)	11(20.4)	8(34.8)	
Aetiology‡, *n*%						0.001
pressure ulcer	248(82.7)	136(75.1)	35(83.3)	54(100.0)	23(100.0)	
arterial ulceration	3(1.0)	3(1.7)	0(0.0)	0(0.0)	0(0.0)	
vascular ulceration	11(3.7)	11(6.1)	0(0.0)	0(0.0)	0(0.0)	
neurotrophic ulceration	19(6.4)	16(8.8)	3(7.1)	0(0.0)	0(0.0)	
traumatic ulceration	18(6.0)	15(8.3)	3(7.1)	0(0.0)	0(0.0)	
Diagnosis‡, *n*%						0.010
spinal cord injury	215(71.7)	111(61.3)	28(66.7)	54(100.0)	22(95.7)	
geriatrics	10(3.3)	10(5.5)	0(0.0)	0(0.0)	0(0.0)	
multiple sclerosis	9(3.0)	5(2.8)	4(9.5)	0(0.0)	0(0.0)	
diabetes mellitus	22(7.3)	18(9.9)	3(7.1)	0(0.0)	1(4.3)	
vascular insufficiency	9(3.0)	9(5.0)	0(0.0)	0(0.0)	0(0.0)	
trauma	34(11.3)	28(15.5)	6(14.3)	0(0.0)	0(0.0)	
Daily duration of treatment†, min						<0.001
0	54(18.0)	0(0.0)	0(0.0)	54(100.0)	0(0.0)	
30	53(17.7)	51(28.2)	2(4.8)	0(0.0)	0(0.0)	
60	18(6.0)	13(7.2)	5(11.9)	0(0.0)	0(0.0)	
120	175(57.3)	117(64.6)	35(83.3)	0(0.0)	23(100.0)	
Healing time*, days	$n=276$	$n=178$	$n=40$	$n=42$	$n=16$	0.631
	63(37–137)	63(36–132)	64(37–132)	83(45–177)	64(36–123)	
Healing rate*, mm per day	$n=300$	$n=181$	$n=42$	$n=54$	$n=23$	0.007
	0.176(0.090–0.315)	0.190(0.114–0.328)	0.168(0.089–0.434)	0.145(0.026–0.261)	0.162(−0.046–0.205)	

Data are *n*% or median (interquartile range). Percentages are calculated using all recorded data ($n=300$)
Attribute types: *continuous, †ordinal and ‡nominal attribute
Injury appear = elapsed time from spinal cord injury to wound appearance
Appear start = elapsed time from wound appearance to beginning of treatment
AC = biphasic-current stimulation; DC = direct-current stimulation; CO = only conservative treatment; and SH = Sham treatment
** Pes (15), calcaneus (25), genu (7), lower extremities (19), molleolus (2), humerus (5), stump (34), and ischium (3)

(−0.046–0.205)) and at the same rate ($p=0.170$) as direct current-stimulated wounds (0.217 mm per day (0.098–0.450)). Direct current-stimulated wounds healed faster, but not significantly ($p=0.085$) faster, than sham-treated wounds.

Wounds stimulated by direct current for 1 h healed ($p=0.067$) slower (0.090 mm per day (0.089–0.120)) than those stimulated for 2 h and significantly ($p=0.001$) slower than wounds stimulated by biphasic current for 1 h (0.260 mm per day (0.190–0.460)). Wounds stimulated by biphasic current for 1 h daily healed significantly ($p=0.017$) faster than those stimulated for 2 h daily and also faster than ($p=0.357$) wounds stimulated by biphasic current for 0.5 h daily (0.207 mm per day (0.152–0.309)). Wounds stimulated by biphasic current for 2 h daily healed at the same healing rate ($p=0.060$) as those stimulated for 0.5 h daily biphasic current stimulated wounds. A lack of wound cases stimulated for 1 h daily ($n=13$) renders this result statistically unreliable. Further study should be performed to optimise the daily duration of electrical stimulation.

