Prognostic factors, prediction of chronic wound healing and electrical stimulation

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Abstract – The aim of the study was to determine the effects of wound, patient and treatment attributes on wound healing rate and to propose a system for wound healing rate prediction. Predicting the wound healing rate from initial wound, patient and treatment data collected in our database of 300 chronic wounds was not possible. After considering weekly follow-ups, we determined that the best prognostic factors were weekly follow-ups of wound healing process, which alone were found to accurately predict the wound healing rate after minimal follow-up period of four weeks (at least five measurements of wound area). After combining them with wound, patient and treatment attributes, minimal follow-up period was reduced to two weeks (at least three measurements of wound area). After follow-up period of two weeks, we were able to predict the wound healing rate of an independent test set of chronic wounds with relative squared error 0.347, and after three weeks with relative squared error 0.181 (using regression trees with linear equations in its leaves). Results show that the type of treatment is just one of many prognostic factors. Arranged in the 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 up to now strongly support our former findings that the biphasic and direct current stimulation contributes to faster healing of chronic wounds.

Presented regression trees in combination with the mathematical model of the wound healing process dynamics represent a core of a prognostic system for the chronic wound healing rate prediction. If the wound healing rate is known, then the provided information can help to formulate appropriate treatment decisions.

Keywords – electric stimulation, inductive learning, predictors of wound healing

1 Introduction

Skin is a vital organ, in the sense that the loss of 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 also occur in a chronic manner, as in skin ulcers.

In more than a decade lasting 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 wound healing process was followed weekly. Up to now, 266 patients with 390 chronic wounds participated in the controlled study involving conventional conservative treatment, sham treatment, biphasic pulsed current and direct current electrical stimulation. Since first reports [JERČINOVIĆ *ET AL.*, 1994] confirmed 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 two hundred fifty chronic wounds of different aetiologies were treated by electrical stimulation. However, dynamics of the wound healing process does not depend only on the type of the treatment, but depends also on wound and patient attributes. The aims of our study were to determine the effects of wound, patient and treatment attributes on wound healing process and to propose a system for prediction of the wound healing rate. Only a limited number of groups have investigated wound and patient attributes which affect chronic wound healing. LYMAN *ET AL.* (1970) found significant relationship between 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: ABpI (ankle/brachial pressure index), liposclerosis (hardening and induration of the skin of the lower limb), edema and wound characteristics (exudate, granulation, ulcer area). None of the listed studies included treatment attributes.

Presently, the quantity of available data permits 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 predominant role in the wound healing process. Then we discussed the possibility to predict wound healing rate at the beginning of treatment based on initial wound, patient and treatment attributes. Finally we discussed the possibility to enhance the wound healing rate prediction accuracy by predicting it after a few weeks of wound healing follow-up.

2 Wound, patient and treatment data

During more than a decade lasting 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. Together, 266 patients with 390 wounds were recorded in our computer database up to date. Unfortunately, many patient and wound data are missing, and not all wounds were followed regularly or until the complete wound closure which is relatively common problem of clinical trials. Wound case inclusion criteria (initial wound area larger than $1cm^2$ and at least four weeks or until the complete wound closure following wound healing process) were fulfilled in 300 wound cases (214 patients). At the beginning of our study in 1989, wounds were randomly assigned into 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 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 other groups of patients.

For the evaluation of the efficacy of particular treatment modality or for the evaluation of the influence of wound and patient attributes on wound healing, it is necessary to periodically follow wound healing process. It was demonstrated [CUKJATI ET AL., 2001] that it is sufficient to follow wound area to determine wound healing process dynamics. Further, it was showed that wound shape can be approximated with an ellipse and it is thus enough to periodically follow mutually perpendicular diameters (largest wound diameter and diameter perpendicular to it) of the wound. From measured diameters, the wound area, the perimeter, and the width-to-length ratio were calculated. Therefore, to measure 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 of the wound, the depth can be underestimated because of invisible edge at the bottom of the wound and degenerative tissue, which fills up the wound. As 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 till complete wound closure. If the wound did not completely heal within the observation (inpatient) 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 the complete wound closure in 174 cases, and shorter in the 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, CUKJATI ET AL., 2001]. No significant difference between actual time to complete wound closure and 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 wound, patient, and treatment data collected in our computer database are listed. These data were selected to be 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 weekly during the observation period or until the complete wound closure. In further analysis we divided listed attributes into wound, patient and treatment attributes.

