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The role of electrical stimulation and skin substitute in enhancing wound healing

Submission date	Recruitment status	[X] Prospectively registered
18/08/2021	Stopped	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
20/08/2021	Stopped	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
07/06/2022	Skin and Connective Tissue Diseases	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Skin is the largest human organ. It forms an essential barrier between the inside of our body and the environment. A wound is formed when there is a break in the skin. Wound healing is crucial to quickly restore skin integrity so that infection is prevented and internal functions can recommence.
The normal undamaged skin cells and tissue in your body possess very small electrical charges. These charges change when an injury breaks the skin's surface and are thought to be very important in helping the body to start the right biological processes in order for the wound to heal quickly. Many scientists have used electrical stimulation safely to encourage the different parts of the healing process in different body tissues for many years.
Additionally, bioengineered "Skin Substitutes" are the most recent development which have shown great promise in wound healing. They are processed to create a material that can be applied to a wound. There is growing evidence from clinical trials that these skin substitutes can speed up healing in chronic wounds including leg ulcers and burns which are often slow to respond to standard dressing treatments. However, there is minimal information about their effect when applied to acute wounds in people who have normal healing abilities.
In view of the positive effects of electrical stimulation and the use of skin substitutes in the treatment of cutaneous wounds, we would like to investigate if the effect of electrical stimulation accelerates the integration of the skin substitutes in normal wounds to speed up wound healing.

Who can participate?
Healthy volunteers aged over 18 years

What does the study involve?
• The total duration of the trial is 28 days.
• Following successful screening, you will sign a consent form
• After the initial appointment on day 0, participants will attend on day 3, day 7, day 10, day 14, day 17, day 21, day 24 and day 28.
• At each visit, non-invasive measurements will be taken to assess the wound/scar using handheld probes, and photographs will also be taken
• On the first visit (day 0) 4 biopsies will be taken from the left arm in order to create the wounds

/scars
• On Day 7, 5 mm biopsies will be taken over two of the wounds and scars so that they can be used to analyse healing at that time point. On day 14, a further two 5mm biopsies will be taken over the top of the remaining two scars on that arm. This process will then be repeated on the right arm starting on day 14 and this will continue to day 28.
• Participants will receive Placebo ES dressings and ES dressings and they will be applied to each arm depending upon randomisation.
• Skin substitute will be applied to two of the wounds on each arm on day 0 for the left arm and on day 14 on the right arm.

What are the possible benefits and risks of participating?
There are no direct benefits to participants in this study. Participants are carefully screened so that risks to them taking part (i.e. allergies to any of the topicals or local anaesthetic/dressings) are minimised. The main risk is that the wound site may bleed after the procedure and may feel a tender. As with any invasive procedure there is also a low risk that the site may become infected. We take precautions to ensure that the wound is clean and apply pressure and a special dressing to the wound to stop any bleeding. They are however left with a scar, which may take time to fade.

Where is the study run from?
Manchester University NHS Foundation Trust (UK) Wythenshawe Hospital Site

When is the study starting and how long is it expected to run for?
November 2019 to December 2022

Who is funding the study?
AccelHeal® Technologies Ltd (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
UREC 2020-9176-14934

Study information

Scientific Title
Role of electrical stimulation in enhancement of cutaneous wound healing and engraftment: Accelerated healing by secondary intention and dermal substitute-assisted tissue regeneration in cutaneous wounds

Study objectives
To assess the effectiveness of electrical stimulation in accelerating cutaneous healing & integration of a skin substitute in acute wounds compared to “normal” unassisted cutaneous wound healing.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/04/2020, University Research Ethics Committee 2 (2nd Floor Christie Building, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK; +44 (0)161 306 6000; research.ethics@manchester.ac.uk), ref: 2020-9176-14934

Primary study design
Interventional

Study design
Interventional single centre double-blind randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Assessment of cutaneous wound healing in healthy volunteers with and without skin substitute using electrical stimulation

Interventions
Participants are screened, consented and recruited. Participants receive 4 x 4mm punch biopsies to both upper inner arms to create the wounds. They are independently randomised as to which arm should receive either treatment or placebo.

Allocation to arm will be by a computer-generated randomised block method. This allocation list will be held by a University of Manchester person independent of the study team. The

participants will either have Active ES treatment on their Left or Right arms and this will be randomised to account for handedness. Both participants and researcher will be blinded as to which treatment is on which arm. Both Placebo/Sham device and Active ES device will look exactly the same. A member outside of the immediate research team will label the devices according to participant number on the randomisation list and the researcher will use these coded devices.

Treatment: Electrical stimulation dressing
Placebo: Sham electrical stimulation dressing
Two wound sites will have dermal substitute applied and two left without.
Wounds will be re-biopsied with 5mm punch biopsies at day 7 and day 14.
Non-invasive measurements are taken on a weekly basis for each participants' duration of the trial.
Final scar biopsies are used for histological, gene and protein analysis.

