The effect of the BeST Device, a Bio Engineered Electrical Stimulation on Hard to Heal Chronic wounds.

Ram Avrahami[1], Zoie Milstein[2], Jonathan Rosenblum[3], Galit Sivak[2,4], Alon Avrahami[5]

Key words
BST; Electrical stimulation; Pain; Wound healing

[1] T.L.M Medical Center, Tel Aviv, Israel
[2]Tel Aviv University, Sackler Faculty of Medicine, Israel
[3] Department of Orthopedic Surgery, Shaare Zedek Medical Center, Jerusalem, Israel
[4] Vascular Department, Rabin Medical Center, Petah Tikva, Israel
[5] Hebrew University of Jerusalem, Faculty of Medicine, Israel

Correspondence to
Ram Avrahami, MD
T.L.M Medical
Center, HaBarzel 31,
Tel Aviv, 6971045
Israel
E-mail: dravrahami@gmail.com

Abstract

Introduction

Electric Stimulation (ES) is a known therapy for the treatment of chronic wounds. The authors evaluate the healing efficacy and pain reducing results of the BeST (E-Qure; Shilat, Israel) ES treatment on both Venous Leg Ulcers and Diabetic Foot Ulcers in a clinically supervised home setting.

Methods

In the period from March 2018 to September 2018, 30 patients having 36 hard to heal chronic wounds were enrolled and treated with the BeST as adjunct to SOC dressing for up to 20 weeks. The regimen was three 30 minutes daily treatments. The wounds and data were evaluated by an independent assessor and an independent statistician respectively. 4 patients were withdrawn for non-compliance. 26 patients having 32 wounds finished the trial Per Protocol (PP).

Results

Out of the 32 wounds PP, the incidence of fully healed wounds during the trial was: in 12 weeks 59% (21 wounds), in 16 weeks 66% (22 wounds) and in 20 weeks 78% (25 wounds).
Intend to Treat (ITT) healing incidence was 58% at week 12, 61% at week 16 and 69% at week 20.
Out of 7 wounds PP that were not fully healed in 20 weeks, in 5 wounds the area was reduced by more than 75%. Two wounds did not improve. Average treatment time for full healing was 55 days in 12 weeks, 60 days in 16 weeks and 73 days in 20 weeks. It was found that variables such as age and duration of the wound had no significant bearing on the final outcome.
At baseline 7 patients reported baseline pain of average 8.2 in Visual Analog Score (VAS). After BeST treatment the reported pain was reduced to average VAS 2.5 in a two weeks period.

Conclusion

The BeST Bio-engineered ES device was shown to be a very effective adjunct therapy for wound healing, while reducing pain, with no side effects. The BeST provides an effective and non-invasive treatment option in home setting and clinics

Introduction

The Problem

Chronic wounds cause great suffering to dozens of million people worldwide, causing tens of billions US$ in annual medical expenses due to long treatments and amputations[1].
The appearance of novel dressings and adjunct therapies such as Negative Pressure Wound Treatment (NPWT) and Hyper-Baric Oxygen Treatment (HBOT) have not altered the scene significantly[2].

Electrical Stimulation

Bioelectric activity in mammal's tissue was discovered already in the 19th century, and its appearance in human skin wounds was measured and documented by Dubois-Reymond[3]. The skin endogenous electrical potential, measured in acute wounds, is well known. It is also known that this potential decays over time in chronic-phase ulcers. Based on that, many researchers assume that endogenous electrical activity is linked to wound healing. (Fig 1)
It set the scene to assume that exogenous Electrical Stimulation (ES) could promote the healing of chronic wounds. It is supported by many in-vitro studies which proves that electrical stimulation enhances intracellular and extracellular processes, as reviewed by Luther C. Kloth[3].

The review describes the plurality of biological regeneration and healing processes promoted by ES, including the three phases of wound healing- (1) inflammation, (2) proliferation and (3) remodeling.

