Research Protocol

Project Title:

Extracorporeal Shockwave Therapy for Diabetic Foot Wounds

A mixed methods feasibility study of extracorporeal shockwave therapy for diabetic foot wounds

Protocol Version 2
IRAS: 233543
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Sponsor and Funding:
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Synopsis

Study Title	A mixed methods feasibility study of extracorporeal shockwave therapy for diabetic foot wounds
Protocol Number	2
Sponsor	Academic Vascular Surgery Unit
Funder	Academic Vascular Surgery Unit
Objectives	Primary Aims: To assess the feasibility of delivering shockwave therapy to patients with diabetic foot wounds Secondary Aims: - Assess the clinical outcomes associated with ESWT on diabetic foot wounds - Define the mechanism of action of ESWT on wound healing - Find the effect of ESWT on patient's quality of life - Understand patient ideas, beliefs and expectations of ESWT - To determine patient tolerability of undergoing ESWT
Study Design	A mixed methods cohort study
Participant Time	12 weeks
Study Parameters	- Recruitment rate - Adherence in treatment - Follow up rate - Reason for exclusions - Reason for drop outs - Change in wound volume – assessed on 3D imaging - Incidence of infection – from positive wound swabs and clinical evidence of infection - Incidence of amputation - Assess local tissue perfusion flow changes – using Doppler Flowmetry - Assess local tissue integrity – using Vapometer - Assess local bacterial growth - from bacterial analysis from wound swabs - Changes in quality of life – assessed on the EQ-D5-3L and SF-12 - Changes in pain score – assessed on Visual Analogue Scale and Brief Pain Inventory - Acceptability and tolerability – assessed on Visual Analogue Scale - Patient's beliefs around shockwave therapy - Patient's reported willingness to try new treatments and motivation for that behaviour

	- Patient's experience of undergoing shockwave therapy - Patient's perceived effect of shockwave therapy on their life
Sample Size	40
Sample Sites	Hull Royal Infirmary
Data Analysis	*Quantitative:* Descriptive analyses *Qualitative:* thematic analysis
Safety analysis	Adverse events for each participant will be collected, summarised and reported

Introduction

Diabetes is one of the most common chronic diseases in the world. In the United Kingdom 3.6 million people have diabetes and an estimated half a million people have undiagnosed diabetes (1), with the incidence rising (2). Diabetic foot complications are common with at least 10% of diabetics developing a foot ulcer in their lifetime. Diabetic foot ulcers precede 84% of non-traumatic amputations (2-4) and are associated with a 70% 5 year mortality rate (4, 5). Diabetic foot wounds have a poor healing rate: 30-45% (6) of diabetic digital amputations fail to heal, resulting in 75% of patients undergoing further higher amputation within the year(7). This is associated with a poor quality of life (8).

The management and prevention of diabetic foot disease is a costly affair affecting all healthcare sectors. For every £150 the NHS spends, £1 goes on diabetic foot care and amputations (4).

The current management of diabetic foot wounds includes glycaemic control, smoking cessation, pharmacological treatment with statins and anti-platelets (2). As well as revascularisation of ischaemic wounds, debridement, off loading and wound dressings (2, 7, 9). Advanced therapies used for complex diabetic foot wounds include bioengineered skin equivalents, and maggots. Even with the best wound management diabetic foot wounds are associated with protracted treatment courses, predisposing patients to developing infection. Proposed advanced therapies include bone marrow derived stem cells growth factor therapy, recombination anti-platelet growth factor (Becaplermin), hyperbaric oxygen therapy and extracorporeal shockwave therapy (ESWT) (2, 7, 9). ECSWT has shown encouraging results in improving the healing of diabetic foot wounds (8, 10-17). It has good efficacy, is safe, non invasive, carries a low complication rate (8, 18) and is cost effective (8). ECSWT has also been shown to be more effective than other treatments in improving poor healing rates in the acute and chronic setting of diabetic foot ulcers, chronic venous ulcers and in burns (8, 15). A systematic review from 2017 reported 'mild to moderate' evidence of the adjuvant use of ESWT with standard wound treatment for chronic lower leg wounds. The trial commented the need for further research to assess the efficacy of ESWT for wound healing (12),.

Currently no studies have investigated the feasibility of delivering ESWT to patients with acute and chronic diabetic foot wounds and have not addressed the potential limitations, for example patient acceptability, patient tolerability and logistics of integrating ESWT into standard care.