3 Prediction of wound healing rate

We defined the wound healing rate Θ as the advance of the wound margin towards the wound centre (CUKJATI *et al.*, 2001)

$$\Theta = 2\frac{S_0}{p_0}\frac{1}{T} \text{ (mm per day)} \quad (1)$$

where S_0 is the initial wound area, p_0 is the initial perimeter, and T is the time to complete wound closure. For the wound healing rate Θ to be appropriately calculated, we thus have to follow the wound healing process until complete wound closure. Because clinical trials are financially and time limited, the time to complete wound closure has to be predicted from measurements taken in the observation period, which can be much shorter than the time to complete wound closure. Another reason for the need to predict the time to complete wound closure is to help clinicians in making a decision whether to change the treatment or not.

We decided to predict the wound healing rate rather than the time to complete wound closure, because the wound healing rate is easier to interpret in cases when the wound is not healing. In these cases, the time to complete wound closure is infinite, and the wound healing rate is zero or negative. A negative value of the wound healing rate is the estimate of wound growth velocity towards double its initial area. From the wound healing rate, the time to complete wound closure can easily be calculated.

3.1 *Estimating wound healing rate from wound healing model*

We determined that the wound area variation over time has a delayed exponential behaviour. The delayed exponential equation is thus the structure of the mathematical model of the wound healing process, and, by fitting this model to a particular chronic wound case, the parameters of the model are calculated. At least four measurements of wound area (performed in at least three weeks) are needed before the parameters of the mathematical model can be estimated. From the parameters of the mathematical model, the time to complete wound closure was estimated (CUKJATI *et al.*, 2001).

Because the exponential function reaches the asymptote at infinite time, we estimated that the wound is healed when its estimated area is smaller than 5% of the initial value and is also, at the same time, smaller than 1 cm^2. The estimated wound healing rate was calculated according to eqn 1. To estimate the wound healing rate even earlier, a model with fewer parameters has to be introduced. Because 50% of wounds had a delay to the wound healing process initiation of less than half of a week, we used the two-parameter exponential model. To evaluate the parameters of this model, we performed a linear regression to logged measurements of wound area. We estimated the time to complete wound closure and calculated the wound healing rate for 300 wound cases as before, considering the delay of wound healing process initiation to be zero.

The estimated wound healing rates for all wound cases were then compared with actual values calculated from observed times to complete wound closure. We found that the estimated wound healing rate after at least four weeks of wound follow-up did not differ significantly from the actual one (Table 5). If a wound was followed up for only three weeks or less, the difference was found to be significant.

From the known structure of the mathematical model, the wound healing rate can be predicted after at least four weeks of follow-up (non-significant difference $p = 0.199$ between predicted and actual wound healing rate). In clinical trials, four weeks is a short period. However, in clinical practice, a shorter time for treatment outcome prediction may be necessary.

Table 5 Comparison of estimated wound healing rate with actual one. Wilcox on rank sum test was used

	Θ	Number of measurements
Θ_1 week	$p < 0.001$	2
Θ_2 weeks	$p < 0.001$	3
Θ_3 weeks	$p = 0.028$	4
Θ_4 weeks	$p = 0.199$	5
Θ_5 weeks	$p = 0.405$	6
Θ_6 weeks	$p = 0.508$	7

Θ = wound healing rate calculated from all collected data throughout follow-up
Θ_i = wound healing rate calculated from wound size measurements performed in first I-weeks of follow-up

3.2 *Prediction of wound healing rate from wound, patient and treatment data*

From the results of the statistical analysis reported above, it is obvious that the wound healing rate is directly dependent on wound treatment and wound grade, whereas the interactions of other wound and patient attributes on the wound healing rate are not easy to determine. We employed tree learning algorithms to build regression and classification trees to predict the wound healing rate based on initial wound, patient and treatment data. We also considered the estimated wound healing rate based on the mathematical model and built trees for the prediction of the wound healing rate after one, two, three, four, five and six weeks of follow-up. We tested several algorithms for attribute selection, among which RReliefF (ROBNIK-ŠIKONJA and KONONENKO, 1997) for regression-tree generation and ReliefF (KONONENKO *et al.*, 1997) for classification-tree generation were found to be the most effective. For models in the leaves of the tree, the most appropriate were linear equations for regression trees and median values for classification trees. A stopping rule of a minimum of five wound cases in a leaf was used. As the sample size ($n = 300$) was moderate, ten fold cross-validation was used as the error estimation method.

The accuracy of the classification trees was measured as classification accuracy (percentage of correctly classified test samples).

