Evidence-based Research

Effects and safety of acupuncture for DFUs: a systematic review and meta-analysis

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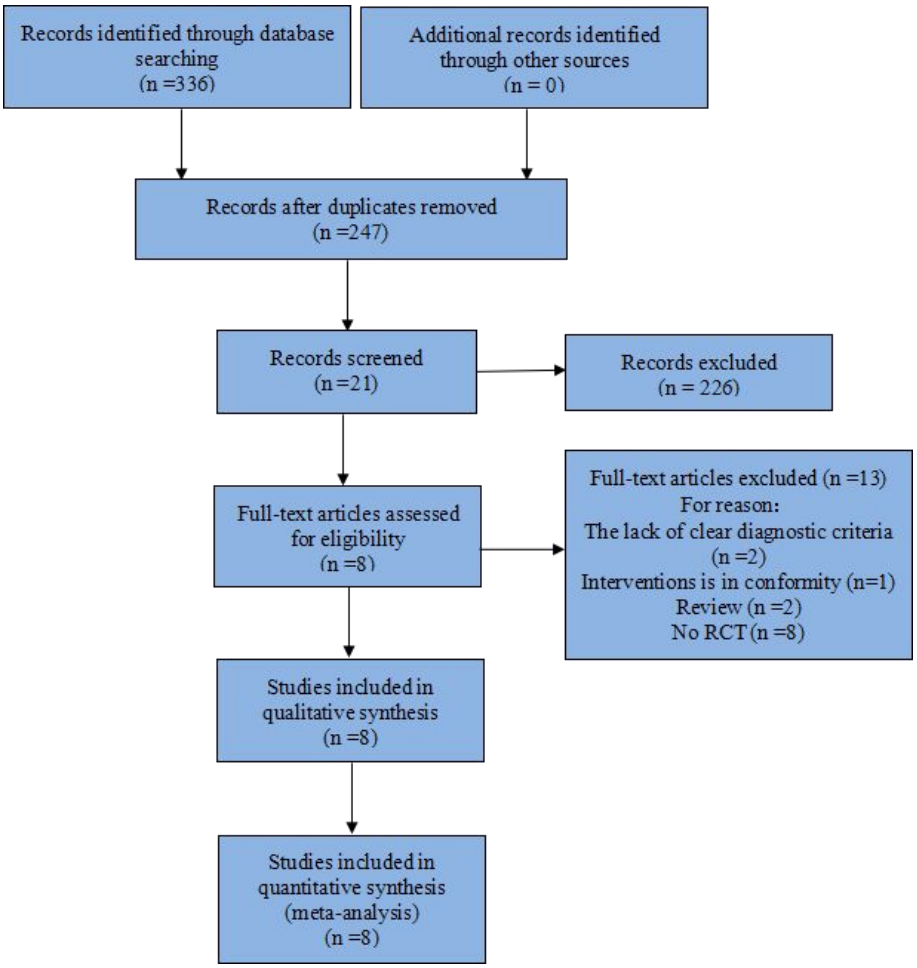
Highlights:

As one of the traditional Chinese therapies, acupuncture has been routinely adopted to treat diabetic foot ulcers (DFUs) for centuries. Plenty of studies focused on the effect of acupuncture for DFUs, but the precise clinical efficacy remains controversial. Here we undertook a systematic review to assess the effectiveness of acupuncture for diabetic foot, and analyze some issues hidden in several outcomes.



Effects and safety of acupuncture for DFUs: a systematic review and meta-analysis

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Abstract

Objective: To systematically evaluate the effect and safety of acupuncture for the treatment of diabetic foot ulcers (DFUs). **Methods:** Six databases, including Pubmed, Web of Science, EMbase, the Cochrane Library, the Chinese Biomedical Literature Database (CBM), and the China National Knowledge Infrastructure (CNKI), were electronic searched for randomized controlled trials (RCTs). Retrieval periods from each database were stopped until 30 October, 2014. Cochrane risk of bias assessment tool was used to assess the methodological quality of included studies. **Results:** A total of 8 trials involving 481 participants met the inclusion criteria. The results of meta and descriptive analysis suggested that acupuncture effectively improved total effective rate of DFUs, shortened ulcer healing time , and improved the blood flow volume, but acupuncture did not ameliorate vessel diameter and peak velocity. No serious adverse events were identified in acupuncture group. **Conclusions:** Acupuncture is more effective in shortening overall treatment time. Acupuncture has advantages over the control group in curative effect.

