Biosensors and Bioelectronics 178 (2021) 112974

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: http://www.elsevier.com/locate/bios

Bioimpedance method for monitoring venous ulcers: Clinical proof-of-concept study

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ARTICLE INFO

Keywords:
Bioimpedance
Electrode array
Chronic wound
Monitoring

ABSTRACT

Evaluation of wound status is typically based on means which require the removal of dressings. These procedures are often also subjective and prone to inter-observer bias. To overcome aforementioned issues a bioimpedance measurement-based method and measurement system has been developed to evaluate the state of wound healing. The measurement system incorporated a purpose-built bioimpedance device, a measurement software and a screen-printed electrode array. The feasibility and the performance of the system and method were assessed in an open non-randomized follow-up study of seven venous ulcers. Healing of ulcers was monitored until the complete re-epithelialization was achieved. The duration of follow-up was from 19 to 106 days (mean 55.8 ± 25.2 days). A variable designated as the Wound Status Index (WSI), derived from the bioimpedance data, was used for describing the state of wound healing. The wound surface area was measured using acetate tracing for the reference. A strong correlation was found between the WSI and the acetate tracing data, $r(93) = -0.84$, $p < 0.001$. The results indicate that the bioimpedance measurement-based method is a promising quantitative tool for the evaluation of the status of venous ulcers.

1. Introduction

Evaluation of chronic wounds is typically based on visual means. Photographing and monitoring the size, the depth and the color of the wound are often applied. Additionally, a number of scoring systems has been developed to assist the wound assessment (Shai and Maibach, 2005). These methods, however, are either subjective and prone to inter-observer error, laborious and each of them require the removal of the wound dressings. The bioimpedance measurement-based method and measurement system has been developed in order to overcome the aforementioned issues (Kekonen et al., 2015, 2017, 2019).

Bioimpedance or biological impedance is defined as the ability of biological tissue to impede electric current. Bioimpedance describes the passive electrical properties of biological materials. Passive response occurs when biological tissues are excited through an external electrical current source. The electrical characteristics of biological tissues are frequency dependent (Kyle et al., 2004; Grimnes and Martinsen, 2008, 2015). The measurement system is comprised of a bioimpedance measurement device and an electrode array printed on a film-like substrate material. The method is based on a quasimonopolar bioimpedance measurement. Bioimpedance method may offer a non-interfering quantitative way to monitor the healing of a wound.

The objective of this study was to examine the feasibility of the bioimpedance measurement-based method and the measurement system in monitoring healing of hard-to-heal wounds. For this purpose we arranged a follow-up study of seven venous origin ulcers.

2. Materials and methods

2.1. The study protocol and population

The study protocol, the measurement method and principle used in this study was accepted to clinical utilization by the ethical committee of the Pirkanmaa Hospital District. Patients enrolled for the study gave an

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https://doi.org/10.1016/j.bios.2021.112974
Received 6 October 2020; Received in revised form 29 December 2020; Accepted 4 January 2021
Available online 7 January 2021
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informed consent prior the inclusion, as stipulated in the Declaration of Helsinki principles. The trial is registered to the ClinicalTrials.gov database provided by the U.S National Library of Medicine under registration number NCT02101645.

Inclusion and exclusion criteria were devised in collaboration with medical personnel. The criteria determined the wound type, the location of the wound, limited the initial surface area of the wounds to maximum 5 cm × 5 cm and the expected healing time for less than two months. This open non-randomized study consisted of seven venous origin ulcers of six patients with diagnosed venous insufficiency. The study consisted of three males and three females with an age range from 48 to 76 years (mean 65.0 ± 8.7 years). The patients and ulcers chosen for the study were assessed by a medical doctor.

The ulcers were studied using the bioimpedance measurement system at the Dermatology Outpatient Clinic, at the Tampere University Hospital, Finland. The ulcers were measured one to three times a week until the complete re-epithelialization of the wound was achieved.

2.2. The bioimpedance measurement system

The bioimpedance measurement system consists of an electrode array printed on a film-like substrate material, a bioimpedance measurement device and a PC software for controlling the measurement sequence (Kekonen et al., 2015).

2.2.1. The electrode array

The electrode array consists of the sensors performing the bioimpedance measurements on the wound area and the intact skin area adjacent to the wound. The circular shape wound electrodes are arranged in a 4 x 4-array formation into the centre area of the patch. The four counter electrodes encircle the electrode array (Fig. 1). The size of the electrode array including the counter electrodes is 9 × 9 cm and the connection tether is 20 × 6 cm. The thickness of the array is 30 μm.