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 distribution of quantitative attributes in groups formed by qualitative attributes we used Kruskal-Wallis one-way analysis of variance. If difference was significant, we used two-sample Kolmogorov-Smirnov test to mutually compare distributions of quantitative attributes at specific values of qualitative attributes. To test relationship of qualitative attributes, we used chi-square test. To determine if two quantitative attributes are correlated, we used Spearman Correlation test.

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

Wound data
Length (of the wound)
Width (of the wound)
Depth (of the wound)
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

2.1 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 determined in 94%. Positive correlation coefficient (rs=0.568, n=128) and p value less than 0.001 show that wound grade tends to increase with increasing wound depth and also tends to increase with increasing initial wound 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). Since wound depth was strongly correlated to wound grade, and wound depth values were often missing, depth was omitted from further analysis. Also due to strong correlation between initial wound area and perimeter (rs=0.969, p<0.001, n=300), 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 were healing slower.

Other collected wound attributes were wound type, location, time elapsed from spinal cord injury to wound appearance (InjuryAppear) 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 long period would heal slowly (negative correlation coefficient when comparing AppearStart with the wound healing rate) (rs=-0.215, p<0.001, n=243). Small initial wound area (rs=-0.261, p<0.001, n=178) of wounds, which appeared a long time after spinal cord injury, is probably a result of better patients self care.

Wounds on 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 locations trochanter and sacrum than on gluteus or other locations (Table 2). Wounds on trochanter, gluteus and sacrum were all pressure ulcers.

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

Location	Trohanter	Sacrum	Gluteus	Other	*p*
Healing rate (*mm/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

Data format is median (interquartile range). *n* is number of collected data.

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 (p=0.236) differ for listed aetiologies though they were not randomly assigned into four treatment groups (p=0.001).

2.2 Patient attributes

Recorded patient attributes were age, sex, total number of wounds, diagnosis and, in case of spinal cord injured patient, degree of spasticity. The number of patients is lower than the number of wounds since one patient can have more than one wound. There were 154 patients with one wound, 45 patients with 2, 3 patients with 9, 4 patients with 3, 5 patients with 2 and 6 patients with 1 wound included in the study. Because 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 sacrum or trochanter were significantly younger (p<0.010) than patients with wounds on gluteus or other locations. No significant difference in age was found between wounds on trochanter and sacrum (p=0.513). Since age was not correlated to the wound healing rate (p=0.541), slow wound healing of trochanter wounds can not be a result of patient's age.

Most frequent diagnosis was spinal cord injury (71.7%). Trauma appeared in 11.3% of cases, diabetes mellitus in 7.3%, geriatrics in 3.3%, multiple sclerosis in 3.0% and venous diseases in 3.0% of wound cases. Wounds of geriatric (healing rate=0.271mm/day) and traumatic (0.224mm/day) patients were healing significantly faster (p=0.005) than wounds of patients with other diagnosis: spinal cord injury (0.173mm/day), vascular insufficiency (0.171mm/day), diabetes mellitus (0.102mm/day) and multiple sclerosis (0.138mm/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 other diagnosis, because there were almost no geriatric or traumatic patients with wounds on trochanter, which were found to heal slowly. The relation could also be otherwise, stating that wounds located on trochanter healed significantly slower than wounds on other locations because there were no wounds of geriatric and traumatic patients on this location. Geriatric (age=77 (72−88), n=77), diabetes mellitus (68 (60−77), n=22) and patients with venous diseases (63 (54−72), n=9) were significantly (p<0.001) older than spinal cord injury (36 (26−51), n=215), multiple sclerosis (41 (33−52), n=9) or traumatic (43 (25−74), n=34) patients. We found diagnosis strongly related to wound aetiology (p<0.001).

2.3 Treatment attributes

Wounds were randomly assigned into four treatment groups. All patients received conservative treatment of their chronic wounds [Feedar and Kloth, 1990]. The conservative treatment included initial selective debridement, the application of a new standard dressing to the chronic wound two or more times per day, as needed, and a broad-spectrum antibiotics in cases of infection, which were rather rare. 54 (18.0%) wounds received only conservative treatment. In addition to the conservative treatment, 23 (7.7%) wounds received sham treatment, where electrodes were applied to the intact skin on both sides of the wound for two hours daily and connected to stimulators, in which, however, the power source was disconnected and they delivered no current. Two different modes of electrical stimulation were used: direct and biphasic current. 42 (14.0%) wounds were stimulated with direct current of 0.6mA for half an hour, one hour, or two hours daily. Positive stimulation electrode overlaid the wound surface and 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 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 literature both electrode placements were shown to accelerate chronic wound healing; and in this way we kept otherwise small direct current stimulation group of wounds at the size that allowed us statistical analysis. 181 (60.3%) wounds were stimulated with biphasic, charge-balanced current pulses [Karba et al., 1991] for half an hour, one hour, or two hours daily with electrodes placed on both sides of the wound. The pulse duration was 0.25ms and a repetition rate 40Hz. The 4s 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 to 25mA) to prevent mechanical damage of the new-formed tissue.