The accuracy of the regression trees was measured as relative error (relative error) (BREIMAN *et al.*, 1984). The relative error is always non-negative and usually less than 1. Trees with a relative error close to 0 produce a good prediction of the wound healing rate, and trees with a relative error around 1, or even greater than 1, produce poor prediction.

Some authors are using a measure of the proportion of the variance explained by the regression tree, although this terminology is not quite appropriate (BREIMAN *et al.*, 1984). It is calculated as (1 − relative error). We also used this measure to compare our results.

To obtain the right-sized tree and to obtain more accurate estimates of the true probability of mis-classification, the trees were pruned.

The idea of the RReliefF and ReliefF algorithms is to evaluate the partitioning power of attributes according to how well their values distinguish between similar observations. An attribute is given a high score if it separates similar observations with different prediction values and does not separate similar observations with similar prediction values. RReliefF and ReliefF sample the space of observations, compute the differences between the predictions and the values of the attributes and form a kind of statistical measure for the proximity of the probability densities of the attribute and the predicted value. Attribute partitioning powers (Table 6) calculated using RReliefF revealed that the initial wound area, followed by the

Table 6 Wound healing rate prediction capabilities of wound, patient and treatment attributes assigned by RReliefF

Attribute	Partitioning power of attributes after observation period of						
	0 week	1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks
Area, mm^2	0.135	0.168	0.171	0.161	0.127	0.123	0.122
Age, year	0.123	0.114	0.094	0.095	0.096	0.092	0.094
Appear start, week	0.119	0.121	0.104	0.131	0.121	0.114	0.115
Width-to-length ratio	0.096	0.098	0.099	0.095	0.103	0.108	0.113
Location	0.085	0.084	0.085	0.081	0.081	0.081	0.081
Treatment	0.066	0.058	0.051	0.052	0.050	0.051	0.051
Injury appear, month	0.062	0.065	0.044	0.050	0.035	0.040	0.039
Daily duration of treatment, min	0.046	0.039	0.031	0.035	0.025	0.025	0.026
Grade	0.046	0.039	0.057	0.048	0.048	0.047	0.043
Diagnosis	0.039	0.039	0.038	0.038	0.038	0.038	0.037
Aetiology	0.027	0.025	0.026	0.024	0.024	0.0239	0.024
Model estimation	0.000	0.399	0.602	0.626	0.663	0.659	0.670

Injury appear = elapsed time from spinal cord injury to wound appearance (month)
Appear start = elapsed time from wound appearance to beginning of treatment (week)
Model estimation = wound healing rate estimated from model of wound healing dynamics

Table 7 Dividing 300 wound cases into four classes according to their wound healing rate

Class	*Condition*	*Number of cases*	*A priori*
Non-healing wounds	$\Theta \leqslant 0.095$ mm per day	77	0.257
Slow-healing wounds	0.095 mm per day $< \Theta \leqslant 0.180$ mm per day	77	0.257
Medium-healing wounds	0.180 mm per day $< \Theta \leqslant 0.300$ mm per day	67	0.223
Fast-healing wounds	$\Theta > 0.300$ mm per day	79	0.263

Θ = wound healing rate

patient's age and time from wound appearance to treatment beginning are the best prognostic attributes. Important prognostic attributes are also wound shape (width-to-length ratio), location and type of treatment.

3.2.1 *Classification trees:* The domain of wound cases was divided into four classes according to Table 7. At the beginning of wound treatment, only the initial wound, patient and treatment data were available. We built classification trees with ReliefF. The resulting classification tree accuracy at the beginning of treatment was 30%, which is not much above the *a priori* probability of the most probable class (26%). Adding the model estimate of the wound healing rate after one week of follow-up improved classification accuracy to 41%. With data available for two weeks, the classification accuracy was 62% and, for three weeks, was 80%. Afterwards it slowly approaches 90% with six weeks of follow-up. In trees built after two weeks of follow-up only, the model estimate of the wound healing rate can be found in tree nodes.

We found that accurate prediction of the wound healing rate is possible when data are available for at least three weeks of follow-up. Therefore, with classification trees, we managed to shorten the required time of follow-up by one week. Only a rough estimate of the wound healing rate is possible after two weeks (Fig. 2).

