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Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus: Systematic Review & Meta-analysis

Prof. Dr. Khalid Abdullah Elfiky[1], Prof. Dr. Ahmed Mohamed Elbadawy[2], Dr. Khaled Rezk Abd-Elaziz[2], Mohamed Salah Eldesoky Abdelhady[1]

[1]General Surgery Department, Faculty of Medicine- Ain Shams University, Cairo, Egypt
[2]Plastic & Reconstructive & Maxillofacial surgery, Faculty of Medicine- Ain Shams University, Cairo, Egypt
msalah23592@gmail.com

Abstract: Diabetic foot ulcers are among the most common complications of patients who have diabetes mellitus which is not well controlled. The standard practices in diabetic foot ulcers management include surgical debridement, dressings to facilitate a moist wound environment and exudate control, wound off-loading, vascular assessment, and infection and glycemic control. Among adjuvant methods that appear to accelerate wound healing, negative-pressure wound therapy (NPWT) seems to be particularly effective in diabetic foot ulcerations. NPWT involves the use of a device that is connected to the wound bed through a special set and generates a negative pressure. We conducted the present systematic review and meta-analysis in order to assess the short-term efficacy and safety data of NPWT use in patients with diabetes mellitus and concomitant neuropathic foot wounds. In the present study, we searched Medline via PubMed, SCOPUS, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar from their inception till March 2019. The search retrieved 1542 unique records. We then retained 58 potentially eligible records for full-texts screening. Finally, 11 RCTs (No. of patients = 972) were included in the present systematic review and meta-analysis. In the present systematic review and meta-analysis, the average age of the patients within the included studies was > 50 years old and the average BMI was around 30kg/m^2. In terms of ulcer characteristics, calcaneal dorsal or plantar foot ulcer was the most common site of ulceration within the included studies. In the present study, the overall effect estimates favoured NPWT over conventional care for complete healing of the ulcer (RR 1.38, 95% CI [1.21 – 1.58]; P <0.001), reduction of time healing (MD -8.07, 95% CI [-13.7 – -2.45]; P =0.005), reduction of ulcer depth (MD -40.83, 95% CI [-45.65 – -36]; P <0.001), and reduction of ulcer area (MD -12.19, 95% CI [-15.87 – -8.5]; P <0.001). In addition, six studies reported the rates of amputation. The overall effect estimates favoured NPWT over conventional care for amputation (RR 0.49, 95% CI [0.32 – 0.76]; P <0.001).

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1. Introduction

Life expectancy in people with diabetes mellitus, particularly the type 2 form of the disease, is shorter compared to the general population (**Wright et al.2017**)

This is mainly attributable to its chronic complications, such as coronary artery disease, stroke, and renal failure. Diabetic foot syndrome (DFS), frequently occurring together with ulceration, is another prominent complication. The pathomechanism of DFS is complex and involves diabetic neuropathy, ischemia, and impaired function of the immune system (**Boulton2008**)

DFS is associated with a high rate of hospitalizations and a 20-fold increase in the risk of lower limb amputations (**Holman et al.2012**), **(Skrepnek GH, et al.,2017)**

Foot ulcers precede more than 80% of nontraumatic lower extremity amputations in patients with diabetes **(Apelqvistand Larsson 2000), (Muller et al.,2002).**

DFS is also associated with increased mortality **(Walsh et al., 2016) (Hoffmann et al., 2015).**

In spite of new therapies for diabetes mellitus that have become available in the recent decades, DFS still affects thousands of patients worldwide and constitutes a large medical, organizational, and economic problem. There are a number of approaches in the treatment of DFS with ulceration that are used either subsequently or simultaneously, depending on the type of the wound, accessibility, and local guidelines **(Schaper et al., 2017)**.