This study aims to add to the growing evidence base in shaping new treatments of diabetic foot wounds to improve the prognosis of diabetic foot wounds and therefore patient's quality of life.

Background

The effect of shockwaves on the body was first noted in lungs of victims subjected to water bombs in world war two(8). Later, high energy focused shockwaves were found to be effective in treating renal stones in lithotripsy. In 1986 low energy defocused

shockwaves were found to improve the healing rate in chronic wounds and delayed healing fractures (19). Extracorporeal shockwave therapy continues to be extensively researched to uncover its beneficial effect in healing tendon injuries, bone fractions, calcific tendonitis and plantar fasciitis (17). More recently its effect on endothelium and lymphatics on the promotion of healing has been popularly researched in human and animal models (8, 13, 20, 21).

Mechanism of Action of Shockwaves

A shockwave is high amplitude sound wave that is generated from a piezoelectric source and propagated into tissues. The sonic waves pass through tissues with low impedance and are reflected by tissues with high impedance. The passing of shockwaves through surfaces of difference impedance creates tension forces. These forces generate bubbles, which contain a vacuum inside. The collapsing of the bubbles induces shear forces on the local tissues.

The basis of how these mechanical energy are translated into chemical energy is by:

1. Generation of oxygen free radicals
2. Hyperpolarisation of cell membranes.

Both the generation of oxygen radicals and hyperpolarisation of membranes triggers release the kinases and growth factors, including Vascular Endothelial Growth Factors (VEGF) and transforming growth factor beta 1 mitogen-activated protein kinases (6). The generation of oxygen free radicals stimulates the release of VEGF, transforming growth factor beta 1, BMP-1, BMP-2 and BMP-7 which induce the differentiation of mesenchymal cells (22). The shockwave used in the treatment of wounds are transmitted from a soft focused applicator, which delivers low energy defocused radial shockwaves to a depth of around 3cm (8, 12).

These factors are known to play an active role in regulating inflammation, haemostasis, proliferating and remodelling vital in the healing process (8, 12).

Basis of Disrupted Healing In Diabetes

Diabetes disrupts the normal healing pattern in three broad areas (11):

1. Hyperglycaemia leads to endothelium dysfunction resulting in low nitric oxide levels leading to vasoconstriction and impaired immune and inflammatory response locally, predisposing to infection.
2. Impaired healing barriers due to deficiency in growth factors needed for inflammation and tissue regeneration. Most notably:
    a. Deficiency in endothelium growth factor (EGF), VEGF, GM-CSF and IL-8, which regulate angiogenesis.
    b. Locally, a lack of PDGF, transformed GF beta and GM CSF leading to impaired extracellular matrix deposition.
    c. Shortage of IGF 1, EGF, basis FGF, IL6 and GMCSF leading to reduced epithelisation and ketatinocyte proliferation.
3. Local infection caused by immunosuppression in diabetes results in raised neutrophils, monocytes, macrophages that create granulation tissue. Leucocytes release cytotoxic, proteolytic and free radicals resulting the disorganised collagen layout in healing wounds.

Analysis of a diabetic wound shows low angiogenic factors, disordered granulation, inflammation and disordered immunity all predisposing to poor wound healing.

Effect of Extracorporeal Shockwave Therapy in Wounds of Various Aetiologies:
In vitro, animal and humans models researching the effect of ESWT on wounds the efficacy of shockwave therapy is currently hypothesised to be through its ability to influence factors vital in angiogenesis and regulation of fibroblasts including:

- Nitric Oxide:
    - Vital in vasodilation via the guanylate cyclase cycle (23)
    - Increases the expression of Tissue Growth Factor beta (TGF-β), b-Fibroblast Growth Factor (b-FGF), Necrosis Factor κb (NF-κb) and Insulin Growth Factor (IGF) to regulate collagen synthesis (13)
    - Keeps NO within physiological limits via down regulation of NF-κb to decrease inflammation by decreasing cytokine levels (8), locally and systemically (24).
- Angiogenesis via:
    - Increasing concentration of Vascular Endothelial Growth Factor (VEGF) to stimulate angiogenesis (8, 10, 11, 13, 20)
    - Increasing platelet endothelial cell adhesion molecule 1 (PECAM) 1 on leucocytes and endothelium to increase cell migration and angiogenesis (8)
    - Increased Stromal Cell Derived Factor 1 (SDF-1) mRNA in endothelial progenitor cells which are low in chronic wounds and ischaemia (8)
- Fibroblasts: increase Proliferating Cell Nuclear Antigen (PCNA), stimulate proliferation and regulate myofibroblast differentiation (13, 25)
- Decrease inflammation by decreasing leucocytes and Tumour Necrosis Factor alpha (TNF-α) (13).