3.2.2 *Regression trees:* Generated regression trees with linear equations in the leaves for the wound healing rate prediction at the beginning of treatment had a relative squared error greater than one, which means that the resulting regression trees are not usable. Adding the model estimate of the wound healing rate after one week of follow-up reduced the relative squared error to 0.64, which means that 36% of variance was explained by the tree. After two weeks, 65%, and, after three weeks, 82% of variance was explained. Afterwards it was slowly approaching 94% of explained variance in six weeks of follow-up (Fig. 3).

Regression trees are more useful than classification trees, because the wound healing rate was estimated as a continuous variable. The minimum follow-up period is two weeks. After five weeks, the wound healing rate predicted by a regression tree is equal to the healing rate estimated by the delayed exponential model. The predicted wound healing rate in a shorter period depends, in addition on wound, patient and treatment attributes. Regression trees built after two, three and four weeks of follow-up are presented in Figs 4, 5 and 6, respectively. The type of treatment is indirectly included in regression trees as daily duration of treatment, which was zero in the case of conservatively treated wounds. Important prognostic attributes seem to be wound area, grade, shape (width-to-length ratio), patient's age,

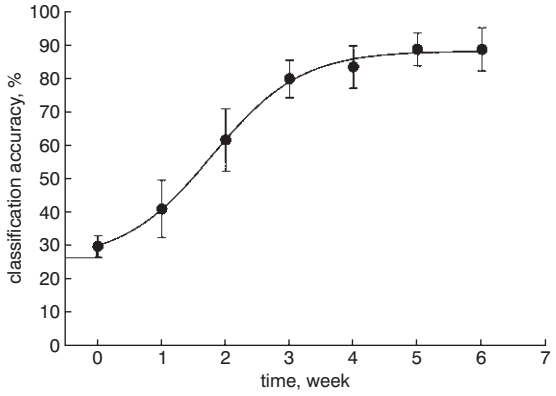

Fig. 2 *Classification accuracy of classification trees for wound healing rate prediction as function of observation time. Error bars present standard deviations of classification accuracy calculated by ten fold cross-validation method. Cases are classified into four domains: non-healing, slow-, medium- and fast-healing wounds*

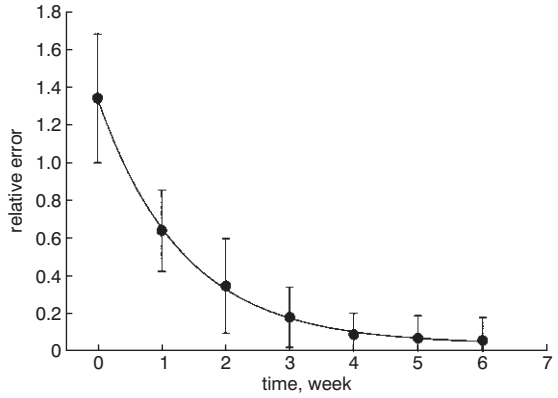

Fig. 3 *Relative error of regression trees for wound healing rate prediction as function of observation time. Error bars present standard deviations of relative error calculated by ten fold cross-validation method. In leaves of trees are linear equations*

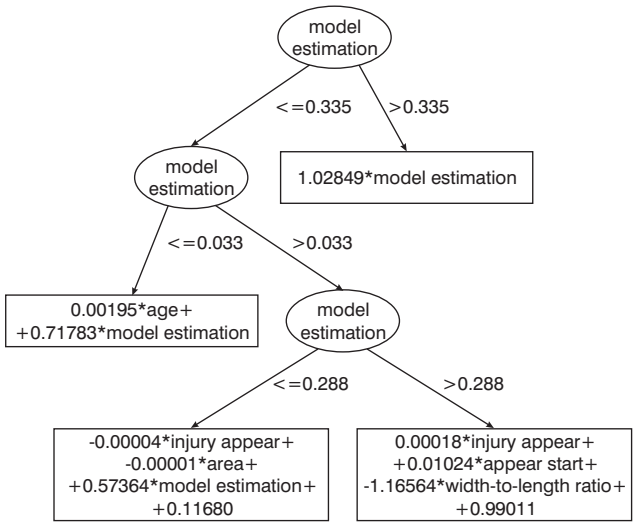

Fig. 4 *Regression tree with linear equations in leaves for prediction of wound healing rate after two weeks of treatment*