This list includes surgical debridement of the injury bed, off-loading of the affected foot, systemic administration of wide-spectrum antibiotics when infection is present, optimization of glycemic control, and endovascular treatment (angioplasty and stenting) or surgery for peripheral artery disease if applicable. Nevertheless, in some patients, these conventional procedures are not effective, resulting in prolonged healing of foot ulcerations. Among adjuvant methods that appear to accelerate wound healing, negative-pressure wound therapy (NPWT) seems to be particularly effective in diabetic foot ulcerations. NPWT involves the use of a device that is connected to the wound bed through a special set and generates a negative pressure **(Hasan et al., 2015)**

Proposed mechanisms of its action at the tissue and cellular level include reduction of the edema, local blood flow improvement, granulation and angiogenesis induction, epithelialization of the wound borders, and facilitation of cell migration and proliferation Macrostrain mechanisms of NPWT involve both union of wound edges and removal of exudates with infectious materials from the wound bed. NPWT has been shown to be safe and effective in wound healing, especially in postoperative lesions. Its efficacy in diabetic foot ulcers was confirmed by several inpatient randomized controlled trials **(Armstrong and Lavery, 2005).**

However, there is still a need for real world observational data from outpatient clinics concerning its use in specific ulcer subtypes.

Aim of the Work

The aims of this study are to assess the short-term efficacy and safety data of NPWT use in patients with diabetes mellitus (DM) and concomitant neuropathic, nonischemic, noninfected foot wounds.

2. Patients and methods

We performed this systematic review and meta-analysis in accordance to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement. PRISMA and MOOSE are reporting checklists for Authors, Editors, and Reviewers of Meta-analyses of interventional and observational studies. According to International committee of medical journal association (ICJME), reviewers must report their findings according to each of the items listed in those checklists (**Moher D, Liberati A, 2009**).

Study Selection and Eligibility Criteria:

The present review included studies that fulfilled the following criteria:

(1) Studies that included adults' patients with diabetes mellitus and concomitant neuropathic, nonischemic, noninfected foot wounds;

(2) Studies that assessed the effectiveness of negative pressure wound therapy (NPWT) for treating foot wounds in people with diabetes mellitus;

(3) Studies that compared the NPWT with none or standard of care;

(4) Studies that reported any of the following outcomes: complete healing of ulcers, healing time, reduction in ulcer area, reduction in ulcer depth, incidence of amputations, participant health-related quality of life/health status, and rate of treatment-related adverse effects.

(5) Studies that were randomized controlled trials (RCTs), comparative studies, prospective cohort, or retrospective charts studies.

We excluded review articles, non-English studies, theses, dissertations and conference abstracts, and trials with unreliable date for extraction.

Search Strategy and Screening

An electronic search was conducted from the inception till July 2019 in the following bibliographic databases: Medline via PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Google Scholar to identify relevant articles. We used different combinations of the following queries: ("Diabetic Foot"[Mesh]) AND "Negative-Pressure Wound Therapy"[Mesh].

Screening:

Retrieved citations were imported into EndNote X7 for duplicates removal. Subsequently, unique citations were imported into an Excel sheet and screened by two independent reviewers; the screening was conducted in two steps: title and abstract screening, followed by a full-texts screening of potentially eligible records.

Data Extraction:

Data entry and processing were carried out using a standardized Excel sheet and reviewers extracted the data from the included studies. The extracted data included the following domains: (1) Summary characteristics of the included studies; (2) Baseline characteristics of studied populations; and (3) Study outcomes. All reviewers' independently extracted data from the included articles and any discrepancies were solved by discussion.

Assessment of Level of Evidence:

The assessment of level of evidence was based on Oxford Centre for Evidence-based Medicine tool. According to study design, each study is allocated one of 10 possible classifications.

Table 1: Levels of Evidence for Therapeutic Studies

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

Dealing with Missing Data:

Missing standard deviation (SD) of mean change from baseline was calculated from standard error or 95% confidence interval (CI) according to Altman (**Altman and Bland**, **2005**).

Data Synthesis:

Continuous outcomes were pooled as mean difference (MD) or standardized mean difference (SMD) using inverse variance method, and dichotomous outcomes will be pooled as relative risk (RR) using Mantel-Haenszel method. The random-effects method was used under the assumption of existing significant clinical and methodological heterogeneity. We performed all statistical analyses using Review Manager (RevMan) 5.3 or Open Meta-analyst for windows.

Assessment of Heterogeneity:

We assessed heterogeneity by visual inspection of the forest plots, chi-square, and I-square tests. According to the recommendations of Cochrane Handbook of Systematic Reviews and meta-analysis, chi-square p-value less than 0.1 denote significant heterogeneity while I-square values show no important heterogeneity between 0% and 40%, moderate heterogeneity from 30% to 60%, substantial heterogeneity from 50% to 100%. If any trials were judged to affect the homogeneity of the pooled estimates, we planned to perform a sensitivity analysis to assess outcomes with and without the trials that were affecting the homogeneity of the effect estimates.

