Extracorporeal Shockwave Therapy for Diabetic Foot Ulcers Protocol for a Systematic Review and Meta Analysis

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Protocol

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Abstract

Introduction: The purpose of this paper is to evaluate the efficacy and safety of extracorporeal shockwave therapy for Diabetic foot ulcers.

Methods and analysis: The databases of China Science and Technology Journal Database, PubMed, EMBASE, Ovid MEDLINE, Web of Science, Embase, Cochrane Central Registry of Controlled Trials and China National Knowledge Infrastructure Database were searched to find the relevant studies. Keywords included the shockwave therapy, diabetic ulcers and related terms. References identified through the electronic search were screened, the data were extracted, and the methodological quality of the included studies was assessed. The meta-analysis was performed for the following outcomes: closure of diabetic foot ulcers, ulcer healing rate, ulcer healing time, ulcer recurrence rate, pain, Participant health-related quality of life/health score, hospital charges and amputation. Two authors independently screened search results, extracted data and appraised studies using the Cochrane risk of bias tool.

Ethics and dissemination: The protocol of this systematic review (SR) does not require ethical approval because it does not involve humans. We will publish this article in peer-reviewed journals and presented at relevant conferences.

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Introduction

There are 22.3 million people with diabetes in the United States, and 15%-25% of them are at risk of foot ulcers.\(^1\) Diabetic foot ulcers (DFUs) is described as a tissue destruction caused by small-vessel occlusion, neuropathy and infection.\(^2\) It is a common complication of diabetes that has dramatic effects on the health and social participation and livelihood of patient as well as being expensive to treat.\(^3\) A study from the United States found that diabetic foot ulcers impose an annual burden of 10.1 billion to 14.5 billion US dollars on the basis of diabetes-related costs.\(^4\)

Angioplasty or bypass surgery has proven its efficacy in the treatment of PAD but is generally ineffective in small-vessel disease. More and more advanced technologies have been invented and applied to enhance healing in the diabetic foot wounds, including hyperbaric oxygen therapy, negative pressure wound therapy, stem cell, and so on, but does not treat the underlying cause of microcirculation disturbance in the feet.\(^5\text{-}^7\) How to make diabetic foot wounds heal completely in a short period of time is still remains challenging.

As a non-invasive means combining energy medicine and physical medicine, extracorporeal shock wave therapy can re-initiate the chronic wound by activating the body's own healing pathways.\(^8\) It is not only widely used in the treatment of refractory fracture, tendon terminal disease and other musculoskeletal diseases, but also shows unique advantages in wound repair, including clinical treatment of acute and chronic wounds.\(^9\text{-}^{13}\) Fioramonti applied ESWT to venous ulcer of lower extremity and concluded that it
was a safe, cost-effective treatment for venous ulcer of lower extremity.\textsuperscript{[14]} Studies have shown that ESWT can stimulate the collateral circulation of the limbs to increase the blood flow of the extremities.\textsuperscript{[15]}

Over the years, clinical evidence of diabetic foot ulcers healing with ESWT has been accumulating. Emerging evidence of several randomized controlled trials (RCTs) published suggests a benefit of ESWT in patients with diabetic foot ulcers.\textsuperscript{[16–19]}

However, the effectiveness and safety of extracorporeal shockwave therapy for diabetic foot ulcers remain unclear. Therefore, we evaluated it through systematic review and meta-analysis.

**Methods**

**Inclusion criteria for study selection**

**Types of studies**

Randomized controlled trials and controlled clinical trials will be included. Including two arm or 3-arm parallel designed trials, animal experiments will be excluded.

**Types of patients**

Patients who were diagnosed as DFU according to the diagnostic criteria were included (Ulcers in or below the ankle in diabetic patients and with no other cause shown or suspected), without restrictions on age, race, gender and geographical location or setting. The diagnostic criteria for DFU: Refer to the 2019 IWGDF Guidelines on the prevention and management of diabetic foot disease.\textsuperscript{[20]}

**Types of interventions**

The intervention must be described as Extracorporeal shockwave therapy.