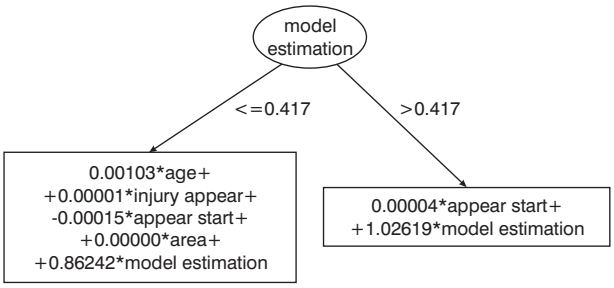

Fig. 5 *Regression tree with linear equations in leaves for prediction of wound healing rate after three weeks of treatment*

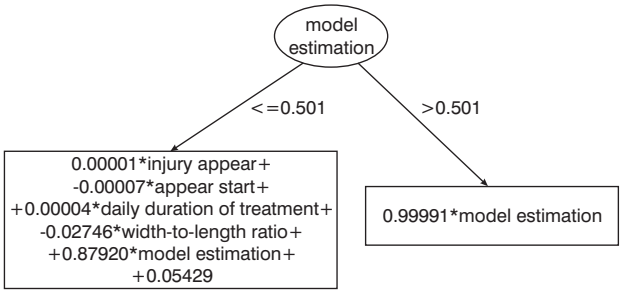

Fig. 6 *Regression tree with linear equations in leaves for prediction of wound healing rate after four weeks of treatment*

elapsed time from spinal cord injury to wound appearance and elapsed time from wound appearance to the beginning of treatment.

4 Conclusions

Electrically stimulated wounds healed faster and at a greater percentage than conservatively or sham-treated wounds. These results strongly support former findings that biphasic-current stimulation contributes to faster healing of chronic wounds (JERČINOVIĆ *et al.*, 1994). We noticed slightly slower healing of wounds treated with direct current than of wounds treated with biphasic current, but it still seems that both treatment modalities are effective. In future, it would be interesting to consider the effect of daily wound stimulation duration on wound healing rate.

The dynamics of wound healing can be accurately predicted after at least four weeks of the wound healing process follow-up. Therefore, for accurate wound healing rate estimation, wounds should be followed up for at least four weeks. In clinical practice, the wound healing rate, or the time to complete wound closure, should be estimated as soon as possible, so that an appropriate treatment can be selected, thus improving patient care.

Predicting the wound healing rate from initial wound, patient and treatment data collected in our database was not possible. The best prognostic factors are weekly follow-up measurements of wound area. We determined that the minimum follow-up period is two weeks. After three weeks, we were able to predict the wound healing rate at a classification accuracy of 80% when using classification trees, and to explain 82% of the variance with regression trees. The best results were obtained using regression trees with linear equations in the leaves.

The prognostic factors of wound healing are rarely analysed in the literature. None of the reports incorporates electrical stimulation as the chronic wound treatment modality. They are mostly based on initial wound and patient attributes. SKENE *et al.* (1992) observed 200 venous leg ulcerations and predicted the time to complete wound closure of the ulcer. They found the wound area, duration of ulceration, patient's age and depth of vein involvement to be the most important prognostic factors. A simple scoring system was presented for estimating the probability of ulcer healing in 40, 80 and 120 days at the beginning of treatment. The system was not tested on an independent set of wound cases, and therefore it may miss the prediction of new cases.

BIRKE *et al.* (1992) found wound depth and diameter significantly related to ulcer healing time. In 80 neurotrophic ulcers, a regression model including depth, diameter and age explained 36% of the variation in healing time on a learning set of wound cases. We managed to explain 36% of the variation in healing rate after a week of wound healing process follow-up on an independent set of wound cases. KANTOR and MARGOLIS (2000) presented a prognostic indicator of healing or non-healing at 24 weeks after following 104 venous leg ulcer areas over the first few weeks. The percentage change in area from baseline to week 4 provided the best combination of positive and negative predictive values (68.2%, 74.7%). In our study, after four weeks of follow-up, the classification tree has 84% classification accuracy. Considering also prognostic factors: deep vein involvement, ankle/brachial pressure index, lipo-sclerosis, oedema, exudates and granulation, which are reported in the literature (SKENE *et al.*, 1992; JOHNSON 1997), our prediction might be even more accurate.