Assessment of publication biases

We intended to test for publication bias using funnel plots if any of the pooled analysis included more than 10 studies in the review (**Higgins 2011**).

3. Results

I. Characteristics of the included studies

In the present study, we searched Medline via PubMed, SCOPUS, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar from their inception till March 2019. The search retrieved 1542 unique records. We then retained 58 potentially eligible records for full-texts screening. Finally, 19 RCTs were included in the present systematic review and meta-analysis (**Figure 1**).

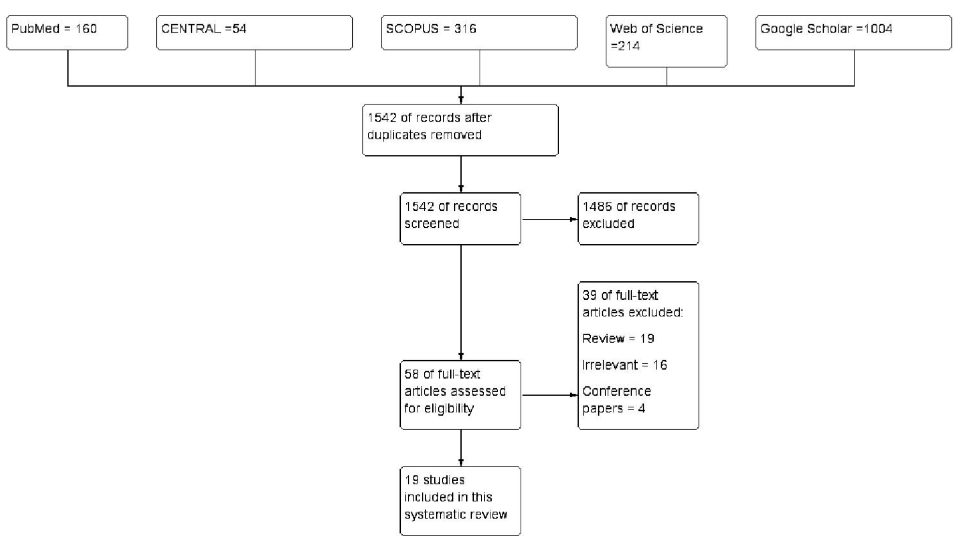

Figure (1): PRISMA flow-chart

II. Characteristics of The included studies

Out of the 19 included studies, eleven studies were RCTs, three studies were retrospective studies, tow studies were systematic reviews, and one study was a prospective study. The studies were conducted in Indian (N =3), USA (N =6), Pakistan (N =2), Turkey (N =2), and one study in each Egypt, Greece, UK, Chile, China, and Iran. The sample size of the included studies ranged from 10 to 1,049. The included studies compared NPWT with either conventional wound care treatment, Saline-moistened gauze, or advanced moist wound therapy. The conclusions of the included studies were inclined to better outcomes with NPWT (**Table 1**).