The currents were applied across the wounds by a pair of self-adhesive skin electrodes (Encore TM Plus, Axelgaard Manufacturing Co. Ltd.) attached to the healthy skin at the edge of the wound. In direct stimulation group, where positive stimulation electrode overlaid 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 percentage of healed wounds against the time elapsed from the beginning of the treatment (Fig. 1) revealed differences between the four treatment groups.

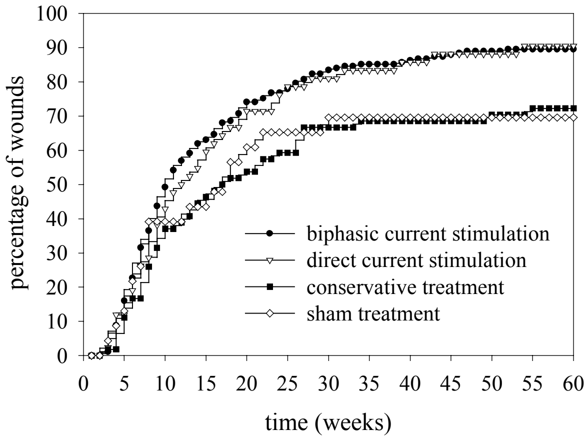

Fig. 1 *The percentage of healed wounds against the time elapsed from the beginning of the treatment for four treatment modalities.*

Electrically stimulated wounds healed at higher rate and extent than other wounds. Over 90% of electrically stimulated wounds healed within 60 weeks, while only 70% of sham treated wounds and 72% of conservative treated wounds healed within the same period. The wound healing rate revealed significant difference between four treatment groups. Results of 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 conservative or sham treated wounds. No significant difference was found in healing rates between wounds treated with direct current and wounds treated with biphasic current pulses. Difference in healing rates between direct current and conservative or sham treatment was considerable, in favour of direct current, although it was not significant. Conservative or sham treated wounds healed at the same rate.

Table 3 *Effects of four treatment modalities on the 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)

Though wounds were randomly assigned into four listed treatment groups, some differences in attribute distributions between 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 nonhealing wounds are not considered) between treatment modalities. Time elapsed from spinal cord injury to wound appearance was significantly shorter (p<0.001) in conservative treated and direct current stimulated group of patients than in sham treated and biphasic current stimulated group 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 sacrum (32%) and trochanter (33%) were significantly (p=0.026) more often included in conservative or sham treated group than wounds on gluteus (13%) and other locations (17%). Wounds on trochanter and sacrum were healing significantly (p=0.048) faster when treated with biphasic current pulses. Since electrically stimulated wounds healed faster than conservative or sham treated wounds, this can reveal why wounds on trochanter and sacrum healed slower than wounds on other locations. Only pressure ulcers were conservative (n=54) or sham treated (n=23). 35 pressure ulcers, 3 neurotrophic ulcers and 3 traumatic ulcers were treated with direct current and 136 pressure ulcers, 16 neurotrophic ulcers, 15 traumatic ulcers, 11 vascular ulcers and 3 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 healing rates obtained with two hour daily wound treatment, biphasic current stimulated wounds healed significantly (p=0.018) faster (0.166 mm/day (0.097–0.328)) than sham treated wounds (0.162 mm/day (-0.046–0.205)) and at the same rate (p=0.170) as direct current stimulated wounds (0.217 mm/day (0.098–0.450)). Direct current stimulated wounds healed faster, but not significantly (p=0.085), than sham treated wounds.

An hour direct current stimulated wounds, healed (p=0.067) slower (0.090 mm/day (0.089–0.120)) than two hour direct current stimulated wounds and significantly (p=0.001) slower than an hour biphasic current stimulated wounds (0.260 mm/day (0.190–0.460)). An hour daily biphasic stimulated wounds healed significantly (p=0.017) faster than two hour daily stimulated wounds and also faster than (p=0.357) half an hour daily biphasic current stimulated wounds (0.207 mm/day (0.152–0.309)). Two hours daily biphasic current stimulated wounds healed at the same healing rate (p=0.060) as a half an hour daily biphasic current stimulated wounds. Lack of wound cases stimulated for an hour daily (n=13), renders this result statistically unreliable. Further study should be performed to optimise daily duration of electrical stimulation.