The regression trees presented in combination with a mathematical model of wound healing dynamics form the core of the prognostic system for prediction of chronic wound healing rate. If the wound healing rate is known, then the information

provided can help to formulate appropriate management decisions, reduce the cost and orient resources to those individuals with poor prognosis.

Acknowledgment—This research was supported by the Ministry of Science & Technology of the Republic of Slovenia

References

BIRKE, J. A., NOVICK, A., PATOUT, C. A., and COLEMAN, W. C. (1992): 'Healing rates of plantar ulcers in leprosy and diabetes', *Leprosy Rev.*, **63**, pp. 365–374

BREIMAN, L., FRIEDMAN, J. H., OLSHEN, R. A., and STONE, C. J. (1984): 'Classification and regression trees' (Wadsworth International Group Belmont, California, 1984)

CUKJATI, D., KARBA, R., REBERŠEK, S., and MIKLAVČIČ, D. (2000): 'Modeling of chronic wound healing dynamics', *Med. Biol. Eng. Comput.*, **38**, pp. 339–347

CUKJATI, D., REBERŠEK, S., and MIKLAVČIČ, D. (2001): 'A reliable method of determining wound healing rate', *Med. Biol. Eng. Comput.*, **39**, pp. 263–271

FEEDAR, J. A., and KLOTH, L. C. (1990): 'Conservative management of chronic wounds' in KLOTH, L. C., MCCULLOCH, J. M., and FEEDAR, J. A. (Eds): 'Wound healing: alternatives in management' (F. A. Davis Co., Philadelphia, 1990), pp. 135–172

JERČINOVIĆ, A., KARBA, R., VODOVNIK, L., STEFANOVSKA, A., KROŠELJ, P., TURK, R., DŽIDIĆ, I., BENKO, H., and ŠAVRIN, R. (1994): 'Low frequency pulsed current and pressure ulcer healing', *IEEE Trans. Rehab. Eng.*, **2**, pp. 225–233

JOHNSON, M. (1997): 'Using cluster analysis to develop a healing typology in vascular ulcers', *J. Vasc. Nurs.*, **15**, pp. 45–49

KANTOR, J., and MARGOLIS, D. J. (2000): 'A multicentre study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks', *Br. J. Dermatol.*, **142**, pp. 960–964

KARBA, R., VODOVNIK, L., PREŠERN-ŠTRUKELJ, M., and KLEŠNIK, M. (1991): 'Promoted healing of chronic wounds due to electrical stimulation', *Wounds*, **3**(1), pp. 16–23

KARBA, R., ŠEMROV, D., VODOVNIK, L., BENKO, H., and ŠAVRIN, R. (1997): 'DC electrical stimulation for chronic wound healing enhancement. Part 1. Clinical study and determination of electrical field distribution in the numerical wound model', *Bioelectrochem. Bioenerget.*, **43**, pp. 265–270

KONONENKO, I., ŠIMEC, E., and ROBNIK-ŠIKONJA, M. (1997): 'Overcoming the myopia of inductive learning algorithms with RELIEFF', *Appl. Intell.*, **7**, pp. 39–55

LYMAN, I. R., TENERY, J. H., and BASSON, R. P. (1970): 'Correlation between decrease in bacterial load and rate of wound healing', *Surg. Gynecol. Obstet.*, **130**, pp. 616–620

ROBNIK-ŠIKONJA, M., and KONONENKO, I. (1997): 'An adaption of Relief for attribute estimation in regression' in DOUCH, F. (Ed.): 'Machine learning: Proc. 14th International Conference on Machine Learning' (Morgan Kaufman Publ., San Mateo, California, 1997), pp. 296–304

SHEA, D. J. (1975): 'Pressure sores classification and management', *Clin. Orthop. Rel. Res.*, **112**, pp. 89–100

SKENE, A. I., SMITH, J. M., DORÉ, C. J., CHARLETT, A., and LEWIS, J. D. (1992): 'Venous leg ulcers: a prognostic index to predict time to healing', *Brit. Med. J.*, **305**, pp. 1119–1121

STEFANOVSKA, A., VODOVNIK, L., BENKO, H., and TURK, R. (1993): 'Treatment of chronic wounds by means of electric and electromagnetic fields. Part 2. Value of FES parameters for pressure sore treatment', *Med. Biol. Eng. Comput.*, **31**, pp. 213–220

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