Table (1): Summary Characteristics of the included studies

Author	Year	Country	Study design	Intervention	Comparison	Study size	Follow-up (weeks)	Main Findings	Level of Evidence
Elbadawy	2019	Egypt	Retrospective, cohort study	NPWT	conventional wound care treatment	44	48	On the basis of current data analysis, the use of NPWT should be recommended for acute diabetic foot wounds in the heel and ankle regions to obtain faster complete healing and desired wound closure in such critical areas.	3A
James et al,	2019	India	RCT	NPWT	conventional wound care treatment	60	NA	VAC therapy significantly decreases the time to complete wound healing, hastens granulation tissue formation, and reduces the ulcer area compared to conventional dressing.	1B
Sukur et al,	2018	Turkey	Retrospective, cohort study	NPWT	conventional wound care treatment	65	NA	The results of this study allowed us to conclude that VAC therapy system appears to be an effective treatment for patients with complex DFUs who had previously undergone partial foot amputation.	3A
Vaidhya et al,	2015	India	RCT	NPWT (modification)	Saline-moistened gauze	60	NA	Economically modified NPWT is more cost-effective to the patients in our setup.	1B
Sajid et al,	2015	Pakistan	RCT	NPWT	Advanced moist wound therapy	278	2	NPWT using VAC was more efficacious than AMWT in the management of diabetic foot ulcers	1B
Ali et al,	2015	Pakistan	RCT	NPWT	conventional wound care treatment	60	2	The application of VAC™ had shown good results in our study	1B
Lone et al,	2014	India	Prospective case–control study	NPWT	conventional wound care treatment	56	NA	VAC appears to be more effective, safe, and patient satisfactory compared to conventional dressings for the treatment of DFUs.	2B
Tansarli et al,	2014	Greece	Systematic review	NPWT	conventional wound care treatment	1,049	NA	The available evidence suggests that the development of infections in wounds treated with VAC depends on the type of wound being treated	1A
Ravari et al,	2013	Iran	RCT	NPWT (KCI)	Moist dressing group	23	2	VAC appears to be as safe as and more efficacious than moist dressing for the treatment of diabetic foot ulcers.	1B
Yarwood-Ross et al,	2012	UK	Systematic review	NPWT	Standard moist wound care		NA	Findings suggest that NPWT could be used as a primary treatment for diabetic foot wounds.	1A
Karatepe et al,	2011	Turkey	RCT	NPWT	conventional wound care treatment	67	NA	vacuum Assisted Closure therapy was found to be effective in the treatment of chronic diabetic ulcers	1B
Nain et al,	2011	India	RCT	NPWT (modification)	Conventional saline-moistened gauze dressing	30	8	NPWT has a definitive role in healing of diabetic foot ulcers	1B
Nather et al,	2010	US	Retrospective, cohort study	NPWT	NA	11	NA	VAC therapy was useful in the treatment of diabetic foot infection and ulcers, which after debridement, may present with exposed tendon, fascia and/or bone.	3A
Sepúlveda et al,	2009	Chile	RCT	NPWT (modification)	Standard wound dressings	24	NA	NPWT reduces the granulation time of diabetic foot amputation wounds by 40%	1B
Blume et al	2008	US	RCT	NPWT (KCI)	Advanced moist wound therapy	342	16	NPWT appears to be as safe as and more efficacious than AMWT for the treatment of diabetic foot ulcers.	1B
Sun and Sun,	2007	China	RCT	NPWT	conventional wound care treatment	38	2	VAC is superior to moist dressings for decreasing DFU	1B
Armstrong and Lavery	2005	US	RCT	NPWT (KCI)	Standard moist wound care	162	16	NPWT delivered by the VAC Therapy System seems to be a safe and effective treatment for complex diabetic foot wounds, and could lead to a higher proportion of healed wounds, faster healing rates, and potentially fewer re-amputations than standard care.	1B
Eginton et al,	2003	US	RCT	NPWT	conventional wound care treatment	10	2	NWPT may accelerate closure of large foot wounds in the diabetic patient	1B
McCallon et al,	2000	US	RCT	NPWT (modification)	Saline-moistened gauze	10	13		1B

RCT, randomized controlled trial; The mean age of the included patients ranged from 48 to 68 years old and the mean duration of DM ranged from 3.6 to 15.96 years. The mean BMI was around 30kg/m^2 in the majority of the included studies. The mean ABI was larger than 1 in the majority of the included studies. In terms of ulcer characteristics, calcaneal dorsal or plantar foot ulcer was the most common site of ulceration within the included studies; while the average size of ulcer ranged from 18.3 to 70.7 cm^2 (**Table 2**).