Keywords: Diabetic foot ulcers; Acupuncture; Systematic review; Meta-analysis

摘要

目的：系统评价单纯针灸疗法治疗糖尿病足的效果。

方法：计算机检索 Pubmed, Web of Science, EMbase, the Cochrane Library, CBM 和 CNKI 等数据库中关于单纯针灸疗法治疗 DFUs 的随机对照试验 (RCTs)，检索时限均为从建库至 2014 年 10 月 30 日。采用 Cochrane 风险偏倚评估工具对纳入研究的质量进行方法学评价。基于固定或随机效应模型。

结果：最终纳入 8 个研究，共 481 人。Meta 分析和描述性分析结果显示：①单纯针灸疗法可以有效地改善总有效率；②缩短溃疡愈合时间；③改善血流量；④在血管直径和峰值速度上无改善；⑤单纯针灸疗法不会引起严重的不良反应。

结论：相对于对照组来讲，接受针灸法治疗组总有效率提高。

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Introduction

People with diabetes mellitus (DM) often suffer from the intractable diabetic foot ulcers (DFUs) secondary to neuropathy, peripheral vascular disease with ischaemia or both [1]. DFUs is the leading contributor to the diabetes-related hospitalization and non-traumatic lower extremity amputation in patients with DM [2,3]. It was estimated that 25% of patients with DM would progress foot ulcer throughout their lives [4], and up to 15% would suffer from amputation [5]. Therapeutic regimens on DFUs include glycemic control, extensive local wound care and prompt revascularization [6], however, poor healing rate is still a fatal cause leading to low quality of life and overwhelming medical expenditures [7].

Acupuncture, one of the complementary and alternative medicines refers to insert the needless, specific medicinal herb or both (e.g. Moxa, Ginger, Garlic, etc.) into the specific acupoints on body for facilitating recovery, was commonly used to treat the DFUs [8-9]. Nowadays a majority of trials evaluated the summary effects of various traditional Chinese medicine TCM interventions, however, these results from different studies are still inconclusive, Although some systematic reviews and meta analyses into the topic published, some weakness can not be avoided and a great deal of randomized controlled trials (RCTs) has failed to complete since then. Therefore , a systematic review and Meta analysis was undertaken by us to critically evaluate the evidence from RCTs regarding acupuncture in DFUs.

Methods

The report of the systematic review and meta analysis is in accordance with the Preferred Items for Systematic Review and Meta Analysis (PRISMA) and Cochrane Handbook for Systematic Reviews of Interventions [10-11]. Ethical approval was not necessary, because this study was conducted based on the completed previous trials.

Inclusion and exclusion criteria

RCTs regarding effect and safety of acupuncture for the treatment of DFUs were eligible for the inclusion criteria. Only articles in English and Chinese language were eligible.

Types of participants

Patients who were definitely diagnosed as DFUs were met the inclusion criteria. Wagner grade of DFUs was not restricted in our meta analysis. However, study involving patients with concurrence of DM and other diseases, such as last-stage of cancer or use the steroid hormone therapy, would be excluded.

Types of interventions

The experimental group involved patients undergoing acupuncture, a combination of acupuncture and other therapies. The control group involved patients undergoing placebo, drug therapy and no-treatment.

Types of outcome measures

Major outcome parameters: total curative effective rate, time to ulcer healing, the hemodynamic parameter, and adverse events.

Exclusion criteria

We excluded these studies that were not RCTs design and the RCTs which tested comprehensive effect of acupuncture plus other interventions. It was ineligible for the study if the data was in-sufficient, lacking or unable to translate into effective sort.

Search strategy

We searched six electronic databases, including PubMed, Web of Science, EMbase, Cochrane library, CBM, and CNKI (from inception to 30 October, 2014). The following search terms were used: ‘acupuncture therapy’, ‘acupuncture*, needling’, ‘acupoint*’, ‘electroacupuncture’, ‘moxibustion’, ‘diabetic foot’, ‘diabetic feet’, ‘DFUs’, ‘diabetic gangrene’, ‘diabetic foot gangrene’. The reference lists of included articles were manually searched to include any eligible studies.

Data extraction and quality assessment

Searches were conducted and data extracted by two independent reviewers (YLJ and TX). Each trial identified in the search was evaluated for design, patient eligibility criteria, and outcome measures. Divergences were resolved by discussion with a third review reviewer (SGM). Duplicate records were excluded based on screening of titles and abstracts. All remaining articles were screened in full text. Quality assessment of included trials was independently performed by each reviewer according to Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [12].

Statistical analysis

The total curative efficacy, mean time to ulcer healing and the hemodynamic parameters was calculated. We evaluated homogeneity trials included in I^2 statistic. If $I^2 > 50\%$, the trials were considered to be heterogeneity, a random effects model was conducted. If $I^2 < 50\%$, the studies were deemed to be homogeneity, a fixed effects model was performed. Pooled statistics of the differences in the ratio or mean for the individual study are shown. Pooled differences in ratio or means were calculated and a two-sided P value < 0.05 was considered to indicate statistical significance. Subgroup analysis will be performed according to courses of treatment and different comparisons. All analyses were performed using Review Manager (RevMan) 5.3.0 (the Cochrane Collaboration, Copenhagen, Denmark) and Stata software, version 12.0 (Stata Corp, College Station,TX).

Results

A total of 336 citations were identified at the initial literature search stage and added no trial to the searched result. After screened title, abstract and full-text, only 8 trials (included 9 RCTs) [8, 9, 13-18] that included 481 participants according to inclusion and exclusion criteria met quantitative analysis. Among these included articles, Zhang (2008) [8] conducted a three-arm trial, and we divided it into two RCTs. The flow diagram of literature retrieval and study selection was presented (Fig.1).