Listed below are the healing processes enhanced by electrical stimulation, as described by Kloth:

1. Protein (Collagen) and DNA synthesis
2. Inflammation: promoting Macrophage, Neutrophil and Leukocyte migration.
3. Proliferation: promoting Fibroblast migration.
4. Remodeling: promoting Myofibroblast, Keratinocyte and Epidermal cell migration.
5. Bactericidal effect.
6. Angiogenesis.
7. Tissue Oxygenation

Other ES researchers tried many potential ES signal forms, emitting them to wounds of all major etiologies, trying to replace or revive the missing electrical activity. Many of the signal's diversities were found to be significantly effective in wound healing[4,5,6,7].

In this study we used the BeST device, a Bio-Engineered signal device, which mimics the natural electrical activity measured in the vicinity of healing wounds. The BeST signal is also incorporating a TENS (Trans cutaneous Electrical Nerve Stimulation) pain relieving signal, in order to reduce pain, hence to prevent contraction of blood vessels, improve resting quality, patients' comfort and compliance.

The BeST is unique in incorporating this unique mimicked signal and pain-relieving signal, using low and safe voltage and non-intrusive contact to body.

Purpose of the study

The purpose of this study was to evaluate the safety and efficacy of a novel Bio-Engineered Electrical Stimulation device (BeST) on the healing incidence of chronic wounds in a home use environment setting.

Method - Setting and design

A prospective open-label, non-randomized one arm study. Patients with hard to heal diabetic foot ulcers (DFU) or venous leg ulcers (VLU) were enrolled into the study.
The study has been granted a permission by Clalit Helsinki Committee (Clalit is Israel's largest HMO, having about 5 million patients).
The study was performed in an outpatient chronic wounds' clinic, serving 4 geographical districts of Clalit having 2.5 million patients. The clinic treats daily around 50 patients, out of which the long duration ones were chosen for this study.

Inclusion criteria were:

- Patients with Venous Leg Ulcer (VLU) or Diabetic Foot Ulcer (DFU)
- Wound duration between 3 to 36 months
- Screening: Less than 10% wound area reduction during Standard of Care (SOC, i.e. dressing) for 28 days prior to enrolment.
- Wound size up to 25 sq cm.
- ABI (Ankle Brachial Index) > 0.7

Exclusion criteria were:

- Pregnancy
- Patient having cancer, pacemaker or defibrillator
- Patient having kidney malfunction (Creatinine>2.5)
- Malnutrition (Protein<2.5)
- Wounds with sinus tracts
- Infected wound requiring antibiotics

Enrolment took place in February-April 2018, and the treatments ceased in September 2018.

- All patients enrolled in the study were screened for 28 days ensuring there was less than 10% area reduction.
- All patients had gone blood and chemistry tests before enrollment, to measure and assure compliance with participation criteria.
- All patients were given instruction on the proper use of the BeST device, and were instructed to use it three times daily for thirty minutes per session, as least four hours apart. (Morning, Noon and Evening).

Beginning enrolment day and including day one, the patients were monitored, photographed and recorded once every two weeks. The study lasted up to full healing of the wound' or twenty weeks, i.e., up to 11 monitoring events.

Each bi-weekly event included:

- Physician's evaluation of wound condition
- Debridement upon necessity
- Identifying existence of infection
- Photography with a ruler placed in the wounds' plane, in order to record wound size. The picture was analyzed using ImageJ Software, in order to measure wounds' area.
- VAS score recording (only for those reporting pain on enrollment).

The endpoint analysis was executed on weeks 12, 16 and 20, in order to match other physical treatment studies, and to compare endpoints.

The BeST Device

The E-QURE BeST device is a computerized electrotherapy system based upon custom designed software which amplifies an imitation of the inherent electrical activity found on skin in the vicinity of acute wounds.
The BeST device is intended for home use as well as hospitals and long-term nursing homes. It is a self-contained unit with two soft and adhesive disposable electrodes placed in the vicinity of the wound. The distance of the electrodes from the wound is between 2 and 25 cm, depending on the location of the wound and the condition of the adjacent skin (Fig 2).
The BeST device is operated three times daily for thirty minutes per session. At treatment initiation, the BeST software automatically calibrates the amplitude to be attained during the session in accordance with the automatically measured combination of tissue/skin/electrodes impedance. The BeST device generates a balanced low-intensity current (a maximum current density of 0.32 mA/cm2 r.m.s.) with a net zero DC. This signal is a combination of hundreds of pulses per second, different from each other in duration, polarity and energy level emitting a meta-randomized sequence. In order to overcome compliance, safety and discomfort, the signal is emitted to patient through healthy skin only, and the Voltage is limited to +-12V.
There is an additional pain-reducing signal integrated with the healing meta-randomized signal. This additional signal is identical to known TENS (Trance Cutaneous Nerve Stimulation) signals, and is bi-phasic 2Hz square pulse train, requiring only 16 mS per second out of the treatment time.