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 calculated.*

	Total n=300	AC n=181	DC n=42	CO n=54	SH n=23	*p*
Age*	n=297	n=178	n=42	n=54	n=23	0.053
(*years*)	41 (28–59)	43 (30–62)	43 (25–59)	39 (23–51)	37 (23–57)	
InjuryAppear*	n=178	n=94	n=27	n=42	n=15	<0.001
(*months*)	5 (2–38)	11 (3–69)	3 (1–4)	3 (1–10)	6 (4–24)	
AppearStart*	n=243	n=150	n=33	n=44	n=16	0.247
(*weeks*)	8 (3–18)	7 (3–17)	6 (4–12)	13 (4–22)	8 (2–14)	
Area*	n=300	n=181	n=42	n=54	n=23	0.359
(mm^2)	634 (308–1871)	566 (283–1539)	660 (346–2108)	797 (432–2160)	661 (289–1180)	
Perimeter*	n=300	n=181	n=42	n=54	n=23	0.296
(*mm*)	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*	n=132	n=79	n=17	n=28	n=8	0.251
(*mm*)	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)	
II	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[a]	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#						<0.001
0 (*minutes*)	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*	n=276	n=178	n=40	n=42	n=16	0.631
(*days*)	63 (37–137)	63 (36–132)	64 (37–132)	83 (45–177)	64 (36–123)	
Healing rate*	n=300	n=181	n=42	n=54	n=23	0.007
(*mm/day*)	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)	

[a] Pes (15), calcaneus (25), genu (7), lower extremities (19), malleolus (2), humerus (5), stump (34), and ischium (3).
Data are *n*(%) or median (interquartile range). Percentages are calculated using all recorded data (*n*=300).
Attribute types: * continuous, #ordinal and ¤nominal attribute.
InjuryAppear = elapsed time from spinal cord injury to wound appearance,
AppearStart = elapsed time from wound appearance to the beginning of treatment.
AC = biphasic current stimulation, DC = direct current stimulation, CO = only conservative treatment and SH = sham treatment

3 Prediction of the wound healing rate

We defined the wound healing rate as the advance of wound margin towards the wound centre (eq. 1) [CUKJATI ET AL., 2001].

$$\Theta = 2\frac{S_0}{p_0}\frac{1}{T}[mm/day] \qquad (1)$$

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 till the complete wound closure. Because clinical trials are financially and time limited, the time to complete wound closure has to be predicted from performed measurements in observation period, which may be much shorter than time to the complete wound closure. Another reason for the need of prediction of the time to complete wound closure is to help clinicians in making decision whether to change the treatment or not. We decided rather to predict the wound healing rate 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 zero or negative. Negative value of the wound healing rate is the estimate of wound growth velocity towards its double initial area. From the wound healing rate the time to complete wound closure can easily be calculated.

3.1 Estimating the wound healing rate from the wound healing model

We determined that the wound area variation over time has a delayed exponential behaviour. Delayed exponential equation is thus the structure of mathematical model of the wound healing process and by fitting this model to a particular chronic wound case, parameters of the model are calculated. At least four measurements of wound area (performed in at least three weeks) are needed before parameters of mathematical model can be estimated. From parameters of mathematical model the time to complete wound closure was estimated [CUKJATI ET AL., 2001]. Because exponential function reaches the asymptote at infinite time, we estimated that the wound is healed when its estimated area is smaller than five percent of the initial value and also at the same time smaller than 1cm^2. According to Eq. 1 the estimated wound healing rate was calculated. To estimate the wound healing rate even earlier, the model with less parameters has to be introduced. Because 50% of wounds had the delay of wound healing process initiation less than a half of week, we used the two-parameter exponential model. To evaluate the parameters of this model, we performed the 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 to actual values calculated from observed times to the 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 only three weeks or less the difference was found to be significant.

From the known structure of 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. But in clinical practice a shorter time for treatment outcome prediction may be necessary.

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

	Θ	no. of measurements
$\Theta_{1\ week}$	$p < 0.001$	2
$\Theta_{2\ weeks}$	$p < 0.001$	3
$\Theta_{3\ weeks}$	$p = 0.028$	4
$\Theta_{4\ weeks}$	$p = 0.199$	5
$\Theta_{5\ weeks}$	$p = 0.405$	6
$\Theta_{6\ weeks}$	$p = 0.508$	7

Θ is the wound healing rate calculated from all collected data throughout the follow-up, and
Θ_i is the wound healing rate calculated from wound size measurements performed in the first *i*-weeks of follow-up.