Control group consisted of standard care or sham ESWT.

**Types of outcome measures**

The primary outcomes are closure of diabetic foot ulcers and ulcer healing rate.

The secondary outcomes include ulcer healing time, ulcer recurrence rate, pain, Participant health-related quality of life/health score, hospital charges and amputation.

The evaluation of clinical results will be defined as within 6 months after the beginning of treatment. Follow-up time was defined as within 1 year.

**Search methods for the identification of studies**

**Electronics searches**
Electronic databases including China Science and Technology Journal Database, PubMed, EMBASE, Ovid MEDLINE, Web of Science, Embase, Cochrane Central Registry of Controlled Trials and China National Knowledge Infrastructure Database. Two independent researchers (WF and FX) will search all electronic databases above from inception to June, 2020.

The following search terms will be used to search in PubMed and other English databases: “extracorporeal shockwave therapy”, “shockwave therapy”, “shockwave”, “diabetic foot”, “diabetic feet”, “diabetic foot ulcer”, “diabetic ulcer”, “diabetic ulcers”, “chronic diabetic foot ulcers”, “Randomized controlled trial”, “controlled trial”, “trial”. The search strategy for PubMed is shown in Table 1.

**Searching other resources**

The following trials registries will be searched: ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform. We will also review the reference lists of all major studies, and contact relevant experts to identify any unpublished research, or publications of a study in non-indexed journals.

We will contact authors of key papers and abstracts to request further information about their trials when necessary.

**Selection of studies**

All studies will be imported into Endnote software and excluded duplicated studies before the screening. Two authors will independently scan all title and abstract and all irrelevant literatures will be removed. Then, full manuscripts of all remaining studies will be further identified to check if they meet all inclusion criteria. We will note all excluded citations with specific reasons. If there are any different opinions between 2 authors, we will invite another author for consultation and final decision will be made after discussion. The detail of the study selection will be presented in a PRISMA flow diagram (Fig. 1).

**Data extraction and management**

Two review authors (WF and XY) will extract data independently and collect data on a data extraction form. We will resolve discrepancies in the results by discussion. All data will be entered into the RevMan software (V.5.3) after double cross-checking.

We will collect the following information:

- publication details (e.g. year, country, authors);
- study design;
- population data (e.g. age, ethnicity, baseline aspects such as severity, duration, symptoms, history concerning treatments and responses);
details of interventions (e.g. number of treatmentsessions, regimen, fluence, scheme, adjunctive therapies, increasing or decreasing fluence, who delivered the intervention, the location of the intervention);

treatment duration;

the duration of follow-up.

types of outcome measures;

timing of outcomes;

results;

adverse events.

**Assessment of risk of bias in included studies**

Two review authors will independently apply the Cochrane tool for assessing risk of bias to the included studies. This tool assesses six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, other issues (e.g. source of funding).

**Measures of treatment effect**

We will calculate risk ratios (RR) and 95% confidence intervals (CIs) for dichotomous variables. We will calculate the mean difference (MD) and 95% CIs for continuous outcomes that have used similar scales for assessments, and will calculate the standardized mean difference (SMD) and 95% CI for continuous outcomes where different scales have been used. In the event that study authors do not make the necessary information available, we will present the results narratively and insert any data into an additional table.

**Dealing with missing data**

In the case of missing data, we will contact the original trial investigators to request missing data whenever possible. If necessary, we will perform data imputation according to the principles from the Cochrane Handbook. We will explicitly describe our assumptions in case of imputing missing data.

Also, we will address the potential impact of missing data on the findings of the review in the Discussion section.