The transparent substrate of the electrode array is composed of 15 μm thick polyethylene terephthalate (PET) foil on which the biomedical grade carbon ink electrodes are fabricated using the screen printing technique (Appendix B). An additional 15 μm layer of PET with 5 mm diameter circular perforations at each wound electrode location is laminated on top of the first layer to provide insulation between the electrode wiring and the wound constituents. In order to drain the excess moisture of the wound, the electrode array is perforated with varying size holes.

2.2.2. The bioimpedance measurement device and the software

The bioimpedance measurement device incorporation with the PC software, performs a predefined measurement sequence.

The design of the bioimpedance measurement unit is partly based on the examples given by Pliquett and Barthel (2012) and Margo et al. (2013) The impedance measurement functionality is built on the basis of the impedance analyzer chip AD5933 from Analog Devices (Analog Devices Ltd.). The device applies the sinusoidal excitation voltage with 0.4 V_{rms} and measures the impedance in two electrode mode at the discrete frequencies of 150 Hz, 300 Hz, 1 kHz, 5 kHz, 10 kHz, 20 kHz, 30 kHz, 50 kHz, and 100 kHz. Although the basic function of the device is based on the predetermined sequence of bioimpedance measurements, the multiplexer block enables the measurement electrodes to be chosen as desired. The measurement data collected by the device is transferred to the operator's PC wirelessly via a Bluetooth link.

Fig. 1 discloses the predetermined sequence for the wound and the skin impedance measurement, which acts as a reference. The reference impedance is measured according to Fig. 1(b–d) from the intact skin, first by the electrodes k1 and k2, then k2 and k3, and finally k3 and k4. The reference measurement sequence is iterated four times, a total of 12 measurements. The wound impedance is measured according to the example given in the Fig. 1(e–h). The wound impedance is measured using the electrodes a1 and k1, a1 and k2, a1 and k3, and a1 and k4. The same sequence of measurements is performed for all wound electrodes of the array.

2.3. Typical procedures during the patient visit

The patients visited the dermatology outpatient clinic one to three times a week. Wound dressings were removed and the wound was visually assessed by a wound specialist. The wound specialist conducted the standard local wound care procedure according to the state of the wound. The wound was photographed and the wound surface area was measured using acetate tracing (planimetry).

The electrode array was placed on a holder which was covered by a highly conductive silver fabric. A kettlebell weight of was placed over the array to provide a good electrical contact with the fabric. The electrode impedance was measured by performing a full scan of electrodes and frequencies (Appendix B). After the procedure, the array was cleaned using an antiseptic substance.

Before placing the electrode array on the wound, a small amount of mixture of commercial amorphous wound gel (Intrasite™, Smith &