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

From results of statistical analysis reported above, it is obvious that the wound healing rate is directly dependent on wound treatment and wound grade, while 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 mathematical model and built trees for 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 leaves of the tree, the most appropriate were linear equations for regression trees and median values for classification trees. A stopping rule of minimal five wound cases in a leaf was used. Since the sample size (n=300) was moderate, the 10-fold cross-validation was used as the error estimation method.

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

The accuracy of regression trees was measured as relative squared error (relative error) [BREIMAN *ET AL.*, 1984]. The relative error is always nonnegative and usually less than 1. Trees with relative error close to 0 produce good prediction of the wound healing rate and trees with the 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, though this terminology is not quite appropriate [BREIMAN *ET AL.*, 1984].. It is calculated as (1 – relative error). We also used this measure in order to compare our results.

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

	Partitioning power of attributes after observation period of						
Attribute	0 weeks	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
AppearStart (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
InjuryAppear (month)	0.062	0.065	0.044	0.050	0.035	0.040	0.039
Daily duration of treatment (minute)	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

InjuryAppear = elapsed time from spinal cord injury to wound appearance (month),
AppearStart = elapsed time from wound appearance to the beginning of treatment (week),
Model estimation = from model of wound healing dynamics estimated wound healing rate.

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

Class	Condition	No. of cases	Apriori
NONHEALING WOUNDS	$\Theta \leq 0.095$ mm/day	77	0.257
SLOW HEALING WOUNDS	0.095 mm/day $< \Theta \leq$ 0.180 mm/day	77	0.257
MEDIUM HEALING WOUNDS	0.180 mm/day $< \Theta \leq$ 0.300 mm/day	67	0.223
FAST HEALING WOUNDS	$\Theta >$ 0.300 mm/day	79	0.263

Θ – the wound healing rate

To obtain the right sized tree and to get more accurate estimates of the true probability of misclassification, 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. Attributes partitioning powers (Table 6) calculated using RReliefF revealed that initial wound area, followed by patients' age and time from wound appearance to treatment beginning are the most prognostic attributes. Important prognostic attributes are also wound shape (width-to-length ratio), location and type of treatment.

3.2.1 Classification trees

Domain of wound cases was divided into four classes according to Table 7. At the beginning of wound treatment, only 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 a priori probability of the most probable class (26%). Adding 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 with three weeks 80%. Afterwards it is slowly approaching 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 out 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 for one week. Only a rough estimate of the wound healing rate is possible after two weeks (Fig. 2).

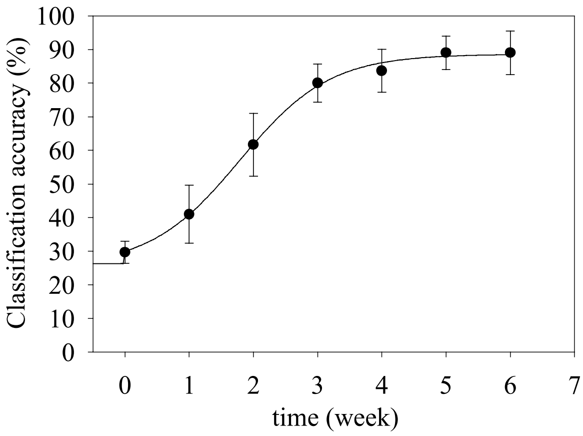

Fig. 2 *Classification accuracy of classification trees for the wound healing rate prediction as a function of observation time. Error bars present standard deviations of classification accuracy calculated by 10-fold cross-validation method. Cases are classified into four domains: NONHEALING, SLOW-, MEDIUM- and FAST-HEALING wounds.*

3.2.2 Regression trees

Generated regression trees with linear equations in leaves for the wound healing rate prediction at the beginning of treatment had relative squared error greater than one, which means that 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).

