Comparisons of negative pressure wound therapy and ultrasonic debridement for diabetic foot ulcers: a network meta-analysis

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Abstract: Objective: a network meta-analysis was performed to compare the strength and weakness of negative pressure wound therapy (NPWT) with ultrasound debridement (UD) as for diabetic foot ulcers (DFU). Methods: PubMed, Ovid EMBASE, Web of Science, Cochrane library databases, and Chinese Biomedical Literature Database were searched till February 2015. Clinical compared studies of negative pressure wound therapy and ultrasound debridement were enrolled. The primary efficacy outcomes included healed ulcers, reduction of ulcer areas and time to closure. Secondary amputation including major and minor amputations was used to assess the safety profile. Results: Out of 715 studies, 32 were selected which enrolled 2880 diabetic patients. The pooled analysis revealed that NPWT including vacuum assisted closure (VAC) and vacuum sealing drainage (VSD) were as efficacious as ultrasound debridement improving healed ulcers, odds ratio, 0.86; 95% CI 0.28 to 2.6 and 1.2; 95% CI 0.38 to 4, respectively. However, both were better to standard wound care in wound healing patients. Compared with the standard wound care treated diabetic foot ulcers, NPWT and UD resulted in a significantly superior efficacy in time to wound closure and decrement in area of wound. No significances were observed between NPWT and UD groups in both indicators. Fewer patients tended to receive amputation in NPWT and UD groups compared to standard wound care group. Conclusions: The results of the network meta-analysis indicated that negative pressure wound therapy was similar to ultrasound debridement for diabetic foot ulcers, but better than standard wound care both in efficacy and safety profile.

Keywords: Negative pressure wound therapy, ultrasound debridement, diabetic foot, network meta-analysis

Introduction

Diabetic foot ulcer (DFU)—an umbrella term for foot problems—is the most common, complex and costly sequelae of diabetes mellitus (DM) [1]. As reported, foot ulceration is affecting 15% or more of people with DM at some time in their lives [2]. According to Hunt’s study [3], the prevalence of foot ulcers ranges from 4 to 10 percent among patients with diabetes, and the lifetime incidence is estimated to be 10 to 25 percent. At present, the standard therapy for diabetic foot ulcers includes glucose control, management of infection, debridement, off-loading high pressure, and use of dressings. However, the treatment outcomes are far from satisfaction, whatever the efficacy or the complications [4, 5]. Negative pressure wound therapy (NPWT) is an ultramodern noninvasive adjunctive therapy system that applies controlled negative pressure using vacuum sealing drainage (VSD) or vacuum-assisted closure (VAC) device to help promote wound healing by removing fluid from open wounds through a sealed dressing and tubing which is connected to a collection container [6, 7]. Some clinical studies have suggested that negative pressure wound therapy is beneficial as an adjunctive treatment for diabetic foot ulcers compared with traditional wound therapy [8-10]. Withal, ultrasound therapy is a noncontact wound therapy to promote healing through the cleansing and debridement of wounds. Actually, therapeutic ultrasound has been used for years by physical therapists for the treatment of a variety of musculoskeletal disorders, using devices...
that operate in the 1 to 3 MHz range [11]. The current trend is toward using low-frequency ultrasound devices that operate in the kilohertz range. In recent years, clinical evidence including randomized [12] or non-randomized studies [13] of improved healing of chronic wounds treated with ultrasound has been accumulating. Because of the lack of head-to-head comparisons between two interventions, using network meta-analysis, we endeavor to put forward a study to compare the efficacy and safety of negative pressure wound therapy and ultrasound therapy through standard wound care therapy in healing of diabetic foot ulcers.

Methods

Search strategy
A bibliographic search of medical literature until January 2015 was performed using databases as PubMed, Ovid EMBASE and Web of Science, Cochrane library. The search string (“negative pressure wound therapy” OR “vacuum assisted closure” OR “vacuum sealing drainage”) OR (“ultrasound” OR “ultrasonic”) AND (“diabetic foot” OR “diabetic wound” OR “diabetic ulcer”) were used to search for relevant articles. Chinese biomedicine literatures databases were also searched. Reference lists of included studies and review articles were manually searched. The network meta-analysis was limited to studies conducted in human.