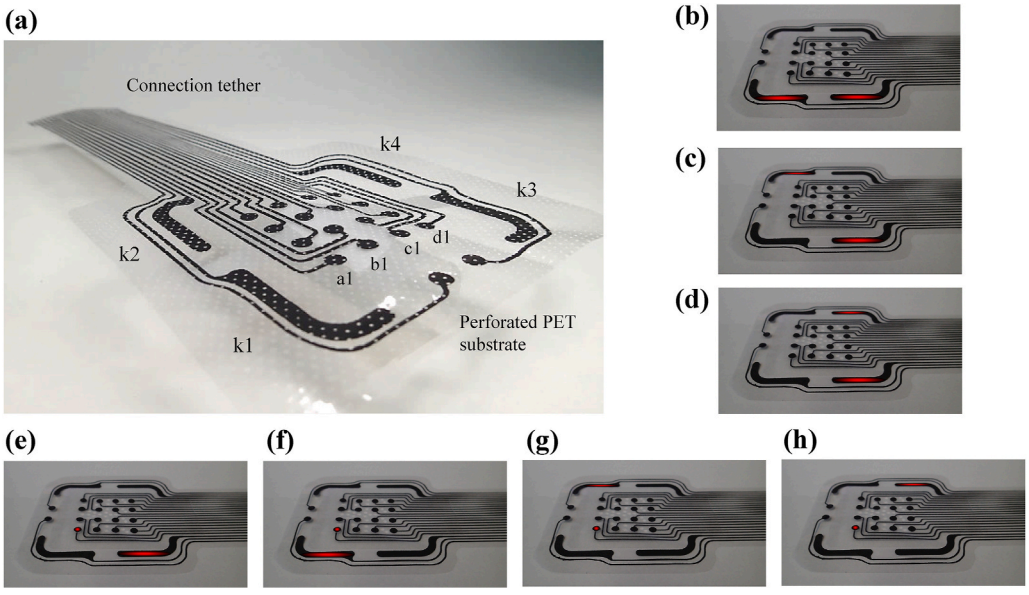

Fig. 1. A photograph of one embodiment of the electrode array (a). The circular wound electrodes a1 to d4 are arranged into 4 × 4 array to the center area of the patch. The counter electrodes k1 to k4 are arranged to the corners of the patch on the intact skin. The reference measurement sequence is represented in (b), (c), and (d). The reference sequence is iterated four times and an average reference value is determined. The wound measurement sequence for electrode a1 in (e), (f), (g) and (h). The wound measurement sequence is performed for all wound electrodes from a1 to d4 in similar fashion.

Nephew) and saline was applied on top of the electrodes as an electrolyte. Saline was added to reduce the viscosity of the Intrasite™ wound gel. Mixture was 75% Intrasite™ and 25% saline. The electrode array was placed on the wound and the application site was marked with a skin marker pen (Fig. 2a). A non-adhesive polyurethane foam dressing was placed on top of the electrode array (Fig. 2b). A gauze sock was then pulled over the wound dressing. Finally, a non-elastic compression bandage was folded around the leg so that the head of the connection tether of the array was left visible. The adapter of the bioimpedance device was then connected to the connection tether. After this, a full impedance scan was performed and the data was stored into a patient specific folder on a computer. The wound dressings and the electrode array were then removed. The array was disposed after the use. Finally the standard wound dressings were reapplied on the wound.

2.4. Data processing and statistical analysis

The modulus of impedance data at the frequencies of 150 Hz, 300 Hz, 1 kHz, 5 kHz, and 10 kHz was used in the data processing. The electrode impedances were subtracted from the reference and the wound impedance measurements. The average impedance of reference measurements (12 results) at each frequency (5 results) was calculated. The average impedance of the wound electrode measurements was calculated (4 results) for each wound electrode and at each measurement frequency (5 results). The ratio of the average wound impedance and average reference impedance was calculated for each wound electrode and at each measurement frequency. If the ratio exceeded the parity, then the ratio was designated as 1. The average of the ratios at each frequency was then calculated and the result was converted as a percentage number, which was named as the wound status parameter (1). The wound status parameters were then summarized in a table and colour encoded according to the value. Red indicates value below 50%, yellow between 50% and 70% and green from 70% to 100%. The area covered by the wound electrodes was divided into 49 × 49 cells and the linear interpolation method was applied to create a map of the area. The average value of the cells, designated as the Wound Status Index (WSI), was calculated with the standard deviation.

$$Wound\ status\ parameter(\%) = \{\frac{\frac{Z(f_1)_W}{Z(f_1)_R} + \frac{Z(f_2)_W}{Z(f_2)_R} + \ldots + \frac{Z(f_n)_W}{Z(f_n)_R}}{n}\}*100\% \quad (1)$$

The demographic data of the study population and the follow-up duration were expressed as mean ± standard deviation. Microsoft Excel was used in statistical analysis. Pearson's linear correlation analysis was applied in evaluation of the relationship between the wound surface area and the WSI.

3. Results

The ulcers were monitored till the full re-epithelization was achieved. The time range of follow-up duration was 19–106 days (mean 55.8 ± 25.2 days). One patient developed an erysipelas infection during the study period, however the infection was regarded as not associated with the study procedures. All patients had an edema in the lower extremities, typical for the venous insufficiency. The edema was treated using a compression bandage.

Fig. 3 represents the follow-up results of a typical ulcer in the study. The location of the wound is represented in (a), the placement of the electrode array and the naming of the electrodes are represented in (b) and (c). The wound status parameters are represented in a table format (d). The selected photographs depicting the progress healing are shown (e) with the corresponding colour encoded interpolation map of the measurement results (f). The interpolation map consists of 49 × 49 array of cells. The average value of cells of the interpolation map, the WSI, is shown with the standard deviation. The complete set of results of the wounds are shown in the Appendix A.