On samples taken and analysed of human wounds treated with ESWT there was found to be higher levels of von Willebrand Factor (vWF), VEGF, endothelium Nitric Oxide Synthase (eNOS), stimulating angiogenesis; higher levels of PCNA, Endothelial Growth Factor (EGF) for increasing cellular proliferation and lower Terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) assay signifying a lower rate of apoptosis (10, 13). Clinically wounds treated with ESWT have a higher epithelisation rate, smaller wound size, better blood flow and better long term healing for up to one year compared to control groups (12, 14-18, 26).

Less is understood about the bactericidal mechanism of ESWT. Studies into the effect of low energy shockwaves on *staphlococus aureus* have shown in vitro ESWT is more effective at eradicating metabolically active bacteria, has a dose dependent response and in combination with antibiotics such as fosfomycin, cefuroxime and rifampicin is highly effective in eliminating bacteria (27, 28). The hypothesised mechanism is derangement of organelles and DNA through free radical formation.

Aims

The study aims to assess the feasibility of delivering ESWT to patients with diabetic foot wounds and ulcers, investigate the clinical effect of ESWT on wound healing, explore the potential mechanism of action and assess whether it offers any patient reported benefits.

Primary Aim:

- To assess the feasibility of delivering extracorporeal shockwave therapy to patients with a diabetic foot wound.

Secondary Aim:

- Assess the clinical outcomes associated with ESWT on diabetic foot wounds
- Define the mechanism of action of ESWT on wound healing
- Find the effect of ESWT on patient's quality of life
- Understand patient ideas, beliefs and expectations of ESWT

Design

A single centre mixed methods cohort study.

Setting

The study will be conducted in the Academic Vascular Surgical Unit Hull York Medical School at Hull Royal Infirmary. Patients will be recruited from Diabetic Foot Clinic and ward 7 and 70.

Sample Size

The sample size will be 40. This is appropriate for a feasibility study and is similar to studies of diabetic foot wounds treatment with standard therapy. Interviews will be conducted until data saturation.

Target Population and Recruitment

Inclusion Criteria

- Diagnosis of diabetes mellitus
- Open wound of the foot
- ABPI >0.8
- Age greater than 18 years old
- Able and willing to give written informed consent
- Be able to adhere to protocol and attend all follow up appointments

Exclusion Criteria

- Pregnancy or breast-feeding
- Current malignancy
- Allergy to materials used in the treatment
- Palliative
- Unable or unwilling to give consent
- Anticoagulation

Screening and Consent

Patient Identification

Potential participants will be identified from the diabetic foot clinic, vascular ward, endocrinology ward and the vascular theatre lists. We will liaise with the appropriate clinical team before approaching potential patients to ensure suitability. If suitable we will introduce the study to the patient, explain what is involved and provide the patient information sheet (Patient Information Sheet Version 3.1 April 2019).

Patient Consent

Informed consent will be taken from participants who express an interest in taking part. We will ensure the participant understands the purpose of the study, what is involved, the possible risks and reinforce the participant is not obliged to take part. The discussion will be documented on the consent form (Consent Form Version 2.1 April 2019).

Following project review (July 2019), all participants will be offered the opportunity to take part in qualitative interviews. New participants will be asked for consent at the start of the study, whereas existing participants will be approached either at a follow up appointment or by telephone. For the latter, we will explain what is involved and provide them with a copy of the Qualitative Study Patient Information Sheet (Version 1.0 April 2019).

Evaluation

Baseline data will be collected from all consenting participants includes:

- Informed consent
- Participants name, date of birth, NHS number, HEY number, address, contact number and name and address of their registered GP
- Past medical and surgical history
- Co-morbidities
- Assessment of concurrent medications
- Smoking history
- Allergy status
- Pregnancy test, if applicable
- BMI
- Baseline pain score
- Baseline quality of life
- Surface area of the wound
- Physical examination, including level of neuropathy and vital observations
- Ankle Brachial Pressure Index

Restrictions

Dietary

There are no dietary restrictions.

Smoking

Smoking will not be permitted in the Study Centre or in hospital groups except in designated smoking areas.

Concurrent medications

Concurrent medications and new medications commenced during the trial will be recorded. Patients taking anti-coagulation medication will be excluded.

