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PROTOCOL

Dosing and efficacy of extracorporeal shockwave therapy for diabetic foot ulcer healing: a systematic review protocol

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Plain English Summary

Why we are undertaking this work: Diabetic foot ulcers are difficult to heal and are often resistant to treatment. Shockwave therapy is a type of treatment that delivers soundwaves onto the surface of ulcers with a gel paddle. Small studies have shown it may improve healing, but the data are not clear.

What we will do: To investigate the effect of shockwave therapy on diabetic foot ulcer healing, we are going to do a systematic review. A systematic review is a way of bringing together the results from existing studies to decide if a treatment is effective or not. This paper describes how we are going to bring all the existing studies on shockwave therapy together to decide if it should be used in routine practice to treat patients with a diabetic foot ulcer. We are going to search databases for published and unpublished studies that randomly allocate people with a diabetic foot ulcer to shockwave therapy or not. We will combine results on how fast ulcers healed in the different studies using a mathematical test. This will tell us if shockwave therapy was better than usual care in healing diabetic foot ulcers.

What this means: The results from the systematic review will tell us if shockwave therapy should be used in routine practice or if more research is needed. It will also allow other researchers to repeat the systematic review if they wish.

Key words: diabetic foot, wound healing, extracorporeal shockwave therapy

Abstract

Background: Effective interventions to improve diabetic foot ulcer (DFU) healing are urgently required. Extracorporeal shockwave therapy (ESWT) has the potential to transform DFU care, but is limited by uncertainties around clinical effectiveness and optimal dosing regimen. This protocol outlines the methodology of a systematic review that will address these unknowns.

Methods: Databases and the grey literature will be searched for randomised controlled trials (RCTs) comparing ESWT plus standard ulcer care to standard ulcer care ± sham ESWT in patients with a DFU. The primary outcome of the review is time to ulcer healing. Two independent reviewers will screen search results against pre-determined eligibility criteria and extract data onto a pre-piloted spreadsheet. A meta-analysis is planned to compare time to healing for ESWT versus standard care and different doses of ESWT. The Risk of Bias 2 and GRADE tool will be used to assess the quality of the evidence.

Outputs, dissemination, impact: The review will provide an estimate of the effect of ESWT on DFU healing and the impact of the ESWT dose on DFU healing. The systematic review will be submitted for publication in a peer-reviewed journal. A plain English summary will be produced. Outputs from the review will guide patient care and research.

Introduction

With the rapidly increasing prevalence of diabetes, effective interventions to tackle the complications are urgently needed. Diabetic foot ulcers (DFU) occur in 25–30% of patients with diabetes and are particularly challenging to heal in a timely manner.[1–4] Delays in ulcer healing increase the risks of localised infection, sepsis, major limb amputation and mortality.[5,6] Current therapies consist of simple dressings, offloading footwear, antibiotics for infection and anti-hyperglycaemic medications.[7,8] The introduction of advanced therapies to treat DFU has been challenging due to inconsistent evidence around

effectiveness. This has resulted in DFU care being left behind medical advances seen in other areas.

Extracorporeal shockwave therapy (ESWT) has been trialled in patients with DFU for over 10 years and previous systematic reviews have reported positive results.[9–11] Despite this, transition into routine care has not taken place. The International Working Group on the Diabetic Foot (IWGDF) guideline on wound healing interventions do not recommend the routine use of ESWT in preference to standard care due to uncertainties around treatment effect.[8]

Another area of consideration in developing ESWT for routine clinical practice is dosing. A previous systematic review highlighted the variation in dosing schedules used by different trialists.[10] Laboratory-based studies using murine and human skin wound models have demonstrated a dose-dependent relationship between number of shockwaves and speed of wound healing and expression of angiogenetic markers.[12,13]

This systematic review is designed to answer the following questions:

- Does ESWT reduce DFU healing time?
- Does the number of shockwaves delivered during ESWT affect DFU healing time?

Methods

This protocol is registered on PROSPERO (CRD42022312509) and reported with reference to the PRISMA-P guidance.[14]

Eligibility criteria

Participants

Inclusion criteria:

- Diagnosis of diabetes mellitus
- Diabetic foot ulcer (neuropathic or neuroischaemic)
- Assessment of lower limb perfusion
- Over 18 years of age

Exclusion criteria:

- Contraindications to ESWT: anticoagulation medication, malignancy in the treatment area, lymphoma, leukaemia, dissemination malignancy, breast feeding or pregnant

The review will include participants who have a diagnosis of diabetes mellitus and a non-healing foot ulcer below the medial malleolus. We will not specify how diabetes is diagnosed nor the minimum age of the ulcer. Method of assessing adequate limb perfusion must be detailed. There will be no limitation on DFU classification used. Additional information on patient factors known to impact healing will also be collected.[15]

If a study population includes all types of 'chronic wounds', it will be considered for inclusion if the study population with a DFU meets the above criteria and is reported separately in the trial. This population will be included in the narrative synthesis only due to biases arising from breaking the randomisation sequence by segregating this population. If this is not clear from the manuscript, the corresponding author will be contacted. The effect of including any studies like this will be explored in the analysis.