The study period of the wound represented in Fig. 3 was 106 days. During the first month the wound size and depth decreased significantly. On day 11 hypergranulation was treated using silver nitrate paste. The paste eroded the hypergranulated tissue. On day 35 a thin layer of neoepithelium was observed covering the wound. On day 40 a scab had formed on the wound. The scab was removed which opened the wound slightly. On day 44, a small calcified matter was removed from the wound. It was suspected that this matter was delaying the complete closure of the wound. Finally, the complete re-epithelization was achieved on day 99.

The scatterplot presented in Fig. 4 contains the wound surface area and the WSI data from all seven ulcers of the study. The wound surface area was determined by the acetate tracing of the ulcer. The variables were strongly correlated, the Pearson correlation coefficient was $r(93) = -0.84$, $P < 0.001$.

4. Discussion

In this study, we have applied the quasimonopolar bioimpedance measurement for the evaluation of venous ulcers. The strong linear correlation was found between the wound surface area and the WSI, the index determined by the bioimpedance measurements. The results indicate the potential of the bioimpedance measurement-based method for monitoring the wound healing.

The bioimpedance is a measure of the passive electrical properties of human tissue, or other biological material (Grimnes and Martinsen, 2015). The bioimpedance measurement has been widely used for measuring physiological phenomena in which the change in the electrical conductivity coincides with the physiological event of interest (Halonen et al., 2019; Kalvøy, 2010; Seppä et al., 2020). Bioimpedance has been also studied in dermatological research (Aberg et al., 2004; Kenworthy et al., 2017; Swisher et al., 2015).

The two electrode system is one of the three standard modes of bioimpedance measurement techniques, other two being the four electrode system (tetrapolar) and the three electrode system (monopolar). The sensitivity field of the four electrode system is complicated and may possess zero or negative values. Furthermore, the sensitivity field is strongly affected by the layout and the placement of the electrodes. By definition the four electrode system discards the high impedance contribution originating from the skin and the polarization impedance of the electrodes. The four electrode system is often used in applications

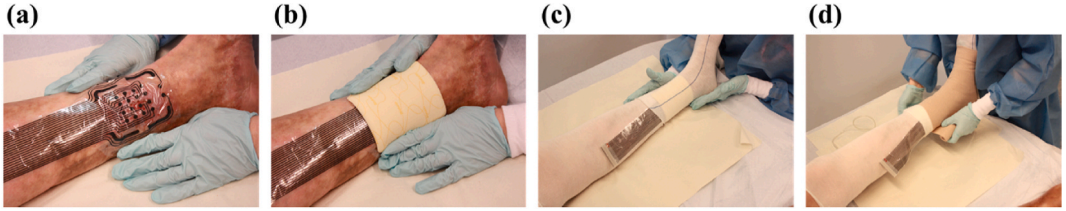

Fig. 2. Placing the electrode array and the dressings. The electrode array is placed on the wound (a). A wound dressing is placed on top of the electrode array (b). A gauze sock is pulled over the wound dressing (c) and the compression bandage was folded around the leg (d). AgNO3 refers to silver nitrate treatment for hypergranulation.