Study Protocols

Study Treatments

Extracorporeal shockwave therapy will be applied using the PeizoWave 2 shockwave system within the device's licensing. The shockwave therapy will be given at 120 pulses/cm^2, penetration 5mm at a dose of 0.1mJ/mm^2 at 5 pulses/second (17). Participants will receive 3 sessions of shockwave therapy in a 7-day period alongside standard wound care.

Environmental Conditions

Patients will be assessed and treated at the Diabetic Foot Clinic, Brocklehurst Centre, ward 7/70, Hull Royal Infirmary and/or Academic Vascular Unit, Hull Royal Infirmary.

Outcome measures

Primary outcome

Feasibility of delivering extracorporeal shockwave therapy to patients with a diabetic foot wound, assessed by:

- Recruitment rate
- Adherence in treatment
- Follow up rate
- Reason for exclusions
- Reason for drop outs

Secondary outcomes:

Clinical outcomes:

- Change in wound volume – assessed on 3D imaging

- Incidence of infection – from positive wound swabs and clinical evidence of infection
- Incidence of amputation

Mechanism of action outcomes:
- Assess local tissue perfusion flow changes – using Doppler Flowmetry
- Assess local tissue integrity – using Vapometer
- Assess local bacterial growth - from bacterial analysis from wound swabs

Patient Outcomes
- Changes in quality of life – assessed on the EQ-D5-3L and SF-12
- Changes in pain score – assessed on Visual Analogue Scale and Brief Pain Inventory
- Acceptability and tolerability – assessed on Visual Analogue Scale

Qualitative Outcomes:
- Patient's beliefs around shockwave therapy
- Patient's reported willingness to try new treatments and motivation for that behaviour
- Patient's experience of undergoing shockwave therapy
- Patient's perceived effect of shockwave therapy on their life

As assessed during qualitative in depth interviews

Assessments

1. **Quantitative Measures:**

Baseline
After consent participant's baseline data, wound measurements, local perfusion, tissue integrity and wound swabs will be taken and quality of life and pain questionnaires will be completed at baseline before the first treatment.

Follow-up
The participant will receive 3 treatments in the first 7 days after surgery. After the third wound measurements, Vapometry, Laser Doppler Flowmetry and wound swabs will be taken and quality of life, pain and tolerability questionnaires will be completed. Wound imaging, quality of life and pain scores will then be repeated at weeks 4, 8 and 12. Infection and amputation rate will be recorded at each contact with the research team.

2. **Qualitative Interviews:**

We will conduct semi-structured interviews after the last treatment of ESWT. The interviews will be undertaken in a way acceptable to the patient. They may take place in person or over the phone or be located in the hospital and occur at a time convenient for the patient. The interviews will last 30-40minutes.

If the patient gives their permission interviews will be recorded on a digital device that is password protected.

The interviews will explore the participant's experience of undergoing ESWT. We will draw on previous research investigating patient's experience of different therapies to treat wounds to create a focused topic guide but also allows for flexibility into areas not previously considered by the researcher or identified in the literature (29-32).
The topic guide will include patient experience in attending for treatment, experience of receiving ESWT, experience after ESWT and any effect it has had on their life.

The researcher will be supervised by experts in qualitative research based at the University of York and the Academic Vascular Surgery Unit, Hull University Teaching Hospitals.

3. **Clinician Surveys;**

We will explore clinician stakeholder's beliefs of extracorporeal shockwave therapy through questionnaires. We will approach vascular surgeons and trainees, endocrinologists, infectious diseases specialists and podiatrists. Our aim is to explore their opinion of offering ESWT to acute wounds, knowledge of the evidence base, reservations they may have, willingness to refer for ESWT and potential to deliver the therapy in their clinics.

Concurrent Medications

No restrictions of medications.

Assessment of Concomitant Medications

Concomitant medications at the start of the trial will be recorded. Any subsequent medication prescribed during the trial period will also be recorded.

Method of Analysis:

Quantitative Data

Recruitment rate, reasons for exclusion and non-consent, as well as follow-up rates and reasons for drop-out (where known) will be presented descriptively. Compliance with treatment will be presented descriptively.

Continuous patient reported and clinical outcomes will be presented as means and standard deviations and categorical outcomes as counts and percentages as at all available follow-up points. Outcomes over time will be summarised graphically where appropriate. Any change in outcomes will be presented with 95% confidence intervals.

Data will be analysed using the SPSS software package.