Intervention

The review will include all dosing schedules of ESWT. This includes how many shocks per cm^2 were delivered, the penetration of shockwaves, the shockwave energy used, how many pulses per second were used and how frequently the treatment was given. We will compare whether variations in schedules of ESWT impacts DFU healing. ESWT must be in addition to standard ulcer care (see below).

Control

The control arm must have either received standard ulcer care alone or standard care plus sham ESWT. Standard ulcer care should include information on types of dressing used, debridement, offloading footwear, glycaemic control and antibiotic use. If sham ESWT was not used, ideally the control would have undergone ulcer assessment at the same intervals as the intervention group during the ESWT treatment period. This is to counter any bias associated with increased frequency of ulcer care.

Outcomes

The primary outcome of the review is time to ulcer healing, measured in days. However, we will include any studies where an ulcer-related outcome is the primary outcome. If an otherwise eligible study does not report any ulcer-related outcomes, we will contact the corresponding author to ascertain whether the protocol was to collect data on ulcer healing and if there are unpublished data on ulcer healing. Secondary outcomes include:

- Proportion of ulcers healed at fixed time points.
- Quality of life: measured with a validated quality of life assessment tool that can either be generic or disease-specific.
- Economic analysis: quantified by cost of treatment, net health benefit, net monetary benefit or incremental cost effectiveness ratio.
- Infection rate: depth of infection will be reported as superficial or deep.
- Amputation rate: minor and major amputation will be reported separately. Minor amputation will be defined as a digital or forefoot amputation. Major amputation will be defined as below, through or above knee amputation.
- Diabetic foot ulcer-related hospitalisation rate.
- Ulcer-free days.

Study design

The review will only include randomised controlled trials (RCTs). A cross-over RCT will be eligible for inclusion in the narrative synthesis but not in the meta-analysis. This is because the length of treatment effect is currently unknown and even mitigating this by using only the first part of the trial data in a meta-analysis would result in a high risk of selection bias and reporting bias, and would

result in the exclusion of more than half of the trial data.

In the highly unlikely situation of a cluster RCT being identified, it will be included in the review but the results will not be used in the meta-analysis as it will not be possible to reliably carry out any individual level statistics.

There will be no restriction based on blinding. If the included trial is blinded, the review will report who was blinded (participant/outcome assessor) and how blinding was achieved. Treatment allocation must be randomised and we will not include any quasi-randomised trials.

Additional information gathered will be country(s) in which the trial took place, sector of care, funding sources, use of blinding and number of arms. We will include published and unpublished trials.

Information sources

Cochrane Wounds Group Specialised Register, Ovid MEDLINE®, PubMed®, EBSCO CINAHL Complete, Ovid EMBASE®, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Clinical Trials Registry will be searched. The reference lists of any included studies will be reviewed to identify any further studies. ESWT companies will be contacted for any unpublished data. If a trial is marked as ongoing or complete on a trial registry database, the chief investigator will be contacted for any available results. Existing systematic review reference lists will be searched for relevant studies.

The review will search the grey literature. This will include searching official publications (eg, NHS, NICE, UK government, Royal College and charity publications). The review will search pre-prints using medrxiv.org work and conference proceedings for unpublished work using OpenGrey. The review will also search for relevant PhD thesis and dissertation work using 'Open Access Thesis and Dissertations' and 'EThOS' databases.

Search strategy

Database searches will be restricted to English language only. This is because we do not have the resources to translate manuscripts. The search will also be limited to manuscripts published after 1 January 2000. ESWT is a relatively modern technique and articles older than 20 years are unlikely to be relevant. Box 1 outlines an example search strategy. Before the final analysis, the databases will be re-searched to identify any new studies. This will be an update of a previous systematic review.[10]

Box 1 Ovid®MEDLINE®ALL search strategy.