Demography of patients and wounds

There were nine (9) males and six (6) females in the DFU group, having eleven (11) and eight (8) wounds respectively. There were five (5) males and six (6) females in the VLU group having six (6) and seven (7) wounds respectively. Total count was 19 DFU and 13 VLU.

The average age of the subjects was 77.4 (range 63-94) years, the average duration of the wounds at baseline was 8 months (range 3-20 month), and the average size of the wounds at baseline was 4.62 cm2 (range 0.11-21.22 cm2).
Wound sizes listed by etiology and sex at baseline and 20 weeks, plus age and duration of wounds are listed (Table 1).
A sub-group of nine (9) patients reported severe pains which had required use of opiate sedatives pain killers. Those 9 patients were monitored for pain using Visual Analog Score (VAS) score.
Baseline average pain was VAS 8.2 before treatment.

Results

Full healing

Out of the 32 wounds PP, the incidence of fully healed wounds during the trial was: in 12 weeks 66% (21), in 16 weeks 69% (22) and in 20 weeks 78% (25).
The full healing results shows a higher healing incidence of females (15) 100% of the group at 20 weeks, and a lower healing incidence of male (10) 59% of the group at 20 weeks. (Tab 1) (Fig 3).

wound improvement: Full healing and 75% area reduction.

An analysis of wound improvement was conducted: measuring the incidence of more than 75% in wound area reduction and full healing at 20 weeks.
In 20 weeks 94% of the wounds (30) either fully healed or were reduced by 75% or more. Male 75% area reduction incidence was 88% and female's area reduction incidence was 100%.
Only 2 wounds (6%) were not declined during treatment.

Pain Reduction

The nine (9) patients reporting pain at baseline had reported reduction of pain from VAS 8.2 to VAS 2.5, in two weeks and switching to moderate painkillers if at all.

Adverse events

There were no reported adverse events or safety issues with the device throughout the study.

Compliance

All patients were treated in a home setting. Four ITT patients dropped for non-compliance, and were omitted from the PP analysis. Repeated communication with the patients and their caregivers showed a high compliance of the patients to the BeST treatment and the study results proves it also.

Discussion

While Electric Stimulation has been an existing technology for more than a century, there has been little in the way of progress as to successfully incorporating the technology into the wound care field.
Kloth et al suggest that there are multiple effects of electric stimulation on tissue healing in chronic wounds[3]. There is an increase in Protein (Collagen) and DNA synthesis causing an immediate uptick in tissue production. There is a promotion of

Macrophage, Neutrophil and Leukocyte migration helping to cleanse the wound naturally. There is an increase in Fibroblast migration which when combined with the promotion of Myofibroblast, Keratinocyte and Epidermal cell migration causes new tissue formation and a closing of the wound. In addition, there is a proven Bactericidal effect. There is also noted Angiogenesis and an increase in tissue oxygenation.

Electric Stimulation can be applied in a multitude of variables. The type of current, shape of the current, method of application, time and duration of the therapy[8]. In accordance with the research, the European Pressure Ulcer Advisory Panel (EPUAP) as well as the American National Pressure Ulcers Advisory Panel (NPUAP) found that Electrical Stimulation enhanced pressure ulcer healing[9]. So did AHRQ, US Government research institute, finding Electrical Stimulation to be the only advanced (physical) treatment to be proven efficient as an adjunct treatment (to dressing) for pressure ulcers[10].