Inclusion and exclusion criteria
Clinical randomized or non-randomizes, controlled reporting relevant outcome measures like efficacy and safety were selected. The study was eligible for inclusion if 1) the study was on diabetes patients; 2) compared studies; 3) outcome measures were including healed ulcers, time to wound closure, decrement in area of wound and secondary amputations. The study was excluded if 1) single arm design; 2) primary endpoints were missing; 4) dual submissions.

Intervention
Negative pressure wound therapy including vacuum assisted closure (VAC) and vacuum sealing drainage (VSD), ultrasound debridement, and standard wound care were as treatments.

Outcomes
The primary outcome was healed ulcers (success of treatment definition: as full epithelialization). Other outcomes included time to wound closure, decrement in ulcer area. Secondary amputations were used to assess the safety of different treatments.

Data extraction
Two investigators independently assessed the quality of trials and any disagreement was resolved through discussion with the third author. The Modified Jadad score was used to evaluate the quality analysis of methodology, including randomization, blinding and withdrawal from study. The Jadad scale scores from 1 to 7. We classified the quality of studies into 3: low quality of 1-2; middle quality of 3-4; high quality of 5-7.

Missing data
The standard deviation of four studies providing mean value including time to wound closure and decrement were missing. Generally, three ways of solutions could address this issue: 1) remove the missing data from our analysis; 2) similar studies could be reference; 3) through calculating if we know the confidence interval or other relevant information. Here, due to primary studies recording both indicators were limited, and confidence interval deficiency, we choose the second choice.

Network meta-analysis
Network meta-analyses were to compare direct and indirect evidence of class or agents using the Bayesian Markov-chain Monte Carlo method. Traditional meta-analyses compare one intervention with another at a time and combine evidence directly from head-to-head clinical trials if such trials exist. A network meta-analysis combines effect sizes for all possible pairwise comparisons (direct and indirect), regardless of whether they have been compared in trials.

Statistical analysis
The statistical analysis was performed using software R (X64, 3.1.2, packages including gemtc and rjags). The output of the data was in
NPWT versus ultrasonic debridement for DFU

The population varied in studies that we had selected for example the age of the subject varied from one study to another, so we took random effect model rather than fixed effect model. The comparison of the effects between two groups was expressed in terms of odds ratio (OR) or standard mean difference (SMD) and its 95% confidence interval (95% CI). In order to avoid risk of bias, we had included only the clinical controlled studies and excluded observational and follow up studies.

Results

Descriptions of studies

A total of 715 relative studies published till February 2015 was obtained by electronic databases searches. Of these, 581 were excluded on the basis of title and abstract. From these remaining 134 articles identified, 63 were rejected because of beyond our inclusion criteria. After reading 71 full text, 39 were excluded for data redundancy, extension study, no primary or secondary endpoints, etc. Finally, 32 [8-10, 12, 14-41] articles met all entry criteria and were included in the network meta-analysis. Among these all chosen studies, 12 of studies published in English, 19 of Chinese. The screening process is illustrated in Figure 1.

The characteristics of the included studies are given in Table 1. Of the 32 studies, a total of 2880 diabetes patients were included. In three of these studies, foot ulcers were characterized using the Texas Diabetic Wound Classification System or the Wagner Scale. Quality of each study was listed in Table 1. All the statistical analysis adopted random effect model due to the variance of each study.

Healed ulcers

20 studies recorded completely healed ulcers. Random effect model was adopted, and the pooled analysis revealed that NPWT including VAC and VSD as well as UD significantly improved the proportion of diabetic foot ulcer healing compared with standard wound care, odds ratio and 95% confidence interval, 2.8 [1.9, 4.2]; 3.9 [2.3, 7] and 3.2 [1.2, 9.1], respectively. No significance was observed between VAC and VSD compared to UD, odds ratio and 95% confidence interval, 0.86 [0.28, 2.6] and 1.2 [0.38, 4] (Figure 2).