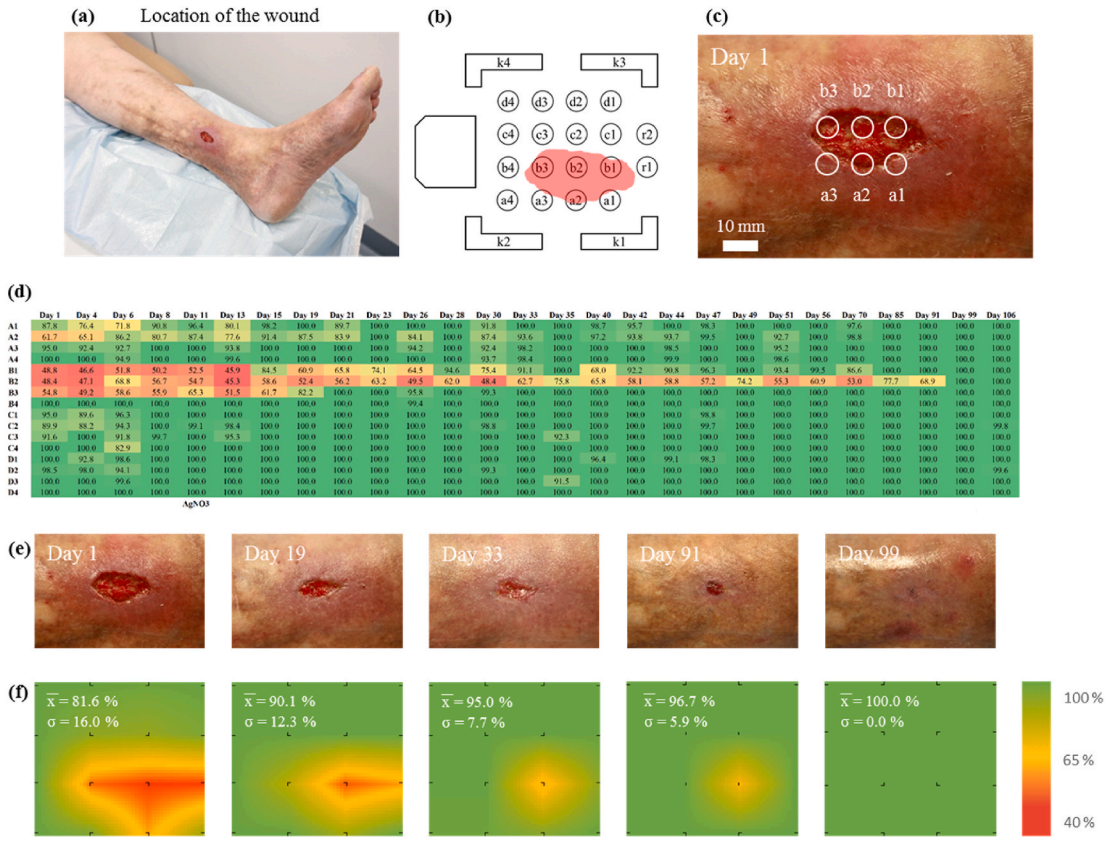

Fig. 3. The results of bioimpedance follow-up of a single wound. (a), (b) and (c) represent the location of the wound and the electrode array on day 1, (d) represent the wound status parameters for each wound electrode calculated according to equation (1). The measurement days are represented on the horizontal axis. (e) and (f) represent the progress of the wound healing. The average (the Wound Status Index, WSI) and the standard deviation are calculated from the data of the interpolation map and acts as an alternative representation of the overall condition of the wound. The photos and the corresponding interpolation maps are not in scale nor oriented. It should be noted that on day 19 the electrode array was accidently placed 2–3 mm above the initial location. The electrode b2 was then in the center of the wound, also electrode b1 was more pronouncedly on the wound, electrode b3 was now on the re-epithelized site. The new placement was used till the end of the study period.

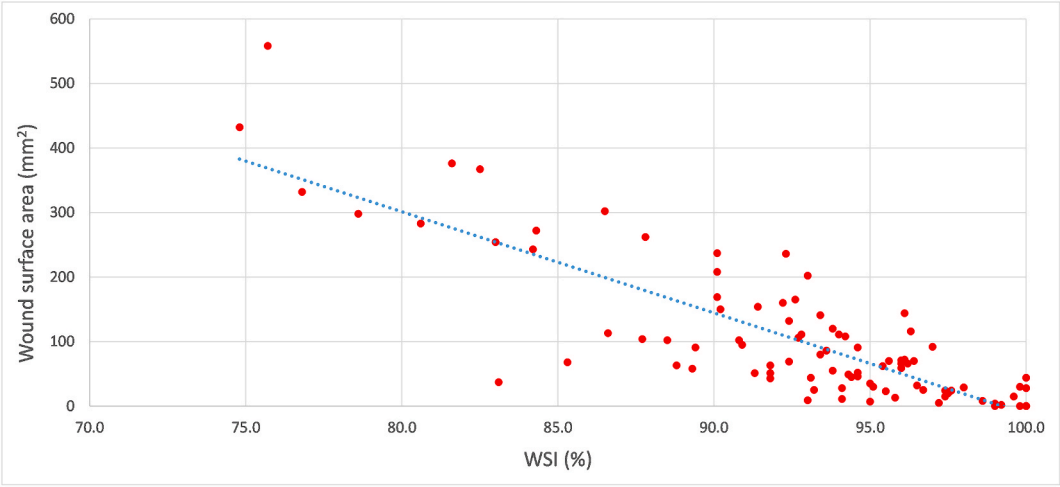

Fig. 4. The scatter plot presentation of the Wound Status Index (WSI) and the wound surface area. The points represent the data pairs gathered during the study from the seven ulcers. The Pearson correlation coefficient was $r(93) = -0.84$, $P < 0.001$.

where a dynamic, often subtle, physiological event (such as breathing parameters, blood circulation or fluid volume shifts) is studied. The three electrode system is affected by the polarization impedance of electrodes. It also has a sensitivity field which is affected by the layout and the placement of electrodes and may contain areas of negative sensitivity. The sensitivity is highest proximal to the measuring electrode, thus unlike the four electrode system, the impedance contribution from the skin is significant (Grimnes & Martinsen, 2008, 2015).