Characteristics of included trials

A total of 481 participants were included. The Characteristics of 8 trials (included 9 RCTs) were presented in Table 1.

Assessment of risk of bias

All included studies described random sequence generation, but only two studies provided adequate information to generate the random sequence. So two studies were judged to be at low risk of bias for this domain. Remaining studies were unclear for risk of bias.

Allocation concealment

No trials mentioned how the randomization sequence were implemented, so they were judged as being at unclear for risk of bias.

Blinding

Blinding for researcher was impossible, but they will appear the operation bias and thus the domain was regarded as "high risk". One trial was designed to blind the outcomes of assessor. Another study reported the blinding for participants, but details cannot be extracted from studies, the domain of which was rated as "unclear". Remained studies did not state whether blinding was employed, which led to an unclear for risk of detection bias.

Incomplete data

For all trials, authors stated that no drop-out, withdrawal and loss to follow-up existed during the research process. Therefore, they were deemed to be at low risk of attrition bias for this domain.

Selective Report

All studies reported outcomes adequately and were deemed to be at low risk of bias. Whereas, conclusion was identified according to methods and participants section of eligible studies due to protocol cannot be provided.

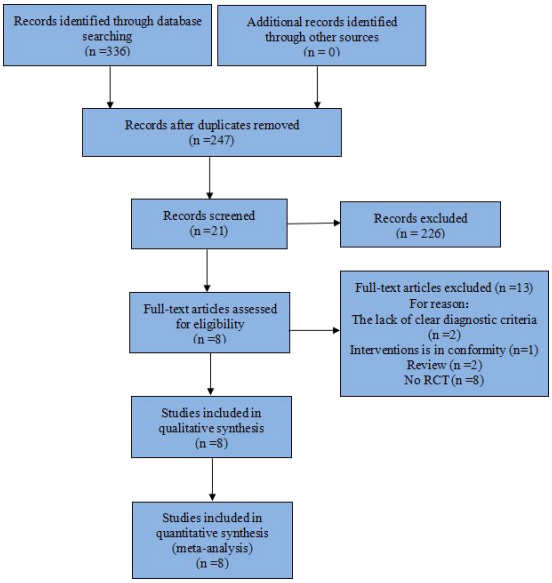

Figure 1 PRISMA flow diagram of reteriveal and selection of literature.

Table 1 Characteristics of 9 trials identified in the literature search.

Studies included	Methods	No. Of Case (T/C)	Interventions		Age（T/C）	Outcomes
			Study group (T)	Control group (C)		
Zhang[a] 2003[7]	Computerised randomisation schedule	43/32	Warm-needle techniques with basic therapy plus external therapy	Chinese herbal medicine with basic therapy plus external therapy	59.6±12.32/58.3±11.79	Ⅰ+Ⅲ+Ⅳ
Zhang[b] 2003[8]	Computerised randomisation schedule	43/32	Warm-needle techniques with basic therapy plus external therapy	Western medicine with basic therapy plus external therapy	59.6±12.32/58.6±11.9	Ⅰ+Ⅲ+Ⅳ
Yi 2007[9]	Rrder of admission	32/31	Acupuncture with moxibustion plus basic therapy	Basic therapy	51～75/52～74	Ⅰ+Ⅲ
Chen 2010[10]	NA	27/27	Moxibustion massager with basic therapy plus dressing change	Basic therapy with dressing change	56.7±11.3/54.6±12.7	Ⅱ
Zhong 2011[11]	Registration order	38/38	Acupoint injection with basic therapy	Basic therapy	65.9±10.1/65.9±10.1	Ⅰ+Ⅲ+Ⅳ
Liu 201112]	NA	26/26	Moxibustion with eroded debridement plus Compound Sihuang wet	Eroded debridement with Compound Sihuang wet	60.1±9.3/62.5±8.1	Ⅰ+Ⅱ
Liu 2014[13]	NA	20/20	Moxibustion with basic therapy	Basic therapy	43.5±6.9/42.8±6.9	Ⅰ
Ma 2013[14]	NA	15/13	Moxibustion with routine dressing change	Comfeel transparent dressing with routine dressing change	70～86/70～86	Ⅰ+Ⅱ
Qi 2013[15]	Table of random numbers	31/30	Moxibustion with complex treatment	Complex treatment	52.6±20.8/54.1±17.3	Ⅰ+Ⅲ+Ⅳ

Other potential source of bias

Three studies were funded by non-commercial organizations and the remaining trials did not report funding information. The methodological quality assessment of included trials was revealed (Fig.2 and Fig.3).