Table (2): Baseline characteristics of the included studies

Author	Year	Intervention size (EG/CG)	Mean age (years)	ABI (mmHg)	BMI (kg/m2)	Duration of DM (years)	Size of ulcers (cm2)	Location of ulcers	Severity of ulcers	Ulcers' duration
Elbadawy	2019	22/22	48.13±7.74	NA	30.39±7.8/31.4 ±9.4	NA	23.6/25.9	Significant soft tissue defect	NA	NA
James et al,	2019	27/27	55.85 (35-95)/52.89 (28-70)	NA	22.99/23.26	NA	70.97/80.44	NA	Wagner's Grades 1 and 2.	NA
Sukur et al,	2018	31/34	60.6 +11.6/ 58.3 +8	NA	NA	3.6 + 2.1/ 2.9 + 1.6	18.3 + 3.1/ 17.6 + 3.3	na	Wagner's scale grade 2 or 3	na
Armstrong and Lavery	2005	77/85	57.2±13.4/60.1 ±12.2	1.1±0.20/1.1 ±0.19	30.8±7.8/31.4± 9.4	NA	22.3±23.4/19.2±17.6	Foot amputation	University of Texas grade 2 or 3 in depth	1.2±3.9/1.8±5.9 months
Blume et a	2008	169/166	58±12/59±12	1.0±0.2/1.0± 0.2	99.2±25.1/93.8 ±25.6	NA	13.5±18.2/11.1±2.7	Calcaneal dorsal or plantar foot ulcer	Wagner's scale grade 2 or 3	198.3±323.5/206.03±6 5.9 days
Lone et al,	2014	28/28	53.79±5.45	NA	NA	NA	NA	NA	NA	NA
Nather et al,	2010	11	53.3	NA	NA	NA	NA	NA	Wagner's scale grade 2 or 3	34.7
Ali et al,	2015	30/30	56.4/52.2	NA	NA	NA	NA	NA	NA	NA
Karatepe et al,	2011	30/37	68.5±11.1/66.3 ±12.6	NA	62.8±14.5/62.1 ±14.4	11.3±9.2/9.3±7.6	35.7±6.4/29.7±5.2	NA	NA	11.3±9.2/8.8± 7.2 weeks
Eginton et al,	2003	5/5 '	NA	NA	NA	NA	Length: 7.7±1.6 cm width: 3.5±0.6 cm	Significant soft tissue defect	NA	≥1 month
Sun and Sun,	2007	19/19	66.5	0.7≤ ABI ≤1.2	NA	NA	24.5±1.4	NA	University of Texas grade 2 or 3 in depth	≥1 month
Sepúlveda et al,	2009	12/12 '	61.5±10/62.1± 8	1.05±0.5/1.1 6±0.6	28.1±4/26.6±4	NA	168.0±8/169.6±6	Transmetatarsal amputation wound of two or more contiguous toes or the first toe	NA	NA
Vaidhya et al,	2015	30/30	56.5	NA	NA	NA	Size >10 cm2	Dorsum of foot	NA	NA
Nain et al,	2011	15/15	61.33±7.63/55. 40±11.54	NA	NA	NA	50–200 cm2	NA	NA	NA
Ravari et al,	2013	10/13 '	NA	NA	NA	NA	39.5/36.9 cm2	Right foot	NA	≥1 month
Sajid et al,	2015	139/139	56.83±11.3/55. 88±10.97	NA	NA	15.96±5.79/15.65±4.86	15.09±2.81/15.07±2.9 2	Calcaneal dorsal or plantar foot ulcer	NA	NA
McCallon et al,	2000	5/5 '	55.4±12.8/50.2 ±8.7	NA	NA	NA	NA	Forefoot, mid-foot	NA	≥1 month

Note: Data presented as mean ± standard deviation.