The two electrode system possesses only positive values of sensitivity. Thus, the measured impedance reflects more directly the

electrical properties of tissue and therefore it is sometimes described as the "true impedance". The undesirable electrode polarization impedance of both electrodes is present in the two electrode measurements. Bipolar electrode system is a two electrode system using two identical electrodes with equal surface area. The sensitivity is proportional to the current density squared. Therefore, the tissue proximal to the electrode surfaces has much higher contribution to the total impedance than the deeper tissue layers. If the homogenous volume (such as subcutaneous tissue) is covered by a poorly conducting homogenous layer (such as the skin) the current takes path perpendicular to the electrode surface to the well conducting layer (Grimnes and Martinsen, 2008). The quasimonopolar bioimpedance measurement consists of a two-electrode system where the electrodes are not equal in surface area. The contribution from the smaller electrode dominates the total impedance due to the higher current density and sensitivity (Grimnes and Martinsen, 2008, 2015). In this study we have utilized this feature to target the sensitivity to the area of interest. The surface area of the counter electrodes k1 to k4, which are placed on the intact skin is approximately 10 times larger than the wound electrodes in the array formation (a1 to d4).

Swisher et al. (2015) proposed a flexible multisensor array for early detection of pressure ulcers. The electrode array with 55 equally spaced electrodes was inkjet printed on a flexible plastic substrate. The measurement principle is based on bipolar bioimpedance method, but also tetrapolar measurement was experimented with lesser success. Each adjacent electrode pair is measured and an impedance and phase angle maps are formed from the results, The measurement frequency was 15 kHz and the excitation voltage 0.4 V_{rms}. The method was demonstrated on a rat models with pressure inflicted tissue damage. The skin area was measured intermittently for three days and distinctive decrease in impedance magnitude (from circa 20 kohm–5 kohm) were reported while irreversible progressive tissue damage occurred in the area of pressure. They also showed that reversible tissue damage with no visual sign of damage can be observed with the electrode system, manifested by impedance recovery from the initial decrease. Xiachuan et al. (2019) proposed a small sized wireless bipolar bioimpedance measurement device and a stretchable star shaped electrode system for monitoring wound healing. The electrode system incorpotes microneedles to ensure good contact with the skin and wound. The impedance is measured in bipolar fashion at 30 kHz frequency by the center electrode and one of the five outer electrode. They verified the measurement system by measuring healing in-vivo of two circular wounds of a porcine model with good results. Initially the wounds had a diameter of 2 cm, after 15 days the wounds had re-epithelized. The impedance increased during the healing process, the rate of increase substantially improved after couple of days and reached stable level after circa 48 h since. Although, studies performed by Swisher et al. (2015) and Xiachuan et al. (2019) are not intercomparable, nor comparable with our study as such due to differences e.g. in electrode geometry, these findings still suggest that the bipolar method is feasible for studying tissue interity or condition.

