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Effects of different treatment measures on the efficacy of diabetic foot ulcers：A network meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No support.

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Conflicts of interest - None declared.

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INTRODUCTION

Review question / Objective Effects of different treatment measures on the efficacy of diabetic foot ulcers：A network meta-analysis.

Condition being studied Diabetes(DM) is a rapidly spreading disease worldwide, posing a significant health challenge globally [1].It is estimated that there were 451 million patients with diabetes in 2017, and this number is projected to rise to 693 million by 2045 [2].Diabetic foot ulcer (DFU) is one of the clinical manifestations of diabetic nerve lesions, defined as structural or functional changes in the foot associated with diabetic nerve lesions and varying degrees of peripheral vascular disease, such as ulcers, infections, or gangrene[3].DFU is one of the most common, most severe, and most costly complications of diabetes [4-8],with approximately 19% to 34% of patients with diabetes experiencing a DFU in their lifetime[9]. It is characterized by complex management, high incidence rate, and high mortality rate[10].The global incidence rate of diabetes foot ulcers is approximately 6.3%, occurring predominantly in patients with type 2 diabetes(T2DM), the elderly, and those with a prolonged history of diabetes[11].According to predictions from the World Health Organization (WHO), by 2030, DFU will affect more than 19% of the world's adult population[12].DFU are also the primary reason for hospitalizations among diabetes patients worldwide. Reports indicate that nearly 88% of lower leg amputations are associated with DFU, often resulting in disability and severely compromising the quality of life[13-14].The 5-year mortality rate for patients with DFU is 30%, while the 5-year mortality rate for those undergoing amputations exceeds 70%[15]. Furthermore, the

annual cost associated with DFU treatment and amputations is extremely high, approximately 10.9 billion USD worldwide[16]. From this, it is evident that DFU are associated with significant incidence rates and mortality rates, as well as imposing a substantial economic, social, and public health burden.

Currently, the standard first-line treatments for DFU include managing blood glucose levels, conventional therapies (such as infection management, debridement, wound unloading, and dressings), and angioplasty for ischemic peripheral artery disease (PAD)[17].However, these treatments are not satisfactory. It has been reported that the complete healing rates for DFU patients after 12 weeks and 20 weeks of standard therapy are only 24% and 31% respectively[18]. Therefore, in recent years, several adjunctive techniques have been developed for the debridement treatment of DFU. These include UD, NPWT (including vacuum-assisted closure (UAC) and vacuum sealing drainage(VSD)), and oxygen therapies (such as HBOT and TOT). Additionally, studies have found that using SCs, growth factors, or tissue-engineering dressings can form the basis for a new treatment approach. Among these, fat-derived SCs, PRP, and ADM have emerged as focal points of research. These treatment methods aim to restore the body's natural healing process [19].DMA have been employed to compare the efficacy and safety of these therapeutic measures in the treatment of DFU [20-27], yet divergent opinions persist. Moreover, there have been no studies that directly compared the therapeutic outcomes of these varied treatments for DFU. In contrast, NMA can utilize both direct and indirect data to compare various interventions, and by ranking the therapeutic effects of all interventions, they can identify the most effective treatment method. Consequently, to further evaluate the impact of different therapeutic methods on the outcome of DFU efficacy, we included relevant RCTs in a NMA, aiming to provide stronger evidence for the effectiveness and safety of various treatments for DFU.

METHODS

Search strategy We searched the PubMed, the China National Knowledge Infrastructure (CNKI), Embase, the WanFang and the WeiPu database. The retrieval time was from database establishment to January 2024, and retrieval entailed subject and free words.The search terms include "diabetic foot ulcers," "platelet-rich plasma," "negative pressure wound therapy," "hyperbaric oxygen therapy," "topical oxygen therapy," "ultrasonic debridement," "acellular dermal matrix," "stem cells," and "randomized controlled trials." The publication type of the studies is restricted to randomized controlled trials (without language or location limitations).

Participant or population Diabetic foot ulcers.