Time to wound closure

15 studies assessed the time to closure of ulcers. The result demonstrated that mean time to wound closure of VAC and VSD as well as UD were significantly shorter compared with standard wound care group, standard mean difference and 95% confidence interval, -18 [-29, -6.6]; -22 [-38, -6.3] and -23 [-46, 0.2], respectively. But the difference between UD and standard wound care was not very significant. On the other hand, VAC or VSD were as efficient as UD, standard mean difference and 95% confidence interval, 5.2 [-20, 31] and 1.1 [-27, 29], separately (Figure 3).
## Table 1. Characteristics of selected studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Original country</th>
<th>Participants</th>
<th>Intervention</th>
<th>Duration</th>
<th>Indicators</th>
<th>N</th>
<th>Arms</th>
<th>Baseline</th>
<th>Quality</th>
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<tr>
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<td>India</td>
<td>20-75 years DM</td>
<td>NPWT/standard wound care</td>
<td>8 w</td>
<td>Wound size, time to wound closure</td>
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<td>Middle</td>
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<td>Randomized, compared</td>
<td>Turkey</td>
<td>Diabetic foot ulcers</td>
<td>NPWT versus ultrasonic debridement for DFU</td>
<td>8 w</td>
<td>SF-36 scale</td>
<td>67</td>
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<td></td>
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<td>Compared study</td>
<td>US</td>
<td>Diabetic patients</td>
<td>VCT/standard wound care</td>
<td>2 w</td>
<td>Wound volume and depth and area</td>
<td>10</td>
<td>2</td>
<td></td>
<td>Middle</td>
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<td>Compared study</td>
<td>Iran</td>
<td>Diabetic patients</td>
<td>NPWT/standard wound care</td>
<td>5 w</td>
<td>Wound size</td>
<td>23</td>
<td>2</td>
<td></td>
<td>Middle</td>
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<td>Compared study</td>
<td>India</td>
<td>Diabetic patients</td>
<td>NPWT/standard wound care</td>
<td>8 w</td>
<td>Wounds healed</td>
<td>56</td>
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<td>Diabetic patients</td>
<td>NPWT/standard wound care</td>
<td>12 w</td>
<td>Time to wound closure</td>
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<td>US</td>
<td>Diabetic patients</td>
<td>NPWT/standard wound care</td>
<td>Unclear</td>
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<td>10</td>
<td>2</td>
<td></td>
<td>Low</td>
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<td>China</td>
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<td>NPWT/UD/NPWT+UD</td>
<td>1 w</td>
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<td>Compared study</td>
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<td>Diabetic patients</td>
<td>NPWT+UD/standard wound care</td>
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<td>80</td>
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<td>Diabetic patients</td>
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<td>NPWT+UD/NPWT</td>
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<td>UD/standard wound care</td>
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<td>VSD/standard wound care</td>
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<td>60</td>
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<td>Diabetic patients</td>
<td>VSD/standard wound care</td>
<td>5 d</td>
<td>Wounds healed</td>
<td>76</td>
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<td>Diabetic patients</td>
<td>VSD/standard wound care</td>
<td>2 w</td>
<td>Wounds healed</td>
<td>100</td>
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<td>Middle</td>
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<td>China</td>
<td>Diabetic patients</td>
<td>VAC/standard wound care</td>
<td>3 m</td>
<td>Wounds healed</td>
<td>100</td>
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<tr>
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<td>Diabetic patients</td>
<td>VAC/standard wound care</td>
<td>1 w</td>
<td>Wounds healed, Time to wound closure</td>
<td>536</td>
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<td>20</td>
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<td>Unclear</td>
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<td>43</td>
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<td>VSD/standard wound care</td>
<td>4 w</td>
<td>Wounds healed</td>
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<td>VAC/standard wound care</td>
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<td>Wounds healed</td>
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<td>VSD/standard wound care</td>
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<td>Wounds healed, amputation</td>
<td>78</td>
<td>2</td>
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<td>46</td>
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<td>China</td>
<td>Diabetic patients</td>
<td>VSD/standard wound care</td>
<td>Unclear</td>
<td>Time to wound closure, amputation</td>
<td>84</td>
<td>2</td>
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</table>
Decrement in ulcer area