Intervention Type
Procedure/Surgery

Primary outcome(s)
1. Assessment of cutaneous wound healing using histological and immunohistochemical and gene studies at day 0, day 7 and day 14 (angiogenesis, inflammatory and neurogenic markers).
2. Wound closure measured by non-invasive devices including 3-dimensional imaging at days 0, 3, 7, 10 and 14 and laboratory analysis including wound contraction markers such as alpha smooth muscle actin measured at days 0, 7 and 14.
3. Angiogenesis measured by non-invasive devices including full-field laser perfusion imaging and dynamic optical coherence tomography at days 0, 3, 7, 10, 14 and protein and gene markers including CD31 and VEGFA on days 0, 7 and 14.
4. Inflammation and neurogenic markers measured by immunohistochemical analysis and QRTPCR on days 0, 7 and 14.

Key secondary outcome(s)
1. Assessment of cutaneous healing using objective non-invasive measurements on both arms on days 0, 3, 7, 10 and 14.
2. Wound elasticity (measured by elastometer) on days 0, 3, 7, 10 and 14. Skin colour (measured by colormeter) on days 0, 3, 7, 10 and 14.
3. Transepidermal water loss (measured by TEWL device) on days 0, 3, 7, 10 and 14.
4. Hydration (measured by hydration probe) on days 0, 3, 7, 10 and 14. Collagen (measured by SIAscopy) on days 0, 3, 7, 10 and 14.
5. Subjective scoring using VAS for pain, itch on days 0, 3, 7 , 10 and 14 for both arms.

Completion date
01/12/2022

Reason abandoned (if study stopped)
This trial was closed following discussions with the sponsors and University due to slow recruitment rate and the departure of the Principal Investigator.

Eligibility

Key inclusion criteria

1. Male and female subjects will be included to allow for gender demographic analysis.
2. Subjects of either gender who are 18 years and older.
3. Subjects who in the opinion of the investigator, are able to fully understand the study requirements and attend all follow-up visits.
4. Subjects must provide written informed consent to participate in the study.
5. Subjects weighing between 40 and 150kg, with a body mass index of 20-35kg/m2 (as described in the Quetelet'sindexQuetelet's index – weight (kg)/height^2(m)).

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Subjects who do not give consent or withdraw their consent to take part in the study.
2. Subjects of either gender who are less than 18 years old.
3. Subjects who have a history of keloid scarring.
4. Subjects who are pregnant or planning to conceive in the next 3 months.
5. Subjects who have a chronic or active skin disorder which may be considered to adversely affect the healing rate of the acute wound by the investigator.
6. Subjects with any likely wound healing impairment due to a clinically significant medical condition such as renal, hepatic, haematological, neurological or immune disease, including:
7. Rheumatoid arthritis
8. Chronic renal impairment
9. Diabetes Mellitus
10. Significant hepatic impairment
11. Inadequately or uncontrolled congestive heart failure
12. Malignancy – diagnosed or treated within the past 5 years.
13. Immunosuppressive, radiation or chemotherapy within the last three months.
14. Subjects who take medication known to alter/influence the healing of skin (e.g. steroids)
15. Subjects who are receiving formal oral anticoagulant therapy (warfarin).
16. Subjects who have received any investigational drugs, or have taken any in the previous month prior to day 0.
17. Subjects who have evidence of drug abuse.
18. Subjects who have had or are known to have hepatitis B or hepatitis C infection including carriers of hepatitis B surface antigen, hepatitis B core antibodies or hepatitis C antibodies. Previous vaccination against hepatitis B or C is not excluded.
19. Subjects who have previously had a positive result to the HIV antibody test, or admit to belong to a high risk group.
20. Any subject, who in the opinion of the investigator is unable to fully understand the

requirements of the trial, consent or is unable to return for follow-up visits and complete the trial.
21. Subjects who become systemically unwell during the research process due to external study causes.
22. Subjects who have been involved in other studies in the past month prior to day 0 must discuss the exact details of the previous studies prior to a decision being made on eligibility for inclusion in this trial.
23. Subjects with known severe allergies to antibiotics as the skin substitutes may contain antibiotic residuals from processing.
24. Patients who are allergic to other amide local anaesthetics.
25. Previous MRSA colonisation or infection
26. Any bleeding disorders
27. Subjects with any heart conditions
28. Subjects who have a pacemaker inserted
29. Subjects who have epilepsy
30. Subjects who currently have cancer

Date of first enrolment
01/09/2021

Date of final enrolment
01/09/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Wythenshawe Hospital
Manchester University NHS Foundation Trust
Southmoor Road
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M23 9LT

Sponsor information

Organisation
AccelHeal® Technologies Ltd

Funder(s)

Funder type
Industry

Funder Name
AccelHeal® Technologies Ltd

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request.

IPD sharing plan summary
Available on request