Meta-analysis

A total of 8 trials (9 RCTs) investigated the effects of acupuncture and reported the total effective rate of the acupuncture group compared with the control group for the treatment of DFUs. Sub-group analysis was conducted due to the different treatment courses. For courses of less than 6 weeks group, five studies (5 RCTs) were involved with clinical and statistical heterogeneity in the overall treatment time (P = 0.12, I^2 = 46%), and thus a fixed effects model of analysis was used. Pooled result revealed the difference between the intervention and the control groups (RR = 1.37, 95% CI was 1.21 to 1.55. P <0.000) (Fig.4). For courses of 8 weeks group, one study was involved and the result showed that acupuncture effectively improved the total effective rates (RR = 1.20, 95% CI was 1.00 to 1.44. P = 0.05) (Fig.4). In courses of 12 weeks group, two studies were pooled without heterogeneity (P = 0.45, I^2 = 0.0%). The meta analysis revealed the intervention groups were significantly better than the control groups (RR = 1.29, 95% CI was 1.09 to 1.53, P = 0.004) (Fig.4).

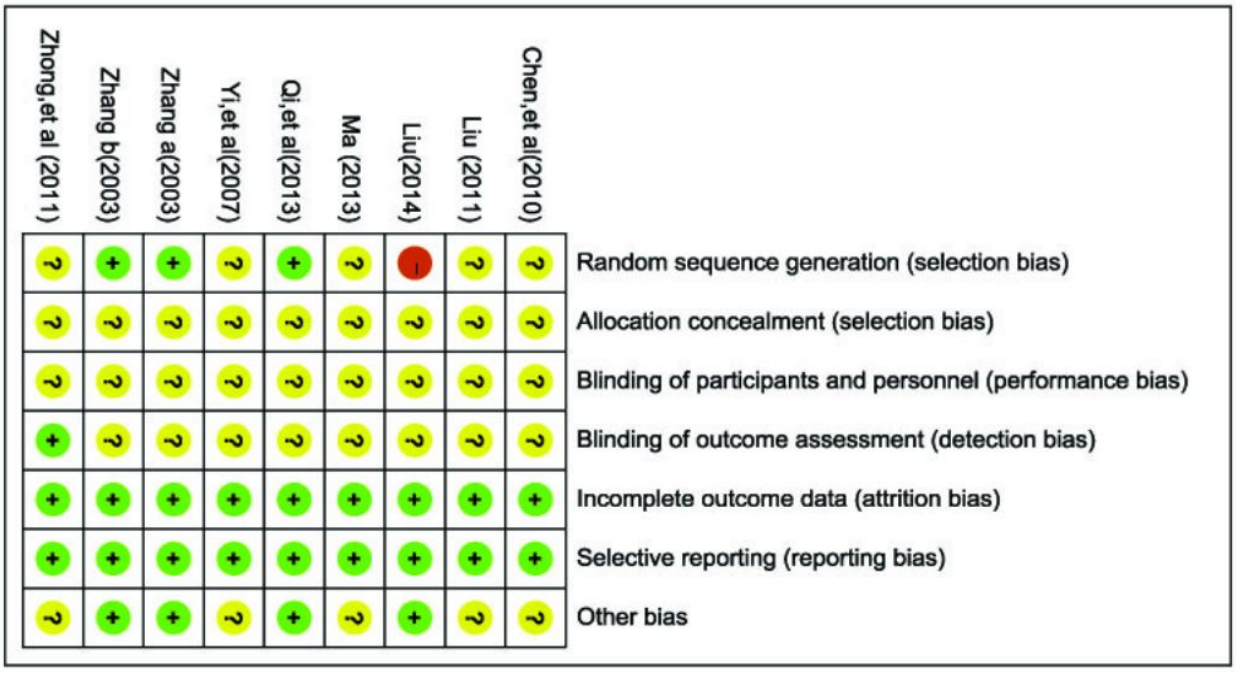

Figure 2 Risk of bias summary:authors' judgments about each risk of bias item for included studies.