In this study we used the BeST device, which mimics the natural electrical activity measured in the vicinity of healing wounds. The BeST signal is also incorporating pain relieving signal. Contrary to high-voltage devices, The E-QURE BeST signal is limited to low voltage and low current density to prevent any cause of harm or inconvenience to the patient. The electrodes are located on healthy skin several cm from the wound and can't neither cause harm or discomfort nor interfere with the local dressing.

This study was a prospective open label study. The study was conducted on patients who were being offered the BeST therapy as part of their wound healing regimen. The drawback of this type of study was that there was no control.

Out of 32 chronic wounds with average duration of 8 months, within 20 weeks of BeST and SOC treatments, twenty-five (25) - 78% were fully healed, and thirty (30) - 94% had major improvement of 75% or more in wound area reduction. There were no adverse events reported during the study.

Conclusion

These study findings demonstrate that the E-QURE BeST device has a very positive effect on chronic wounds healing, while being easy to comply and operate. Further evaluation of a random controlled trial is needed to validate these results. Meanwhile, the device appears to serve as an excellent adjunct modality and to have a significant synergistic effect promoting wound healing of diabetic foot ulcers (DFU) and venous leg ulcers (VLU) in a clinic or home setting environment.

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Emily Haesler (Ed.)

EPUAP/NPIAP/PPPIA: 2019.