1. Diabetic Foot/
2. diabetic foot.mp.
3. DFU.mp
4. Wound Healing/
5. wound healing.mp.
6. High-Energy Shock Waves/ or Extracorporeal Shockwave Therapy/
7. wound heal*.mp.
8. re-epithelialis*.mp
9. ECSWT.mp.
10. extracorporeal shockwave*.mp.
11. ESWT.mp.
12. shockwave.mp.
13. shock wave.mp.
14. diabet*.mp.
15. Foot Ulcer/
16. heal.mp.
17. Ulcer/ or ulcer.mp.
18. wound.mp. or "Wounds and Injuries"/
19. 1 or 2 or 3 or 14 or 15 or 17 or 18
20. 4 or 5 or 7 or 8 or 16
21. 6 or 9 or 10 or 11 or 12 or 13
22. 19 and 20 and 21
23. limit 22 to (english language and yr="2000 -Current")

Study records

Study selection process

Two assessors will independently review the search results with reference to the study eligibility criteria for inclusion. The assessors will be blinded to each other's decision. Disagreements in studies will be discussed between assessors and, when a decision cannot be made, a senior researcher will make the final decision. The assessors will base their decision on article title, abstract or, if required, after reading the full article. Rayyan, a bespoke tool for conducting systematic reviews, will be used to enter search results and record decisions.[16]

Data extraction

Data will be extracted onto a specifically designed Microsoft Excel spreadsheet. The spreadsheet will be piloted prior to data extraction. Two reviewers will extract the data. Once extraction is completed, the reviewers will compare results. Any discrepancies will be checked and a third reviewer will be consulted if an agreement cannot be made.

Data items

- Study design: Only RCTs will be included. Information on method of randomisation, blinding, number of treatment arms and details of the power calculation will be collected.
- Participants: The number of participants in each study, number of participants in each arm and number of participants lost to follow-up/withdrawal will be collected. The following patient demographics will be collected: age, sex, ethnicity, diabetes type, HbA_{1c}, comorbidities and ambulatory status. The following ulcer demographics will be collected: number of active ulcers, site of index ulcer, duration of index ulcer, type or classification

of index ulcer, area and depth of ulcer and presence of infection.
- Intervention: The review will record the dosing schedule of ESWT. This includes type of ESWT (focused or radial), number of shocks per cm^2 delivered, the depth of shockwave penetration, shockwave energy density used, number of pulses per second and how frequently the treatment is delivered per week and total treatment course (in weeks). Standard wound care will be collected as below.
- Control: Standard wound care should be defined as per local, national or international guidelines. Details on type of dressing (as classified in the BNF wound management products), offloading footwear (as defined in the IWGDF guidance on footwear and offloading interventions), glycaemic control, antibiotic use and other adjuvant therapy will be collected.
- Measure of effect: All studies must report an ulcer-related outcome. This could be time to healing, proportion of ulcers healed at a time point or reduction in ulcer size. Secondary outcomes are quality of life, adverse events (amputation, infection, mortality) and economic outcomes. We will also record whether the analysis was an initiation to treat or per protocol analysis.
- Funding: The sources of trial funding will be recorded.
- Location/setting: The country in which the trial took place and healthcare setting (eg, outpatient clinic, community clinic, inpatient setting) will be recorded.

Where it is not possible to gain the above information from the full article, the corresponding author will be contacted.

Risk of bias

The Cochrane Risk of Bias 2 tool will be used to judge sources of bias in the included manuscripts.[17] Each manuscript will be judged for risk of bias for the primary outcome within the study. The risk of bias for outcomes across all the included studies will be summarised. Two reviewers will independently judge each study for bias and then compare results, coming to a decision if discrepancies arise. A third reviewer will be included if required to make the final decision.

The GRADE tool will then be used to judge the overall quality of the evidence in the review.[18]

Data synthesis[19]

The included trials' population, interventions, control and outcomes (PICO) will be tabulated and compared. ESWT, sham ESWT and standard ulcer care will be described and coded.

The trials will then be compared for similarity. The review will explore whether there are significant differences in the demographics of the trial populations, the dose of shockwaves and outcome measures.

The review will then determine whether the trial outcomes are suitable for synthesis. We wish to report time to healing; if the study does not report time to healing but reports the number of healed ulcers at certain time points, the corresponding author will be contacted for time to healing data. If the studies report reduction in ulcer size, we will derive the number of ulcers healed over the follow-up period. If the data are unclear, we will contact the study authors for further clarification.