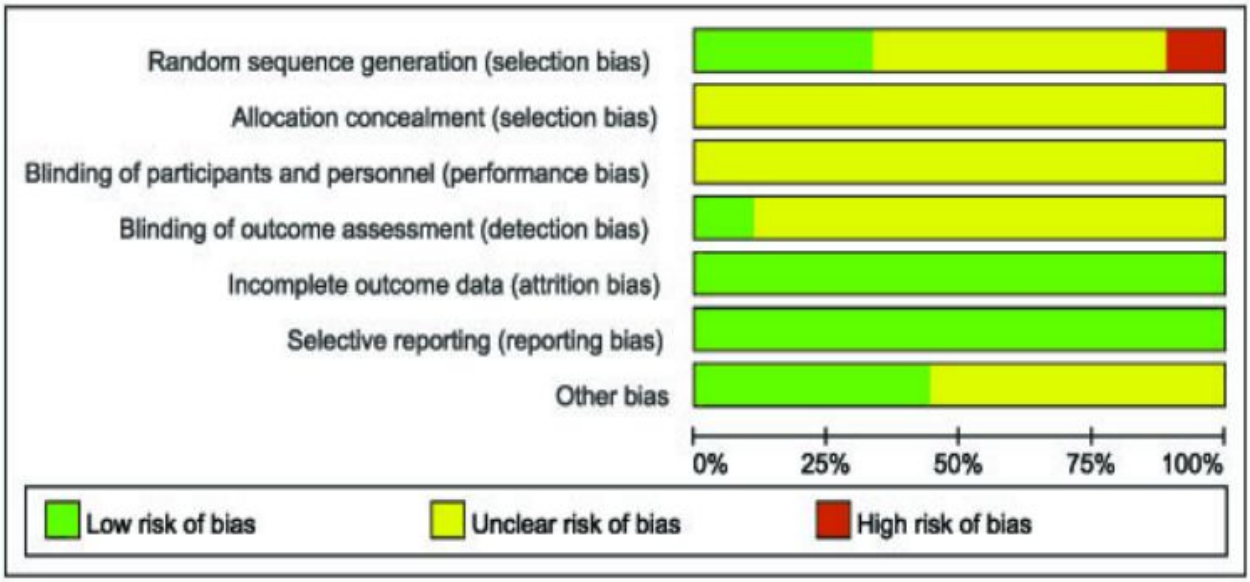

Figure 3 Risk of bias graph: authors' judgments about each risk of bias item for included studies.

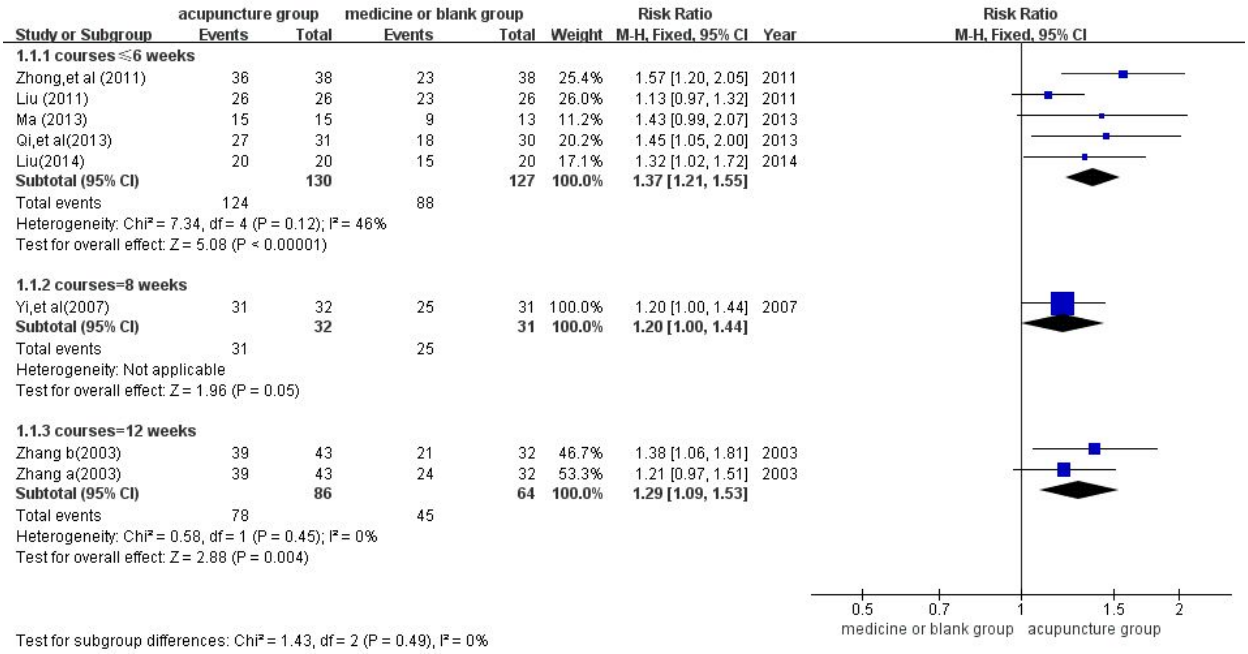

Figure 4 Meta-analysis for total effective rate.

Time to ulcer healing

Three studies employed ulcer healing time as outcomes and were divided into sub-groups according to the diversity of control types. For acupuncture versus blank group, two studies (2 RCTs) were included. A random-effects model of analysis was adopted, as statistical heterogeneity had been detected (P = 0.04, I^2 = 75%). The pooled result suggested that the acupuncture shortened the healing time (SMD = -1.31, 95% CIwas -2.57 to -0.05. P = 0.04). After the pooled analysis, we found the participants' average ages of Chen, et al (2010) were older than the Liu (2011)'s. Therefore,the age's difference of participants between two trails led to significant clinical heterogeneity existed in these two trials. Moreover, basic interventions were different between them, Liu (2011) did more specialized and meticulous nursing. Hence, methodological heterogeneity existed in the 2 trials and the research team performed a descriptive analysis to interpret the results above: Chen,et al (2010) reported that the observation group could obviously shorten the healing time of diabetic foot ulcers (SMD = -0.72, 95% CI was -1.42 to -0.02) and Liu (2011) had the same conclusion (SMD = -2.02, 95% CI was -3.07 to -0.96, Fig.4). In acupuncture versus medicine group, only one study was involved. The result indicated differences between the two groups statistically. In the aspect of minimizing the wound healing time, acupuncture group was obviously superior to the control group (SMD = -5.00, 95% CI was -7.33 to -2.68, P < 0.001, Fig.5).