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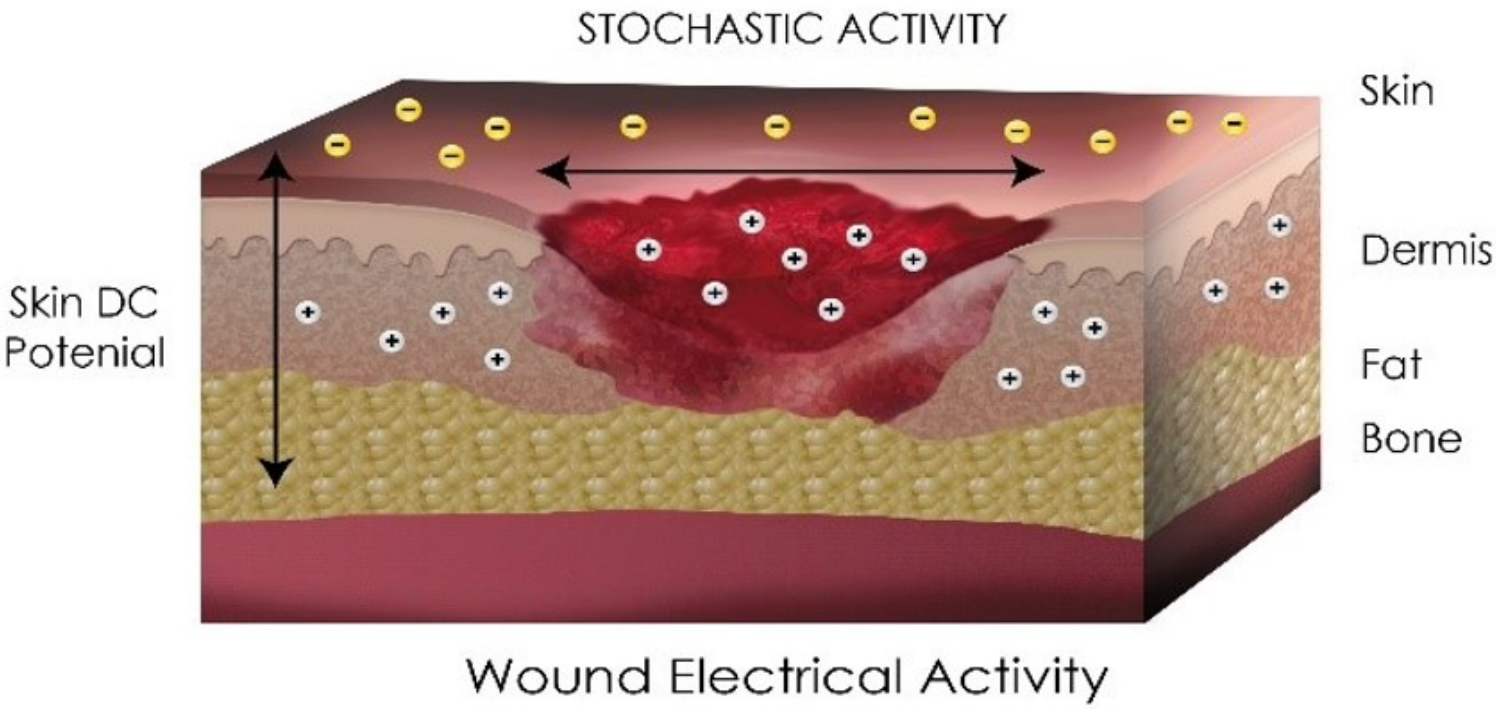
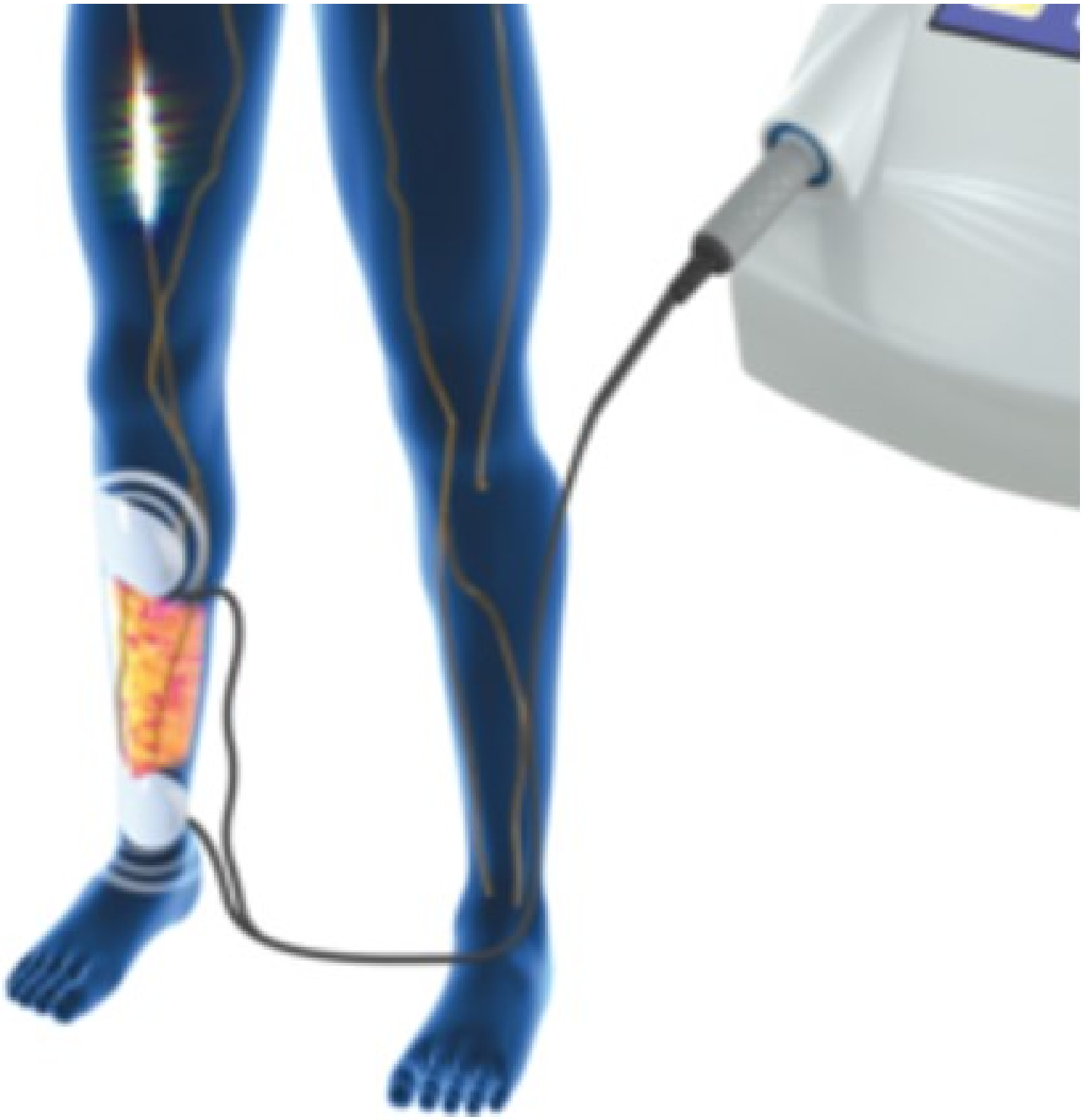
Table 1:

etiology and gender	patients no.	wounds no.	fully healed 12 weeks	**fully healed 12 weeks**	fully healed 16 weeks	**fully healed 16 weeks**	fully healed 20 weeks	**fully healed 20 weeks**
*VLU*males	5	6	3	50%	3	50%	3	50%
VLU females	6	7	6	86%	7	100%	7	100%
total VLU	11	13	9	69%	10	77%	10	77%
DFU males	9	11	6	55%	6	55%	7	64%
DFU females	6	8	6	75%	6	75%	8	100%
total DFU	15	19	12	63%	12	63%	15	79%
total males	14	17	9	53%	9	53%	10	59%
total females	12	15	12	80%	13	87%	15	100%
total	26	32	21	**66%**	22	**69%**	25	**78%**

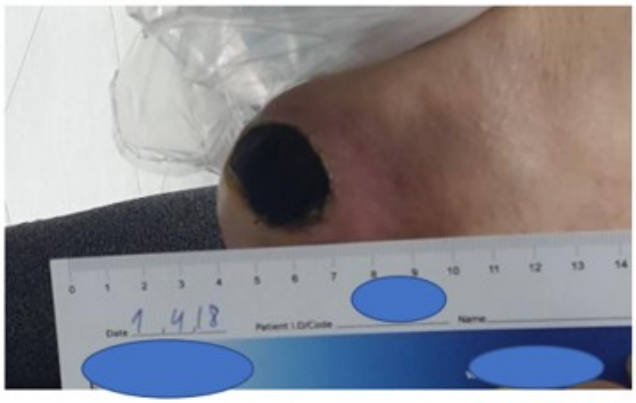

STOCHASTIC ACTIVITY
Skin
Dermis
Fat
Bone
Skin DC
Potenial
Wound Electrical Activity



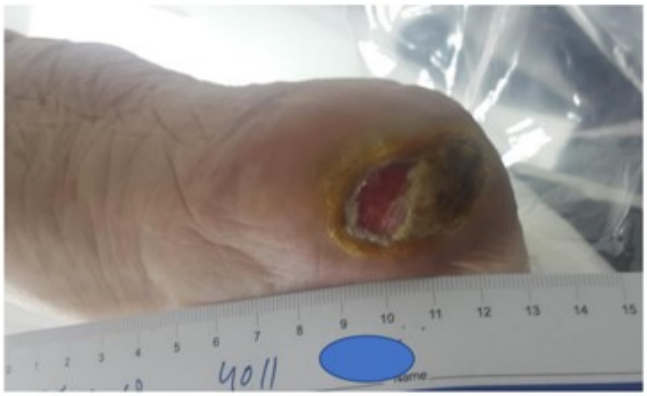
92 Years Old F, Pressure Wound (3 month wound duration)

Area reduction from 6.14 to 0 cm2 in 16 weeks

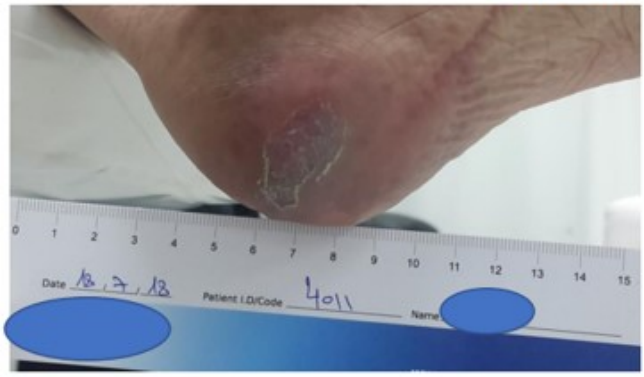
Week 0



Week 3



Week 16



Week 12