Data analysis[20]

We plan to undertake a pairwise analysis to compare ESWT and standard wound therapy using a random effects model. We also plan to undertake a meta-regression to explore any effect of different doses of ESWT, comparing high-dose ESWT (500 shocks/cm^2 and above) and low-dose ESWT (250 shocks/cm^2 and below). Data will first be examined for skewness from the means and standard deviations by using the technique described by Altman and Bland.[21] If the data are skewed, they will be presented as medians and interquartile ranges in a table.

Time to event data will be analysed using the O-E and Variance method. We will convert the data into a log-rank scale and report the hazard ratio and standard error. Continuous ulcer-related outcomes (eg, reduction in ulcer size) will be reported as a mean difference with 95% confidence interval (CI). Dichotomous data (eg, healed/unhealed) will be reported as the risk ratio with 95% CI. The synthesis will be presented on a forest plot. The interpretation of mean differences will be: <0.2 is very small, 0.5 is moderate and 0.8 is a large effect.[22]

- Meta-regression: If there is a sufficient number of studies and data, we plan to undertake a subgroup analysis. There must be 10 studies for this to be undertaken.[20] We plan to undertake this because we are hypothesising that the more shockwaves delivered per cm^2, the quicker the time to DFU healing will be.
- Heterogeneity: Heterogeneity will be estimated and considered in the context of the studies and potential bias, as well as meaning on the meta-analysis overall result. We will consider the χ^2 and associated p-value as well as the I^2 statistic. If the inconsistency (I^2) is greater than 40% we will: check the data were entered correctly onto RevMan, consider whether the meta-analysis is appropriate (eg, if the direction of effect is in a uniform direction, if the interventions/populations are too different), consider whether the effect measure is appropriate and exclude studies.
- Missing data: In the first instance, missing data will be sought from the trial authors. If they are not available, they will be imputated from the dataset with replacement values from the mean.

Dissemination

The systematic review and meta-analysis will be submitted to a peer-reviewed journal for publication. We will also publicise our results on social media and will produce reports for the NIHR and Diabetes UK, including a Plain English Summary for patient groups.

KEY MESSAGES

- There is uncertainty about the role of ESWT in the promotion of DFU healing.
- Current clinical trials investigating ESWT in DFU report varying effectiveness.
- This protocol outlines a rigorous systematic review designed to evaluate whether ESWT reduces the time to DFU healing and whether the dose of ESWT has an impact on clinical outcomes.

Discussion

This protocol outlines the methods for systematically reviewing and summarising the evidence regarding ESWT for DFU healing to address uncertainties over the treatment effect and optimal dosing. The completed review is expected to guide clinicians, researchers and policy makers on the role of ESWT in DFU.

Previous systematic reviews on this topic, published by Omar *et al* in 2017, Hitchman *et al* in 2018 and Huang *et al* in 2020, report positive findings from the literature but call for further RCTs to increase confidence in the treatment effect.[9–11] The systematic review undertaken by Omar *et al* included all clinical trials (randomised, quasi-randomised, before-and-after and crossover) investigating ESWT in chronic ulcers of the lower limb. DFU contributed 39.6% of the combined population. The authors concluded there was 'mild-to-moderate' evidence for the use of ESWT in wound care.[9] High risk of bias and low certainty of evidence was highlighted in the review by Hitchman *et al* in 2018. The systematic review and meta-analysis of RCTs comparing ESWT to standard care reported ESWT was associated with improved DFU healing but called for further RCT evidence of ESWT before recommending it for routine care.[10] Huang *et al* repeated this review in 2020, but included two non-randomised trials (quasi-randomised[23] and a case-control study[24]) despite the inclusion criteria for only RCTs.[11] The review also did not include the large multicentre RCTs published by Snyder *et al* in 2018.[25] Huang *et al* concluded the same as the previous systematic review authors – more RCT evidence is needed.

The aim of this update is to synthesis data from the trials by Snyder *et al*[25] with existing data and to examine the effect of different doses of ESWT. For ESWT to translate into routine patient care, an evidence-based treatment protocol needs to be developed. Laboratory studies using wound models have found high-dose ESWT to be more efficacious than low-dose ESWT in augmenting healing.[12] Dosing in the current studies ranges from 100 shocks per cm^2 to 500 shocks per cm^2 and others give additional shocks over the anatomical location of arteries supplying the ulcer.[10] The impact of this needs to be further examined in humans to understand the mechanism of action of ESWT in DFU healing. This will guide treatment decisions and advance this potentially transformative therapy in the care of patients with DFU.

Conclusion

This protocol outlines how the evidence for the effectiveness of ESWT and optimal dosing of ESWT will be explored to answer key questions limiting the wider application of this potentially transformative therapy.

Conflict of Interest: None.

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