The hemodynamic parameters

A total of 4 trials (5 RCTs) reported the variation of the relative hemodynamic parameters which were measured by color to Dopple before and after intervention. According to the different hemodynamic parameters, sub-group analysis was generated. With vessel diameter (VD), 3 trials (4 RCTs) were involved with clinical and statistical heterogeneity (P <0.001, I^2 = 74%). A sub-analysis was conducted to explore whether the heterogeneity could be partially explained by the different control types. For acupuncture versus blank group, two studies (2 RCTs) were involved. Three studies were pooled without obvious heterogeneity (P = 0.88, I^2 = 0.0%). The result revealed a difference between acupuncture group and the control group (SMD = 1.01, 95% CI was 0.66 to 1.37, P < 0.001). For acupuncture versus medicine group, only one study (2 RCTs) was involved. Two RCTs were pooled without heterogeneity (P = 0.85, I^2 = 0.0%). The result indicated that no better improvements were observed after acupuncture treatment (SMD = 0.18, 95% CI was -0.14 to 0.51, P= 0.27, Fig.6).

Two studies (3RCTs) reported the measure of peak velocity and no heterogeneity was detected across studies (P = 0.97, I^2 = 0.0%). The pooled result indicated no difference between acupuncture group and the control group (SMD = 0.20, 95% CI was -0.07 to 0.48, P = 0.14, Fig 7). A total of two trials (3 RCTs) which change data into blood flow volume two groups statistically. In the aspect of minimizing were presented and were incorporated without heterogeneity (P = 0.14, I^2 = 48%). The meta analysis showed the acupuncture group was significantly superior to the control group (SMD = 0.33, 95% CI was 0.07 to 0.60, P = 0.01, Fig 8).

Adverse events

Three of the 8 studies evaluated the safety of interventions. Zhang (2003) reported 7% of patients were burnable and bullate after acupuncture. Zhong et al (2011) stated a low incidence of injection site pain (some 5.26%). Qi et al (2013) reflected no occurrence of adverse events after acupuncture. None of the participants withdrew or dropped out due to adverse events.

Publication Bias

The research team performed the analyses of all studies which were involved in the measure of total effective rate, using Begg's and Egger's plot to determine publication bias in all the

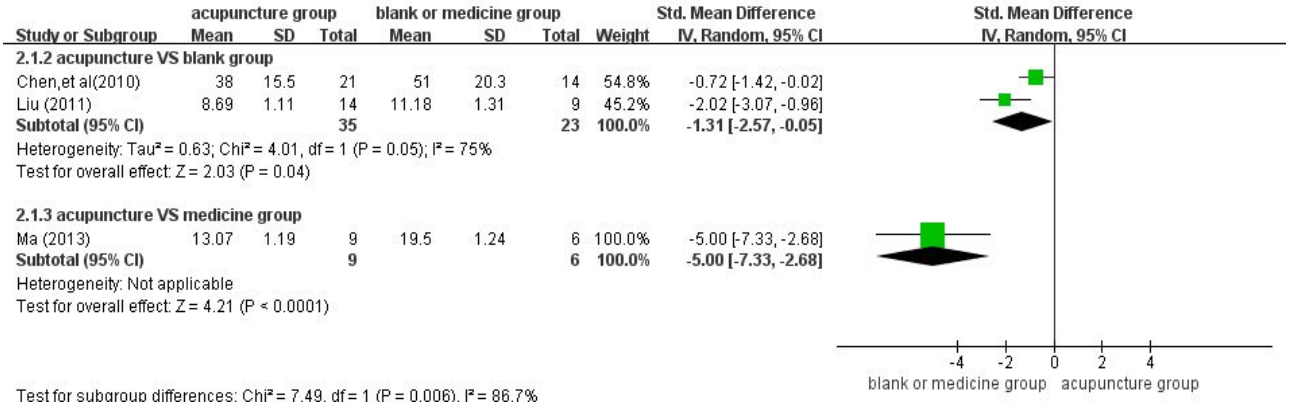

Figure 5 Meta-analysis for the ulcer healing time.