Qualitative Analysis

We will use thematic analysis approach to data analysis using the phases described as Braun and Clarke, 2006 for analysis of the interviews(33). We will complete the following steps (33):

1. Familiarisation: the interviews will be transcribed and re-read to ensure familiarity with the generated data
2. Code generation: from reading through the interviews potential codes will be assigned to the data
3. Identifying theme: after codes have been assigned they will be reviewed and grouped into themes
4. Reviewing themes: to ensure the themes represent the data we will compare the theme to the codes and the data from which they were derived, in doing this we will create a thematic map of analysis
5. Define theme: we will explore each theme separately, looking at the codes and extracts, to assign names to the themes. The themes will be compared for fit with the rest of the data
6. Produce a report: thematic analysis, along with example extracts, will be reported to answer our research question and be discussed in the context of existing literature

The data will be transcribed using NVIVO and reviewed by two researchers (LH and GS) to ensure internal validity. The results discussed between three researchers (LH, GS, IC) to ensure appropriate interpretation. The results will be also be reviewed by the University of York Masters supervisors to reduce any researcher associated bias.

Adverse events

Any Serious Adverse Events will be reported to the Sponsor and National Research Ethics Service recognised Research Ethics Committee. All side effects reported will be recorded throughout the study.

The Device

The PiezoWave 2 FBL 10x5 G2 device will be used to deliver extracorporeal shockwave therapy.

Safety and Tolerability

The device will only be used by trained staff members familiar will be device and deliverance of treatment. The environment of application of treatment will be equipped for emergency situations.

Ethics and Safety Reporting

Ethical approval will be sought from IRAS and the recruitment of participants will be in line with the declaration of Helsinki (2008). All patients will be informed of the study purpose, design, treatments, duration, risk and benefits and allowed to clarify additional questions during the consenting procedure. All participants must give informed consent and the consent form must be signed by the relevant parties, dated and kept with the

clinical trial forms in the patient's notes. The participant will be informed if any new information arises and informed consent must be gained again before carrying on with the trial.
The device will be used under the licensed indications and there are no anticipated adverse reactions. All adverse events or reactions and device failure will be reported on specific forms and action will be taken to treat the patient. If the event is deemed to be a serious adverse event or reaction the principal investigator will be informed within 24 hours. If an adverse event or reaction occurs the investigator will collect all possible information and the Principal Investigator will be informed to undertake the necessary action. Previous adverse reactions reported in the literature associated with extracorporeal shockwave therapy include: itching, burning, pain, skin pigmentation (12). Each participant will be given emergency contact details for the Principal Investigator if any concerns develop about the trial.
The trial will also comply with HEY research and development standards.

Withdrawals and Drop Outs

Patients are permitted to drop out at any point during the trial. The research investigators reserve the right to withdraw any participant if their health is at risk or if the participant fails to comply with the study protocol. If the subject develops an adverse event or reaction they will also be withdrawn from the trial.

Trial Exit

Participants will exit the trial completely when they complete the follow up period or if they:

- Withdrawn their consent to continue
- Withdrawn by the investigator due to health concerns or non-compliance
- Undergo angioplasty, bypass grafting or further surgery
- Experience an adverse event or reaction
- Die

Overall timescale for the study

Recruitment will begin when Ethics and Trust Research and Development approval has been gained. The patients will be involved in the trial for 12 weeks.

Follow up assessments

Where possible all follow up will coincide with standard dressing and clinic follow ups to minimise the additional visits for participants. The follow up weeks are 4, 8, 12 after randomisation.

Data management

Data will be handled in line with the Data Protection Act 1998. The trial data will be registered with the local Data Protection officer.
For participants entering the study after the second amendment data will be handled in line with the GDPR 2018 guidelines. Patients will also be given information relating to this in the patient information sheets.
The data will be collected entered onto a excel spreadsheet created by the research team. The data will be kept on password protected NHS trust computers with firewalls and antivirus software on files with limited access to the trial investigators.
The storage of data will be in line with the IT department standards. Data will remain on the servers and be backed up on secure HEY IT systems. The data will be accessible to investigators and those seeking permission for monitoring and auditing.
Paper records will be stored and locked in the Academic Vascular Unit when not in use.

Study Report

The final pilot study report will outline the background, methods, results, discussion and conclusion of the trial in line with the CONSORT guidelines. The data from the participants will be anonymous. It will be submitted for publication in a peer-reviewed journal.

Administration

Participant Reimbursement

There is no provision for participant reimbursement. The trial follow up will coincide with routine follow up appointments.

Finance

Sponsors will not influence the trial or its publication.

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