A. Complete healing rate

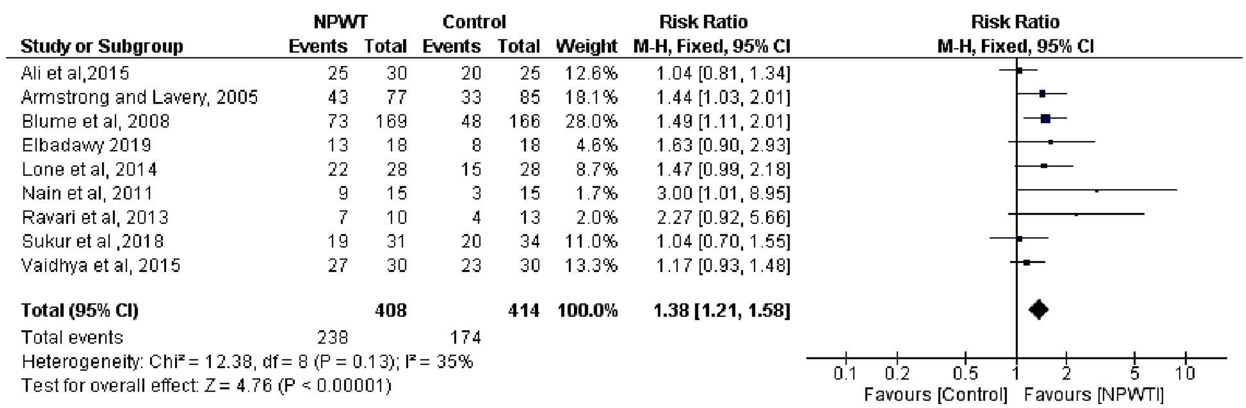

Figure (2): Forest Plot of rates of complete healing

Overall, nine studies reported the rates of complete healing. The overall effect estimates favoured NPWT over conventional care for complete healing of the ulcer (RR 1.38, 95% CI [1.21 – 1.58]; P <0.001). The pooled studies showed no significant heterogeneity (p =0.13; I^2 =35%; **Figure2**).

B. Time of healing

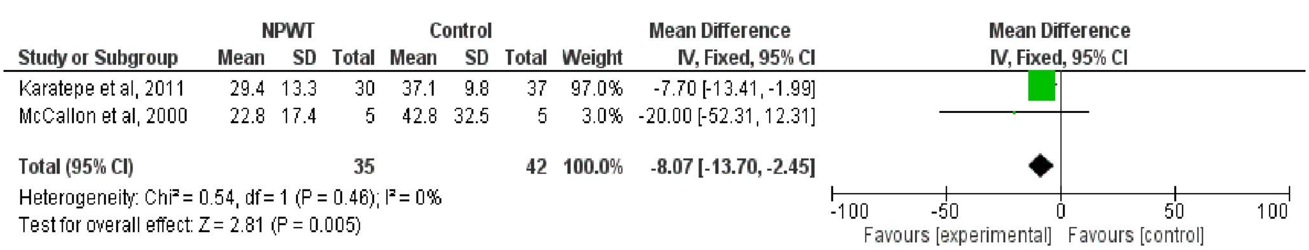

Figure (3): Forest Plot of time to heal

Two studies reported the reduction in the time of healing. The overall effect estimates favoured NPWT over conventional care for reduction of time healing (MD -8.07, 95% CI [-13.7 – -2.45]; P =0.005). The pooled studies showed no significant heterogeneity (p =0.46; I^2 =0%; **Figure 3**).

C. Ulcer Depth

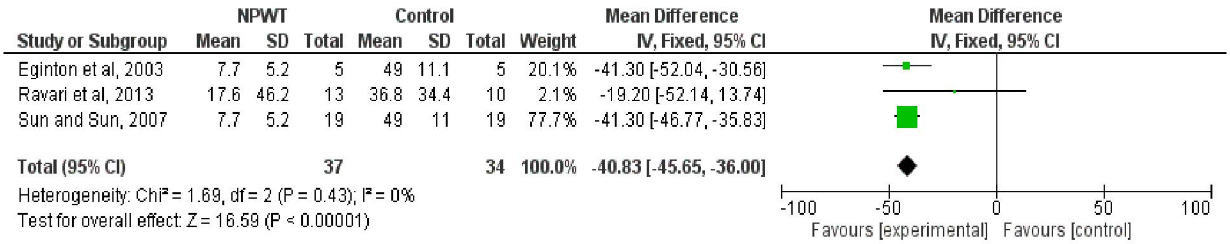

Figure (4): Forest Plot of ulcer depth

Two studies reported the reduction in the ulcer depth. The overall effect estimates favoured NPWT over conventional care for reduction of ulcer depth (MD -40.83, 95% CI [-45.65 – -36]; P <0.001). The pooled studies showed no significant heterogeneity (p =0.43; I^2 =0%; **Figure 4**).