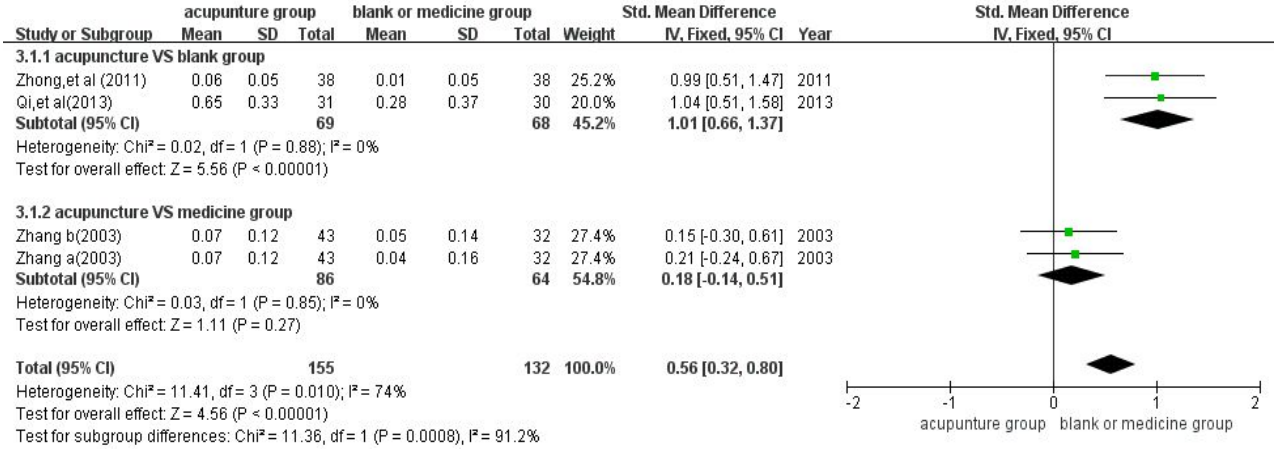

Figure 6 Meta-analysis for VD.

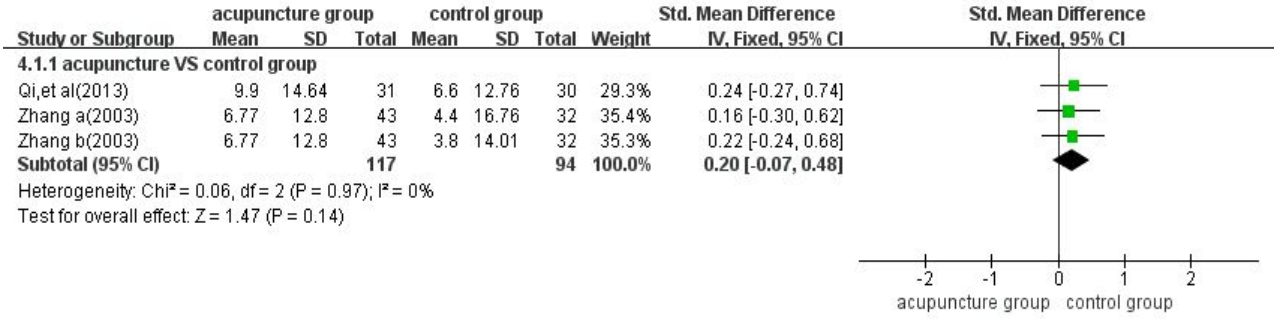

Figure 7 Meta-analysis for Peak velocity.

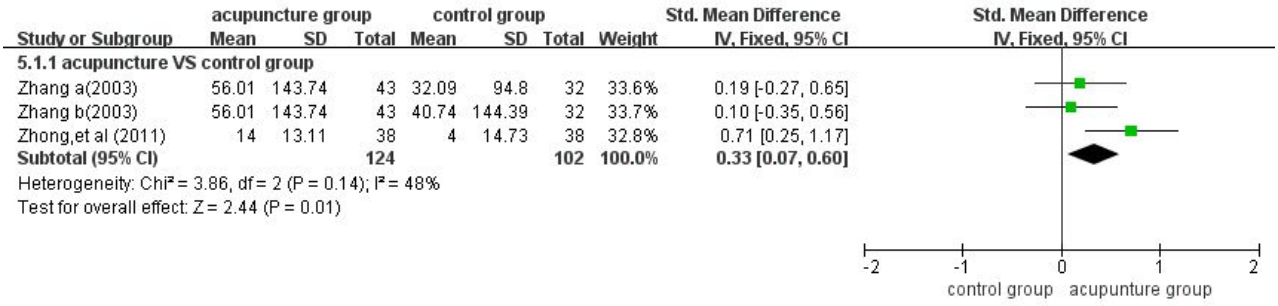

Figure 8 Meta-analysis for blood flow volume.

literature. The *P* value from the Begg and Egger was 0.063 and 0.005, respectively, and the asymmetry of Egger's plot indicated that publication bias possibly exists (Fig. 9).

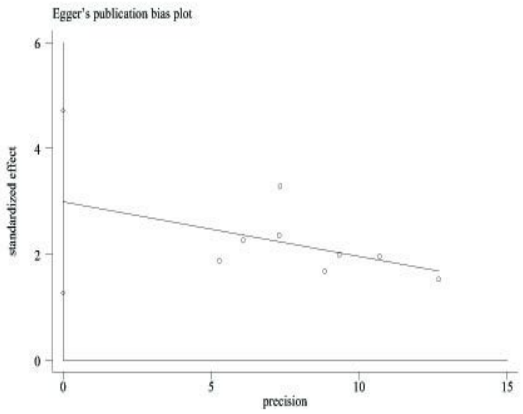

Figure 9 Egger's funnel plot of publication

Discussion

The purpose of this Meta analysis is to critically evaluate the effectiveness of acupuncture in relation to total effective rate, ulcer healing time, the hemodynamic parameters and adverse events. The review emphasized several issues with respect to both clinical practice and future research on each of these outcome areas.

