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Effectiveness and acceptableness of a portable device to deliver oxygen directly to long-standing foot ulcers

Submission date
29/07/2019

Recruitment status
No longer recruiting

Registration date
11/09/2019

Overall study status
Completed

Last Edited
22/11/2023

Condition category
Skin and Connective Tissue Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Diabetic foot ulcers (DFU) can lead to infection and further deterioration to health. They are a considerable burden to both the NHS and the patient. Clinicians have the option to treat the wound conservatively or more aggressively with oxygen. At present there is a lack of data available to aid clinicians in deciding what approach is best. Oxygen has been shown to be essential in wound healing, and extra oxygen supply to a wound may help it to heal quicker. This study will test if this is indeed the case by using a 'Natrox topical oxygen therapy device' that supplies extra oxygen directly to foot ulcers. We will also evaluate what patients think of the treatment and monitor for any safety events.
The device would be applied to the wound by the patient's podiatry team and the patient's normal dressings will be placed over the top. The patient is asked to wear the device until the wound is healed, or for 12 weeks, whichever comes first. The plastic tubing and 'web' that touches the wound will be replaced at regular podiatry appointments (maximum of 7 days apart). About every month, the battery pack may be replaced.
The main aim of the study is see if it is practical to evaluate the Natrox oxygen delivery device as a treatment for foot ulcers. We will also look at how quickly foot wounds heal and compare normal care versus normal care plus Natrox oxygen therapy. We will do this by measuring and taking photos of the wound (six times over 12 weeks).
The study would also like to answer the following questions; how is the device to use (feedback from people using Natrox)? How does having a foot ulcer affect quality of life, and does Natrox affect the presence of any bacteria present in the foot ulcer? We will do this by asking participants to complete some short questionnaires, and by taking some microbiology swabs from the wound.

Who can participate?
Patients with a foot ulcer being managed by the podiatry service can take part who meet all of the following criteria: who are over 18 years of age, where the foot ulcer is at least 6 weeks old, with no active infection in the foot ulcer currently being treated by intravenous antibiotics

What does the study involve?
There are no extra appointments involved in taking part in this study. Any activity relating to the study should take place at the patient's usual Podiatry appointment. The first 4 weeks of the study are called the 'screening phase'; if the wound heals by 50% or more than the patient is not eligible for the main 'trial' phase and participation ends.
If the foot ulcer heals by less than 50% then the patient will continue into the 12-week trial phase. At the 4-week point, the patient will be randomised to either care as usual or care as usual plus Natrox oxygen therapy. This a one in two chance of being allocated to the Natrox treatment arm of the study. After allocation, you will be followed up for a further 12 weeks, meaning that participation will last 16 weeks in total.

What are the possible benefits and risks of participating?
Participants receiving the Natrox device may benefit from improved foot ulcer healing (compared to usual care). However, although there is some evidence that this is the case, it is not yet proven beyond doubt. This study aims to see how effective the Natrox device is.

Natrox is a licensed medical device, and the product has a CE mark. Risk of a reaction, or increased risk because of the use of Natrox, will be extremely low, because the oxygen flow is relatively low at 15 ml/hour. Because of the strict manufacturing standards, there should be no risk of infection from the medical device itself. However, if a healthcare professional or the research team learn of important new information that might affect the willingness of a participant to remain in the study, they will let the patient know. Also, this study aims to check the safety of using the Natrox device for the treatment of foot ulcers. Appropriate precautions are in place to ensure all medical and personal information is kept safe. The number of visits associated with the study is not any more than the number of visits that would be involved in usual treatment. If the wound heals before the end of the 12-week intervention phase then the patient will be discharged as per normal care.

Where is the study run from?
The study is run by Cumbria Partnership NHS Foundation Trust, through the Community Services and Research Department

When is the study starting and how long is it expected to run for?
The study is recruiting participants from August 2019 until July 2022.

Who is funding the study?
1. Inotec AMD Limited, UK
2. Academic Health Sciences Network

Who is the main contact?
Ms Katie Boichat (Specialist Podiatrist), Chief Investigator for ANODE
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Contact information

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Scientific

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Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
41693

Study information

Scientific Title
Prospective, multicenter, randomised controlled feasibility trial of the application of NATROX® topical oxygen therapy in patients with chronic and delayed healing foot ulcers

Acronym
ANODE

Study objectives
ANODE wishes to determine the feasibility of conducting a full RCT in the future, while also assessing the acceptability and effectiveness of the Natrox oxygen device. As such, the study

does not lend itself to a hypothesis. However, a future hypothesis would be that chronic and delayed-healing foot ulcers will heal quicker using a “Natrox topical oxygen therapy device” compared to standard care.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 19/07/2019, Health and Care Research Wales (Castle Bridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; HCRW.approvals@wales.nhs.uk; +442920 230457), ref: 19/ES /0073
2. Approved 19/07/2019, East of Scotland Research Ethics Service (Tayside Medical Science Centre, Residency Block Level 3, George Pirie Way, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK; eosres.tayside@nhs.net; +44 1382 383871), ref: DL/19/ES/0073

Study design
Non-randomised; Interventional; Design type: Treatment, Device

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Not specified

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Foot ulcer

Interventions
Current intervention as of 03/03/2022:
The NATROX® oxygen wound therapy device is a licensed battery-operated class II medical device, which via a ‘web’ shaped applicator delivers approximately 15 ml of oxygen per hour to the wound.