D. Ulcer Area

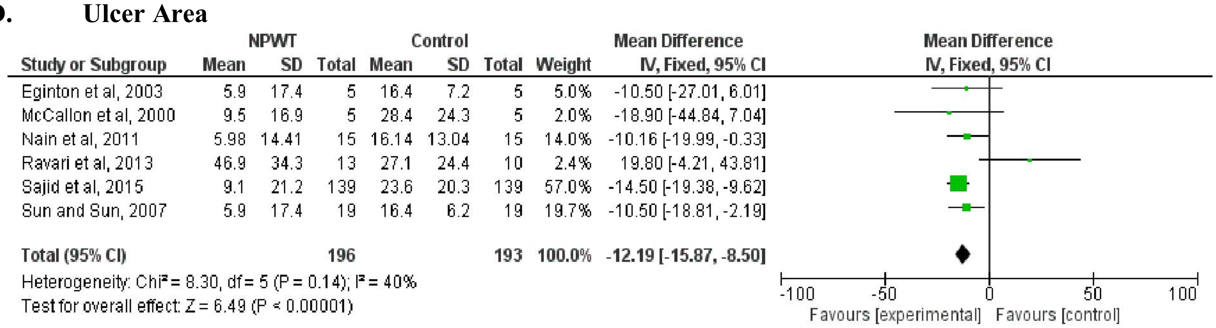

Figure (5): Forest Plot of ulcer area

Six studies reported the reduction in ulcer area. The overall effect estimates favoured NPWT over conventional care for reduction of ulcer area (MD -12.19, 95% CI [-15.87 – -8.5]; P <0.001). The pooled studies showed no significant heterogeneity (p =0.14; I^2 =40%; **Figure 5**).

E. Amputation

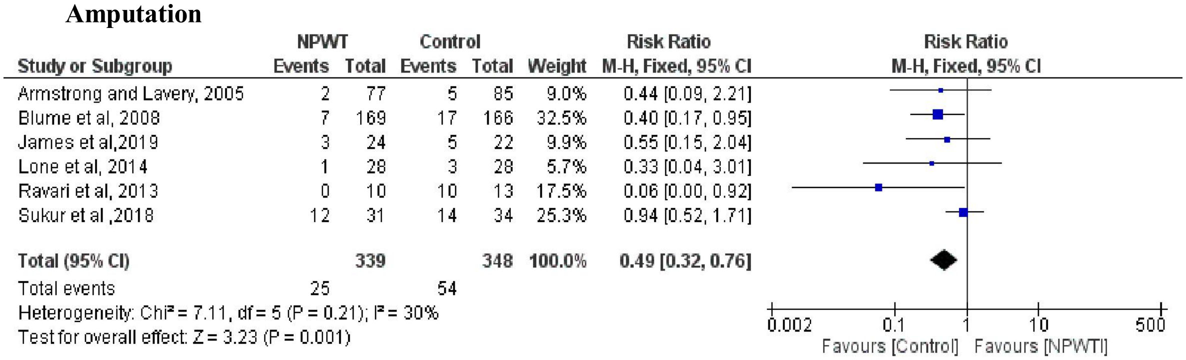

Figure (6): Forest Plot of rates of Amputation

Overall, six studies reported the rates of amputation. The overall effect estimates favoured NPWT over conventional care for amputation (RR 0.49, 95% CI [0.32 – 0.76]; P <0.001). The pooled studies showed no significant heterogeneity (p =0.21; I^2 =30%; **Figure 6**).

F. Treatment-related Adverse Events

Study or Subgroup	NPWT Events	NPWT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Armstrong and Lavery, 2005	9	77	11	85	44.4%	0.90 [0.40, 2.06]
Blume et al, 2008	16	169	11	166	47.1%	1.43 [0.68, 2.99]
Nain et al, 2011	1	15	2	15	8.5%	0.50 [0.05, 4.94]
Total (95% CI)		**261**		**266**	**100.0%**	**1.12 [0.66, 1.90]**
Total events	26		24			

Heterogeneity: Chi² = 1.16, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)

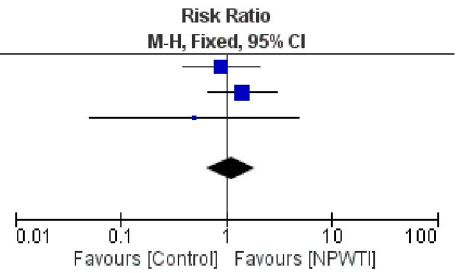

Figure (7): Forest Plot of rates of treatment-related adverse events

Three studies reported the rates of treatment-related adverse events. The overall effect estimates did not favour NPWT over conventional care for treatment-related adverse events (RR 1.12, 95% CI [0.66 – 1.9]; P =0.88). The pooled studies showed no significant heterogeneity (p =0.56; I^2 =0%; **Figure 7**).