**Assessment of heterogeneity**

We will assess statistical heterogeneity using the $\chi^2$ test (a significance level of P value less than 0.10 will be considered to indicate statistically significant heterogeneity) in conjunction with the $I^2$ measure. We will consider that $I^2$ values of 25%, or less may not indicate important heterogeneity and values of more than 75% indicate considerable heterogeneity. Where there is no clinical or statistical heterogeneity, we will use
a fixed-effect model. In the absence of clinical heterogeneity and in the presence of some statistical heterogeneity ($I^2$ over 50%), we will use a random-effects model; however, we will not anticipate pooling data across studies where heterogeneity is considerable ($I^2$ over 75%). Where there is evidence of considerable heterogeneity we will explore this further if required.

**Assessment of reporting bias**

If more than 10 studies are included in the review, we will attempt to identify existence of any reporting bias by constructing a funnel plot. If we detect evidence of asymmetry, we will explore possible explanations such as reporting bias, selective outcome reporting, poor methodological design, inadequate analysis and true heterogeneity.

**Subgroup analysis**

We will conduct subgroup analysis for the following groups, where data permit:

- types of shockwave devices;
- different fluences and schemes;
- duration of treatment.

If we find substantial heterogeneity (when the $I^2$ statistic exceeds 50%), and there are sufficient data, we will investigate the possible causes by exploring the impact of the condition of the individuals and interventions (i.e. participant characteristics, addition of adjuvant therapies) using subgroup analyses.

**Sensitivity analysis**

We will perform a sensitivity analysis to determine whether our results are robust by excluding those studies assessed as having a high risk of bias. The following sensitivity analyses will be performed to test whether critical methodological factors or decisions have affected the main result, where there is a sufficient number of studies in the meta-analyses:

- removing unpublished data
- changing effects model

**Grading the quality of evidence**

The evidence quality from each study will be assessed by 2 researchers independently.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines will be used and divided into 4 level: Very low, low, moderate or high.
Limitation of study design, imprecision, inconsistency, indirectness and bias of publication will be assessed.

**Protocol development and potential amendments**

This is an original research protocol, any changes will be stated in the final review manuscript and updated via PROSPERO and INPLASY.

**Discussion**

Extracorporeal shockwave therapy is an option currently used in the treatment of diabetic foot ulcers, but there is no systematic review assessing its effects and safety.

This meta-analysis will provide a relatively convincing conclusion as to whether patients with diabetic foot ulcers can benefit from Extracorporeal shockwave therapy.

**Abbreviations**

95% CIs = 95% confidence intervals, ESWT = Extracorporeal shockwave therapy, DFUs = Diabetic foot ulcers.

**Declarations**

**Contributors:**

Conceptualization: Weijing Fan, Wenhui Li

Data curation: Xvhong Wang, Changgeng Fu

Formal analysis: Xvhong Wang

Funding acquisition: Guobin Liu

Investigation: Wenhui Li

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Resources: Wenhui Li

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Supervision: Wenhui Li
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Competing interests:

None declared.

Patient consent for publication:

Not required.

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Table
Table 1. 
Search strategy used in PubMed database

| Search strategy (PubMed database) |
|-----------------------------------|
| **NO** | **Search terms** |
| #1     | Extracorporeal shockwave therapy (MeSH) |
| #2     | Extracorporeal shockwave therapy |
| #3     | Extracorporeal shockwave |
| #4     | shockwave therapy |
| #5     | shockwave |
| #6     | ESWT |
| #7     | #2 OR #3 OR #4 OR #5 OR #6 |
| #8     | diabetic foot (MeSH) |
| #9     | Diabetes foot |
| #10    | Diabetic Ulcer |
| #11    | diabetic foot ulcers |
| #12    | Diabetic foot |
| #13    | Diabetic foot ulcer |
| #14    | Diabetic feet |
| #15    | Chronic ulcer |
| #16    | Chronic wound |
| #17    | Leg ulcer |
| #18    | Leg wound |
| #19    | #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 |
| #20    | Randomized controlled trial (MeSH) |
| #21    | Randomized controlled trial |
| #22    | Controlled clinical trial |
| #23    | Clinical trial |
| #24    | trial |
| #25    | #20 OR #21 OR #22 OR #23 OR #24 |
| #26    | #7 AND #19 AND #25 |