In this study, twenty patients, recruited from two NHS Trusts, will be enrolled in a real-world evaluation study. Patients will be eligible for NATROX® therapy if, according to standard practice, their wound has not healed by at least 50% in the four weeks prior. Clinical (wound status) and patient-reported outcome measures will be collated at baseline, and periodically up to 12 weeks. The wound-related costs, including staffing, clinics, dressings and diagnostics will be included in this analysis. Since the NATROX® device is already CE-marked, it can be

incorporated in standard wound care practice across the UK without the need for regulatory delays and with minimal need for staff training. However, this is provided NATROX® proves to be effective, safe, and cost-effective.

If patients decide to take part in the study, one of the research staff, which may be the regular podiatrist, will take written consent. Once written informed consent has been obtained, they will enter the 4-week long screening phase (week -4 to 0).
After the first four weeks, they will either qualify for randomisation and 12-week intervention phase (if healing is less than 50% in screening phase) or they complete the study (if the wound heals 50% or more in screening phase).

Those who are randomised are allocated to either:
- treatment as usual (control) arm
- treatment as usual plus Natrox oxygen therapy arm

Then they will all start the trial phase, which lasts 12 weeks, but there will be no change to how many times they see their podiatrist and where they see them. The research visits that coincide with podiatry appointments are:
- Week -4. Informed consent. Ulcer size and wound characteristics/baseline clinical information
- Week 0. Collection of Ulcer size and wound characteristics plus patient questionnaires (quality of life, wound impact), microbiology swabs.
- Week 3, 6 , 9, 12, Research follow-up visit (at same time as regular visits to podiatry), measurement of wound (all visits), quality of life and wound-related pain (week 0, 6, 12 only), and patient experience questionnaire (week 12 only, or when wound has healed).

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- Week 0. Collection of Ulcer size and wound characteristics plus patient questionnaires (quality of life, wound impact), microbiology swabs.
- Week 3, 6 , 9, 12, Research follow-up visit (at same time as regular visits to podiatry), measurement of wound (all visits), swab of wound for microbiology testing , quality of life and wound-related pain (week 0, 6, 12 only), and patient experience questionnaire (week 12 only, or when wound has healed).

Intervention Type
Device

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
NATROX® oxygen wound therapy device

Primary outcome measure
1. Natrox arm only: Participants' experience of and compliance with Natrox oxygen therapy is measured using a bespoke questionnaire at 12 weeks.

Assessed at the end of the study:
2. Recruitment and attrition rates, willingness of patients to consent and to be randomised, response rates to questionnaires, and degrees of missing data
3. Testing of eligibility criteria and ability/willingness of clinical staff to partake in recruitment and follow-up of participants
4. Adequacy of duration of follow-up (e.g. in relation to foot ulcer healing) as measured by the number of appointments made for and attended by the patient relating to the foot ulcer
5. Appropriateness of inclusion/exclusion criteria and outcomes measures (both clinical and patient-reported)

Secondary outcome measures
Current secondary outcome measures as of 03/03/2022:
1. Clinical characterisation of the wound -- including clinical opinion of infection (none, possible, infected), erythema (none, slight, significant), purulence (none, slight, significant), and odour (none, low, moderate, high) – is completed at the start of the screening period (-4 weeks), baseline, 3, 6, 9, and 12 weeks
2. Ulcer size is measured by Coloplast grid or suitable equivalent at the start of the screening period (-4 weeks), baseline, 3, 6, 9, and 12 weeks
3. Ulcer severity is measured by the Pressure Ulcer Scale for Healing (PUSH) at the start of the screening period (-4 weeks), baseline, 3, 6, 9, and 12 weeks
4. DFU ulcers only: diabetic ulcer severity is measured by the Site, Ischemia, Neuropathy, Bacterial Infection, and Depth (SINBAD) classification system at the start of the screening period (-4 weeks), baseline, 3, 6, 9, and 12 weeks