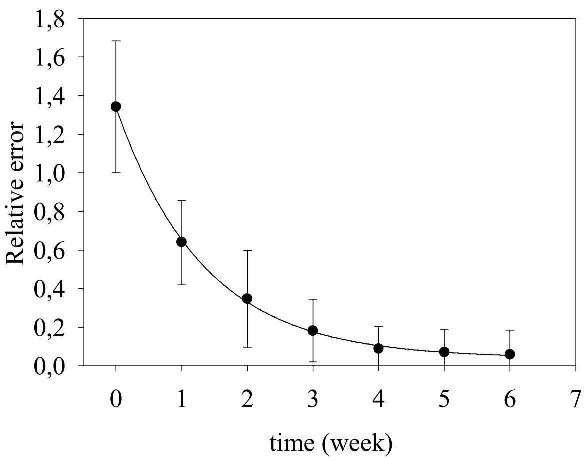

Fig. 3 *Relative error of regression trees for the wound healing rate prediction as a function of observation time. Error bars present standard deviations of relative error calculated by 10-fold cross-validation method. In leaves of trees are linear equations.*

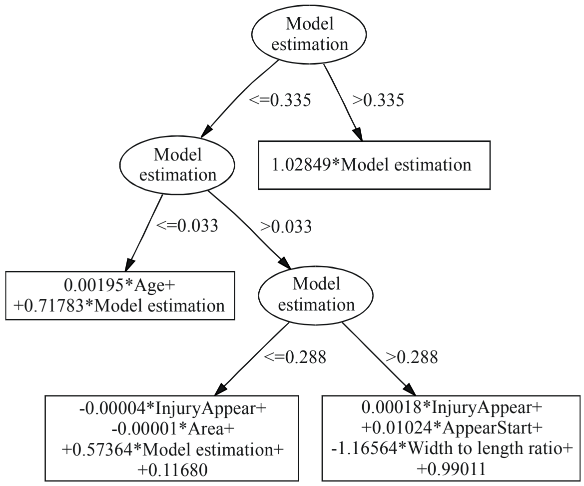

Fig. 4 *Regression tree with linear equations in leaves for prediction of wound healing rate after two weeks of treatment.*

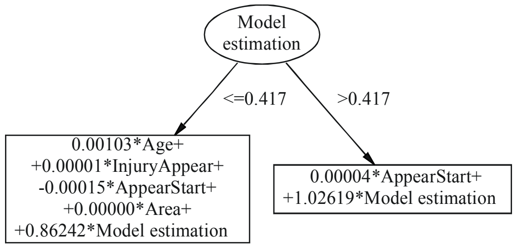

Fig. 5 *Regression tree with linear equations in leaves for prediction of wound healing rate after three weeks of treatment.*

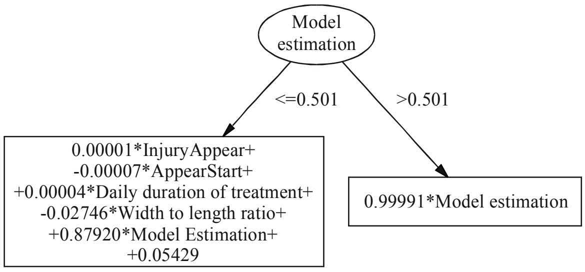

Fig. 6 *Regression tree with linear equations in leaves for prediction of wound healing rate after four weeks of treatment.*

Regression trees are more useful than classification trees because the wound healing rate was estimated as a continuous variable. The minimal follow-up period is two weeks. After five weeks, the wound healing rate predicted by regression tree is equal to the healing rate estimated by the delayed exponential model. The predicted wound healing rate in shorter period in addition depends on wound, patient and treatment attributes. Regression trees built after two, three and four weeks of follow-up are presented in Fig. 4, Fig. 5 and Fig. 6, respectively. Type of the treatment is indirectly included in regression trees as daily duration of treatment, which was zero in case of conservative treated wounds. Important prognostic attributes seems to be wound area, grade, shape (width to length ratio), patients age, elapsed time from spinal cord injury to wound appearance and elapsed time from wound appearance to the beginning of treatment.

4 Conclusion

Electrically stimulated wounds healed faster and at greater percentage than conservative 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 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.

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 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 to select an appropriate treatment and thus improve patient care.

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

Prognostic factors of wound healing are rarely analysed in the literature. None of 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, patients' age and depth of vein involvement as most important prognostic factors. 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 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 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 area over the first few weeks. 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, liposclerosis, edema, exudates and granulation, which are reported in the literature (SKENE ET AL., 1992; JOHNSON, 1997), our prediction might be even more accurate.

Presented regression trees in combination with mathematical model of wound healing dynamics present a core of the prognostic system for prediction of chronic wound healing rate. If the wound healing rate is known, then the provided information can help to formulate appropriate management decisions, reduce the cost and orient resources to those individuals with poor prognosis.

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