The low water content of the superficial layer of the skin, the stratum corneum, provides relatively poor electrical conductivity properties. Intact stratum corneum layer of the skin provides the far highest contribution to the total measured impedance. Even slight abrasion or addition moisture increases the conductivity of the skin. The electrical conductivity of biological tissues is strongly frequency dependent. At low frequencies (1 Hz–10 kHz), the conductivity of dry human skin is 10^{-7} S/m whereas wet skin has the conductivity of 10^{-5} S/m. The viable skin layers (dermis) and the subcutaneous tissue have significantly better conductive properties. For example, at low frequencies the muscle tissue has conductivity of 0.05–0.4 S/m. The blood and saline, which may be considered as comparable to wound exudate, have even higher conductivity, 0.7 S/m and 2.0 S/m (Grimnes and Martinsen, 2008). If the aforementioned tissue types are exposed, the measured impedance will considerably decrease. This was clearly observed from the WSI data in our study. The strengthening film-like neoepidermis most likely provides highest impact on increasing wound impedance as the wound heals, which was also discovered from the WSI data and supported by the findings of Swisher et al. (2015) and Xiachuan et al. (2019). Healing of a chronic ulcer is not straightforward, the healing may be halted or even take an adverse path. These implications were tried to be avoided by recruiting patients with good prognosis and recovery potential, also the wounds were chosen to be fairly small in size and depth to reduce the expected healing time for a reasonable period. Hypergranulation was removed in several occasions and debriding was also often required. Debriding was not controlled by its extent and occurred when needed, this may have affected into the impedance measurement results particularly in the early phases of healing. In certain occasions also treating the skin around the wound had to be done. The flaking skin had to be carefully removed and the skin area was then treated with skin oil or cream. In general, the overall condition of the intact skin area surrounding the ulcer is rarely completely unaffected. Daily variation of the skin moisture due to e.g. environmental conditions affect to the skin impedance. The gel provides insignificant contribution to the open wound impedance, but may also affect to the skin impedance via moistening effect. Therefore, in long-term monitoring (days) it might advisable to use more viscous electrolytes such as solid type hydrogels. The aforementioned factors have impact on the reference impedance and to the wound measurement, although it was not observed as substantially detrimental to the WSI results. The reference measurement was performed from multiple sites and averaged to migitate excess variation.

The existing standard wound assessment and monitoring regimes are typically based on visual evaluation and measuring the wound size. The current practices require the removal of wound dressings. Additionally, these methods are often subjective and prone to inter-observer bias. Removal of dressings, without medical necessity, expose the wound to cross-contamination and may induce re-injury, resulting in pain and delayed wound healing (Sood et al., 2014). Additionally, it may cause unnecessary loss in work time and materials. We have previously shown that the quasimonopolar bioimpedance method is feasible for long-term monitoring of an acute wound from beneath the primary wound dressings (Kekonen et al., 2019). It may be found particularly useful in home-care environment where wound care professionals are not readily available. In this study, we have shown that the quasimonopolar bioimpedance measurement-based method is a promising tool for monitoring the healing of venous ulcers in non-continuous manner. Strong linear correlation was found between the wound surface area and the WSI, regardless the fact that the wound surface area does not take into account e.g. the changes in the wound bed or moisture which fundamentally affect to the WSI. Semiquantitative wound charts similar to Bates-Jensen Wound Assessment Tool might provide a better comparative method for WSI than the acetate tracing as they typically record observations such as predominant tissue type of the wound bed and the amount of exudate among the other relevant factors (Harris et al., 2010).

The application of the bioimpedance method in the assessment of wound healing could decrease the number of unnecessary dressing changes, thus improve the healing outcomes and decrease the costs in wound care.

5. Conclusion

Clinical proof-of-concept study was arranged to evaluate the feasibility of the bioimpedance measurement based method and system for determining the status of wound healing. In this study seven venous ulcers were examined. Healing of the ulcers was followed till the complete re-epithelialization was achieved. A strong linear correlation was found between the wound surface area and the WSI, the index determined by the bioimpedance measurements. The results indicated that the bioimpedance measurement-based method is a promising quantitative tool for monitoring the status of venous ulcers. In the future, a study with a larger cohort should be arranged to validate the feasibility of the bioimpedance method. The study should focus on long-term

monitoring of the venous ulcers.

CRediT authorship contribution statement

Atte Kekonen: Writing - review & editing, Writing - original draft, Conceptualization, Methodology, Formal analysis, Visualization, Data curation. **Mikael Bergelin:** Writing - review & editing, Formal analysis, Conceptualization, Project administration, Funding acquisition, Supervision. **Jan-Erik Eriksson:** Writing - review & editing, Formal analysis, Conceptualization. **Annikki Vaalasti:** Writing - review & editing, Supervision, Resources. **Heimo Ylänen:** Writing - review & editing, Project administration, Funding acquisition, Supervision. **Sami Kielosto:** Writing - review & editing, Software, Resources. **Jari Viik:** Writing - review & editing, Conceptualization, Formal analysis, Supervision, Funding acquisition, All listed authors have reviewed the manuscript and have approved the manuscript for publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the Finnish Cultural Foundation (grant number: 00150386), the Graduate School of Tampere University and the Finnish Funding Agency for Technology and Innovation (TEKES) (project number: 1433/31/2012).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bios.2021.112974.

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