5. Wound closure status in terms of healed, not healed, or recurrence is recorded at the start of the screening period (-4 weeks), baseline, 3, 6, 9, and 12 weeks
6. Quality of life is measured using two tools -- the Cardiff Wound Impact Questionnaire (CWIQ) and the EQ-5D-5L -- at baseline, 6, and 12 weeks
7. Safety of applied oxygen therapy in comparison to standard care arm is an ongoing outcome measure and is quantified by wound infection incidence and need for secondary interventions, such as surgery

Previous secondary outcome measures as of 17/08/2021:
1. Clinical characterisation of the wound -- including clinical opinion of infection (none, possible, infected), erythema (none, slight, significant), purulence (none, slight, significant), and odour (none, low, moderate, high) – is completed at the start of the screening period (-4 weeks), baseline, 3, 6, 9, and 12 weeks
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7. Wound swabs are taken and processed to determine culture (bacterial growth and species identification) and antibiotic sensitivity at the start of the screening period (-4 weeks), baseline, 3, 6, 9, and 12 weeks
8. Safety of applied oxygen therapy in comparison to standard care arm is an ongoing outcome measure, and is quantified by wound infection incidence and need for secondary interventions, such as surgery

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5. Wound closure status in terms of healed, not healed, or recurrence is recorded at the start of the screening period (-4 weeks), baseline, 3, 6, 9, and 12 weeks
6. Pain is measured using the visual analogue score (VAS) at the start of the screening period (-4 weeks), baseline, 3, 6, 9, and 12 weeks
7. Quality of life is measured using two tools -- the Cardiff Wound Impact Questionnaire (CWIQ) and the EQ-5D-5L -- at baseline, 6, and 12 weeks
8. Wound swabs are taken and processed to determine culture (bacterial growth and species identification) and antibiotic sensitivity at the start of the screening period (-4 weeks), baseline, 3, 6, 9, and 12 weeks

9. Safety of applied oxygen therapy in comparison to standard care arm is an ongoing outcome measure, and is quantified by wound infection incidence and need for secondary interventions, such as surgery

Overall study start date
01/05/2019

Completion date
31/10/2022

Eligibility

Key inclusion criteria
1. Clinical diagnosis of a Foot Ulcer, present on area that is measurable with a grid sheet (this can include plantar, calcaneus, dorsal, hallux, apex, or ankle based ulcers). This includes DFU, peripheral arterial disease related wound, or other aetiology
2. No minimum chronicity applicable for the index foot ulcer
3. Adult patients aged > = 18 years
4. Patients with recurrent wounds, including multiple wounds, are eligible. The largest of the wounds, that is measurable with a grid sheet, will be selected for the trial
5. Mental capacity to give consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 24; UK Sample Size: 24

Total final enrolment
28

Key exclusion criteria
Current participant exclusion criteria as of 03/03/2022:
1. Limited life expectancy, i.e. undergoing palliative care
2. Active infection in foot ulcer that cannot be managed in podiatry service (ie requires specialist secondary care intervention)
3. Ulcer penetrating the tendon, periosteum, or bone.
4. Foot ulcer in area of the foot, e.g. in between toes, which would make exact ulcer size measurement, or application of the Natrox device, impossible.
5. Pregnant, actively planning to become pregnant, or lactating (all self-reported)
6. Currently receiving intravenous antibiotics, or within one week of receiving iv antibiotics

(topical and oral antibiotics are not an exclusion criterion).
7. Participating in another research study involving an investigational product that is related to the DFU or a co-morbidity that may influence wound healing (incl diabetes, peripheral arterial disease, or immune disorders).
8. Use of barrier cream/ointment and honey-based dressings (as per Natrox device instructions)
9. Concurrent (medical) conditions that in the opinion of the investigator may compromise patient safety or study objectives, or significantly impede compliance with NATROX® therapy.

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Date of first enrolment
10/10/2019

Date of final enrolment
31/07/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Carleton Clinic
Cumwhinton Road
Carlisle
United Kingdom
CA1 3SX

Study participating centre
South Tyneside District Hospital
Harton Lane

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United Kingdom
NE34 0PL

Sponsor information

Organisation
Cumbria Partnership NHS Foundation Trust

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Sponsor type
Hospital/treatment centre

Funder(s)

Funder type
Industry

Funder Name
Inotec AMD Limited

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Internal report to the funders of the trial, Natrox wound care (part of Inotec AMD Limited) and the Academic Health Sciences Network.

A summary of the main findings will be supplied to participants who request this option on the informed consent form.

Intention to publish date
31/12/2022

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file		17/07/2019	11/09/2019	No	No
Protocol file	version 4	07/05/2021	17/08/2021	No	No
Protocol file	version 5.1	14/01/2022	04/03/2022	No	No
HRA research summary			28/06/2023	No	No
Other unpublished results		14/12/2022	22/11/2023	No	No