Decrement in ulcer area was described in 10 studies. In the random effects mode, there were significant differences in ulcer area reduction from baseline in VAC and VSD groups compared with standard wound care group, standard mean difference and 95% confidence interval, -18 [-29, -6.7] and -22 [-38, -6.1]. UD could decrease the ulcer area compared to standard wound care, however, the significance was not observed. When compared with UD, we did not find any significance in VAC and VSD groups, standard mean difference and 95% confidence interval, 4.9 [-21, 31] and 0.93 [-27, 29] (Figure 4).

Secondary amputations

Amputation contains major amputation defined as amputations above the ankle joint and minor amputation distal to the ankle joint. Only 7 studies represented data of secondary amputations in this network meta-analysis. The incidence of secondary amputation in the NPWT group (including VAC and VSD) and the standard wound care group were 3.2 percent (12/376) and 11.1 percent (43/386). In the forest plot, compared to standard wound care, secondary amputations was less in VAC and VSD groups, odds ratio and 95% confidence interval, 0.21 [0.026, 0.8]; 0.14 [0.0053, 1.4] (Figure 5).

Discussion

The present network meta-analysis was conducted to compare the strengths and weakness profile of negative pressure wound therapy and ultrasound debridement as an adjunctive treatment for diabetic foot ulcers. 32 clinical studies were identified and the data was pooled and analyzed. Healed ulcers, decrement of ulcer areas, time to closure, Secondary am-
putation were compared within all groups. Overall, there was no significant difference between negative pressure wound therapy and ultrasound debridement both in efficacy and safety, but both better to standard wound care.

To our knowledge, this study is the first network meta-analysis to evaluate negative pressure wound therapy and ultrasound debridement in patients with diabetic foot ulcers, and also the first to distinguish VAC from VSD for diabetic foot ulcers. The International Working Group of the Diabetic Foot conducted two systematic reviews [42, 43] on negative pressure wound therapy treatment for diabetic foot ulcers and obtains the conclusion that negative-pressure wound therapy is possibly partially effective for diabetic foot ulcers. Whereas previous studies demonstrated that ultrasound therapy was shown to be clinically effective in healing of diabetic foot ulcers or common wound types compared to traditional wound care [12, 44]. We are wondering which treatment could be more effective for DFU, so through conducting this network meta-analysis, final conclusions are obtained.

Endpoints such as ulcer healing, time to wound closure, decrement of wound area and amputations may be the most clinically relevant outcomes. Complete wound closure was defined as 100% re-epithelialization without drainage. Assessments were based on data from wound investigations and photographs done by the treating clinician. Other indicators like formation of granulation, wound infection and adverse events are also essential. Due to missing information of some articles, they were not included in our analysis. Secondary amputations are the most serious complications of diabetic foot ulcers, and severely impair the quality of life. Our results revealed that negative pressure wound therapy could reduce the incidence of secondary amputations compared with standard wound therapy.

In summary, negative-pressure wound therapy appears to be as effective as ultrasound debridement for diabetic foot ulcers compared
Figure 4. Forest plots with the random effect model comparing decrement of wound area in different treatments. Standard mean difference and 95% CI for each study are plotted on the graph.

Figure 5. Forest plots with the random effect model comparing secondary amputations in different treatments. Risk ratio and 95% CI for each study are plotted on the graph.
with standard wound therapy. Despite of the limitation of studies on ultrasound therapy for diabetic foot, future well-designed clinical trials that should overcome the existing limitations are still needed to provide more convincing evidence for clinical practice.

Disclosure of conflict of interest

None.

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NPWT versus ultrasonic debridement for DFU


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