Intervention "platelet-rich plasma," "negative pressure wound therapy," "hyperbaric oxygen therapy," "topical oxygen therapy," "ultrasonic debridement," "acellular dermal matrix," "stem cells,".

Comparator standard ofcare.

Study designs to be included Randomized controlled trials.

Eligibility criteria (1) The subjects are patients with DFU. (2) The study type is a RCT. (3) The study provides at least one effective efficacy indicator: complete healing rate, healing time required, reduction in ulcer area, amputation rate, and adverse reactions (infection, allergy, pain, etc.). (4) The study compares the efficacy and safety of different treatment measures in patients with DFU.

Information sources The PubMed, the China National Knowledge Infrastructure (CNKI), Embase, the WanFang and the WeiPudatabase.

Main outcome(s) Include ulcer healing rate, time required for ulcer healing, reduction in ulcer area, amputation rate, and adverse reactions (infection, allergy, pain, etc.).

Data management Two evaluators independently searched the database based on inclusion and exclusion criteria, searching the full text of the initially included articles. They used a uniform form to extract data, including: author name, publication year, country, research subjects (sample size, gender ratio, average age, and smoking history), interventions (experimental group and control group), duration of the study, duration and area of DFU, and main research results.

Quality assessment / Risk of bias analysis The included studies were evaluated from five aspects: randomization method, baseline comparability, intervention measures, blind method, and result analysis by using the Centre for Evidence-Based Medicine at Oxford University, UK. Evaluators made "yes", "no", "unclear" judgments for each evaluation item.We recorded the scores by using a scoring method ranging from 0 to 5, with 1 point for each project. The total score ≤2 points was

considered as low-quality research, and ≥3 points was considered as high quality research.

Strategy of data synthesis We searched the PubMed, the China National Knowledge Infrastructure (CNKI), Embase, the WanFang and the WeiPu database. The retrieval time was from database establishment to January 2024, and retrieval entailed subject and free words.The search terms include "diabetic foot ulcers," "platelet-rich plasma," "negative pressure wound therapy," "hyperbaric oxygen therapy," "topical oxygen therapy," "ultrasonic debridement," "acellular dermal matrix," "stem cells," and "randomized controlled trials." The publication type of the studies is restricted to randomized controlled trials (without language or location limitations).

Subgroup analysis Direct meta-analysis (DMA)
For DMA, we used STATA12.0 software for statistical analysis, using odds ratio (OR) and 95% confidence interval (CI) as the evaluation index of the results, represented by mean difference and 95% CI. First, heterogeneity was assessed using the X2 test (a=0.05) and a quantitative analysis of I2 for heterogeneity (I2 ≥ 50%) conducted. In cases of no heterogeneity between the research results, the meta-analysis was conducted. In cases of statistical heterogeneity between the research results, the source of heterogeneity was further analyzed, and the random heterogeneity model was used after excluding the influence of obvious clinical heterogeneity. Funnel maps created using the STATA software were employed to detect publication bias.
Network meta-analysis
We performed a Bayesian NMA using R and STATA software. NMA can combine direct and indirect comparisons to further analyze the effects of different treatment options on DFU. The results of the comparison effect are expressed as OR and its 95% CI. Moreover, we built a network diagram using the mtc.network“command of the gemtc” package in the R software. Furthermore, we calculated the percentage area under the cumulative ranking (SUCRA) curve, ranking the different interventions. One intervention had a higher SUCRA value than others, indicating that the better the treatment effect, the lower the incidence of adverse reactions. A node splitting method was used to evaluate the consistency hypothesis of direct and circumstantial evidence. When direct evidence of the results was consistent with circumstantial evidence (P> 0.05), the consistency model was adopted.

Sensitivity analysis Funnel maps created using the STATA software were employed to detect publication bias.

Country(ies) involved China.

Keywords Diabetic foot ulcers;Ultrasonic debridement;Negative pressure wound therapy;Stem cells;Hyperbaric oxygen therapy;Topical oxygen therapy;Platelet-rich plasma;Acellular dermal matrix;Standard of care.

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