Total effective rate

The findings of meta-analysis suggest that acupuncture therapy has advantages over the control group for the treatment of DFUs in overall efficiency. However, the included trials are mostly of poor quality, so the pooled result is likely to be overestimated. Clinically, the most important question is only what kind of patients with DFUs the acupuncture therapy is appropriate for. But the present evidence is still uncertainty. From the included studies, we found the patients of the target groups were distributed in 0 to 4 Wagner grades, excluding the patients in 5 Wagner grade. So it is useful to considering whether the acupuncture therapy is suitable for those excluded participants and thus increase management of DFUs'cost-effectiveness. These problems need the randomized controlled trials of higher quality with larger sample sizes to explore the potential causes. Furthermore, using purposeful sampling could lead to the distortion of clinical curative effect of acupuncture therapy. Therefore, the acupuncture-treatment populations must be determined at our reasonable discretion and founded on facts.

Another related problem was the way to choose the period of treatment and dose of acupuncture. Up to now, there are no relevant provisions. The optimum treatment cycle and dose of acupuncture are still unknown. Combining the third figure, we find the effectiveness of acupuncture changes over time and tend to be non-linear correlation. So it is important to understand whether we should adjust acupuncture stimulation dose and frequency in the light of the dynamics and tolerance of acupuncture therapy's time effect, and undertake acupuncture therapy according to its maximum effect size and resistance profile. It is critical to objectively choose the time of treatment and the courses. After all, the incidence of injuries of acupuncture for these patients is relatively high. Studies with a multilateral, larger sample size are needed to explore a series of problems.

Time to ulcer healing

Injured skin as a portal of entry for bacteria can contribute to wound infection [19]. Consequently, accelerating wound closure as early as possible is one of the most critical strategies for the treatment of DFUs. A total of 3 studies included the contemporary articles discussed the issue. The descriptive analysis agreed that acupuncture had a therapeutic benefit in shortening the healing time. Immense amounts of research for acupuncture mechanism are more concerned with diabetic peripheral neuropathy (DPN) which contains DFUs, but there is less documentation aimed at DFUs. The findings of meta-analysis suggest that acupuncture therapy has advantages in overall efficiency. There are some explanations why acupuncture therapy may be effective in accelerating healing: a) Improve the local blood circulation and strengthen metabolism to stimulate tissue repair [20], b) Adjust and enhance the body immunity and resistance, and it is likely to minimize the range of risk factors [21], and c) The thermal effect of moxibustion therapy promote the ulcer dry [13].

The hemodynamic parameters

Lower extremity arterial diseases in patients with DFUs are characterized by arterial stenosis and thickened vascular wall [22]. These pathological variations often lead to local circulatory deficiency and quickened blood flow velocity, accordingly, aggravate the destruction of vascular wall [22]. So it is considered abnormal vessel and flow are one of the core reasons for foot lesions [23]. In this study, acupuncture therapy was more effective than the control group in blood flow volume. However, insufficient evidence suggests that acupuncture is in a position to dilate vessel diameter and increase peak velocity. The mechanism of acupuncture should be explored further with more rigorous studies because acupuncture continues being widely used for this condition, which suggests that acupuncture may be an effective intervention for DFUs.

Adverse events

Two of the studies, severally, reported injection pain and burn caused by acupuncture, but none was serious. It is necessary to explore whether we should make a prophylactic use of analgesic for patients with pain and generalize a safer therapy method, such as an application of moxibustion massager. Another related problem is that studies failed to mention the follow-up effect, hence, there is no knowledge of recurrence rate of DFUs in the long term. And it is not conductive to assess the long-term efficacy of acupuncture which can form the basis for consolidation therapy. Future studies must provide some account of this patient-centred outcome as it's clearly a vital consideration in establishing the use of this therapy.

Limitations of the review

Our review has multiple limitations. The most significant one is clearly the paucity of the primary studies. Both of low methodological quality studies and small sample size seem to be the problems for this meta-analysis, which does not provide strong evidence in favour of acupuncture therapy.

Another potential limitation of the review is that all trials were conducted and published in China and used different

treatment sessions and various simulation methods. Consequently, the generalizability of the evidence found in this study may be seriously limited given separate treatment contexts or cultural backgrounds. Moreover, the restriction of languages might lead to a publication bias and affected the validity and reliability of this systematic review.

Finally, a possible critique is that the meta-analyses combined different endpoints and control groups, such as total effective rates and the hemodynamic parameters, measured at different times.

Conclusion

By analyzing the 8 included trials, this systematic review indicates that acupuncture therapy is a safe way for DFUs. It may be most effective in shorten overall treatment time and has advantages in curative effect. It is well known that small, poor-quality studies tend to spuriously inflate the effect of an intervention, hence, well-designed and conducted trials were needed to further definitely substantiate the conclusion.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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