**Review question / Objective:** To find out whether ozone therapy were effective in either of all these chronically infected wounds; which types of wounds were most suitable; and if those treated experienced any adverse events; whether is superior to antibiotics for infected wounds.

**Condition being studied:** Ozone therapy has been used extensively in managing wounds by mechanism including antioxidant capacity, pathogen inactivation, hemorheology and endogenous growth factors modulations, immune system activation and so on. The toxicity of it, however, has slowed the advancement of experimental data with human trials. Chronic wounds are notoriously difficult to treat because they usually take the form of non-healing ulcers with fibrotic tissue, dead necrotic slough, and multiple infections. Although antibiotics are necessary for treating infected wounds, substantial morbidity and amputation rate with stunning resistance prompt us to explore newly therapeutic methods as effective and safe as possible based on the number of ulcers completely healed, the measured change in wound size, presence or absence of biomarkers in favour of healing these outcomes.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 April 2020 and was last updated on 22 April 2020 (registration number INPLASY202040148).

**INTRODUCTION**

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**Rationale:** Ozone has been demonstrated as being useful in promoting wound healing as well as adverse events in individual studies.

**METHODS**

**Search strategy:** The Cochrane Central Register of Controlled Trials(CENTRAL)---The Cochrane Library; Pubmed; Web of Science; Ovid Embase; Chinese Biomedical Literature Database; The Chinese Clinical Registry. We will use heading terms plus free words as search strategy which decided by all the reviewers.

**Participant or population:** Included human subjects of any age with chronic wounds, including war wounds, burns, and non-healing diabetes, venous, or arterial ulcers; cutaneous ulcers of any aetiology whether clinically infected or uninfected in any care setting. But ulcers or wounds in dentistry, palatal epithelial fields, jaw, lung, disc, atmosphere and meteorology are excluded.

**Intervention:** The primary intervention was formulation of ozone topically or systematically applied by any means, alone or in combination with other dressings or components.

**Comparator:** The comparator group was various involving sham ozone therapy, with concomitant interventions such as antibiotics, topical agents or conventional care as long as the same concomitant treatment was carried out in both groups; or any standard treatment regimens designed to promote wound healing.

**Study designs to be included:** Randomised controlled trials (RCTs) were considered for inclusion, irrespective of publication status or language.

**Eligibility criteria:** Only randomized controlled trials (RCTs) on human subjects of any age with refractory wounds in any care setting with the use of ozone.

**Information sources:** The Cochrane Central Register of Controlled Trials (CENTRAL)---The Cochrane Library; Pubmed; Web of Science; Ovid Embase; Chinese Biomedical Literature Database; The Chinese Clinical Registry. We will search manually the bibliographies of all identified and relevant publications to identify any further appropriate trials and will seek clarification for insufficient or ambiguous information by contacting the authors with e-mails for exact data.

**Main outcome(s):** Proportion of participants with completely healed wounds (as defined by study authors); Time to achieve complete ulcer healing (as defined by authors); Change in wound size (as defined by authors).

**Additional outcome(s):** Incidence of adverse events, such as toxicity, irritation; Amputation; Quality of life; Length of hospital stay; Cost.

**Data management:** We are about to use a predefined electronic data extraction spreadsheet for collecting data accordant to the study's requirement. Eligible data will be extracted and recorded by two review authors followed by checking carefully via another reviewer differences will be resolved by discussion. The data extracted included the following: first author/title; year of publication; study design; location of the trial; sample size; study design; intervention and...
comparison including any concomitant treatments; outcomes including methods used to measure outcomes; duration of follow-up; withdrawals and reason for withdrawal; Number of participants completing; Adverse events.

**Quality assessment / Risk of bias analysis:** Three investigators will assess the methodologies of the studies included using the Cochrane risk of bias tool to evaluate the risk of bias, and any applicability concerns.

**Strategy of data synthesis:** We will provide summaries of the intervention effects for each study by calculating risk ratios (RR) (for dichotomous outcomes), standardized mean differences (SMD) or mean differences (MD) (for continuous outcomes). MD can be adopted when the same scale is utilized across different studies to measure an outcome. If not the same scales, SMD is eligible. In addition, its standard error of mean (SEM) only obtainable in a study will be transformed into standard deviation (SD) using a statistical theorem for calculation. 95% confidence intervals (CI) and two-sided P values, furthermore, will be computed for each outcome. With regards to pooling the results, chi-square test and I² statistic will be taken into account for investigating heterogeneity of included studies and we prepare to apply a random-effects meta-analysis with MD or SMD for continuous outcomes and RR for binary outcomes provided I² > 50%, P < 0.05 considered as being indicative of substantial heterogeneity. If I² > 0.05, this represents negligible heterogeneity with a fixed-effects model. If a meta-analysis is not available, descriptive summarize of individual findings will be performed instead.

**Subgroup analysis:** Subgroup analysis will be carried out to find out possible sources of statistical heterogeneity following several aspects: wound type, measure of comparators, duration of follow-up, using that provided in each included study.

**Sensitivity analysis:** We are going to provide sensitivity analyses according to study quality. Omitting the RCTs with a high risk of bias one by one followed by pooling the data and analysis again. We can identify the stability of the results and whether an individual study impacts the overall ones by comparing the difference between the original effects and the reobtained results.

**Language:** No.

**Country(ies) involved:** China.

**Keywords:** ozone therapy; wound; ulcers; chronic; systematic review; meta-analysis; protocol.

**Dissemination plans:** We intend to publish the study results in a journal or conference presentations.

**Contributions of each author:**
- **Author 1 - Qing Wen** drafted the manuscript.
- **Author 2 - Dongying Liu** made contributions to the manuscript of formal analysis and methodology.
- **Author 3 - Xian Wang** made contributions to the manuscript of data curation.
- **Author 4 - Yanli Zhang** made contributions to the manuscript of conceptualization.
- **Author 5 - Song Fang** made contributions to the manuscript of investigation.
- **Author 6 - Xianliang Qiu** made contributions to the manuscript of validation.
- **Author 7 - Qiu Chen** made contributions to the manuscript of conceptualization, methodology and review.