G. Granulation Tissue Formation

Four articles assessed the granulation tissue formation, but the evaluation results were not unified; therefore, we used descriptive analysis. **Armstrong et al.** showed that the time during which 76%–100% of granulation tissue formed in the NPWT group, was shorter than that in the moist dressings change group. **Sepúlveda et al. and Vaidhya et al.** provided the average time to reach 90% or over 90% of wound granulation tissue formation (18.8±6 days and 17.2±3.55 days, respectively) in the NPWT group; both time periods were shorter than corresponding times in the control group.

H. Quality of Life

Karatepe et al had patients fill out the 36-item short form health survey (SF-36) questionnaire at the beginning of treatment and in the follow-up month, to ascertain whether the patients' quality of life improved after treatment. The SF-36 questionnaire included two sections regarding the patient's physical and mental state. The results showed that the effect of the NPWT treatment was significantly positive for both mental (*P*=0.0287) and physical (*P*=0.004) health in comparison to treatment using conventional wound dressing.

4. Discussion

Diabetic foot ulcers are among the most common complications of patients who have diabetes mellitus which is not well controlled. It is usually the result of poor glycemic control, underlying neuropathy, peripheral vascular disease, or poor foot care. It is also one of the common cause for osteomyelitis of the foot and amputation of lower extremities. Diabetic foot ulcers are a serious complication of diabetes that results in significant morbidity and mortality. Mortality rates associated with development of diabetic foot ulcers are estimated to be 5% in the first 12 months, and 5-year morality rates have been estimated at 42%. (**Oliver & Mutluoglu**, **2019**).

The standard practices in diabetic foot ulcers management include surgical debridement, dressings to facilitate a moist wound environment and exudate control, wound off-loading, vascular assessment, and infection and glycemic control. These practices are best coordinated by a multidisciplinary diabetic foot wound clinic. Even with this comprehensive approach, there is still room for improvement in diabetic foot ulcers outcomes. Several adjuvant therapies have been studied to reduce diabetic foot ulcers healing times and amputation rates(**Everett & Mathioudakis**, **2018**).

Among adjuvant methods that appear to accelerate wound healing, negative-pressure wound therapy (NPWT) seems to be particularly effective in diabetic foot ulcerations. NPWT involves the use of a device that is connected to the wound bed through a special set and generates a negative pressure(**Borys et al.**, **2018**).

Despite growing number of published literature that supports the efficacy of NPWT for diabetic foot ulcer, there is, still, a scarcity in high-level evidence that assesses the safety and efficacy of NPWT. Thus, we conducted the present systematic review and meta-analysis in order to assess the short-term efficacy and safety data of NPWT use in patients with diabetes mellitus and concomitant neuropathic foot wounds.

In the present study, we searched Medline via PubMed, SCOPUS, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar from their inception till March 2019. The search retrieved 1542 unique records. We then retained 58 potentially eligible records for full-texts screening. Finally, 11 RCTs (No. of patients = 972) were included in the present systematic review and meta-analysis.

Research indicates that diabetic foot ulcer is affected by several factors including patient age, educational status of the patient, and weight of patient. The risk of ulceration and amputation among diabetic patients increases by two to four folds with the progression of age and duration of diabetes regardless of the type of diabetes(**Al-Rubeaan et al.**, **2015**). On the other hand, overweight diabetic patients are two times more likely to develop diabetic foot ulcer as compared with those who had a normal weight (**Mariam et al.**, **2017**).

In the present systematic review and meta-analysis, the average age of the patients within the included studies was > 50 years old and the average BMI was around 30kg/m^2.

In line with our findings, **Al-Rubeaan and colleagues** (**2015**) performed a cross-sectional study of a cohort of 62,681 patients aged ≥25 years from Saudi National Diabetes Registry database, selected for studying foot complications associated with diabetes and related risk factors. Out of them, 780 patients had foot ulcer with average age of63.72±12.48 years old and average BMI of29.03±6.38 kg/m^2.

Similarly, **Mariam and colleagues** (**2017**) conducted a cross-sectional study in Gondar University Hospital, Ethiopia, to investigate foot ulcer occurrence in diabetic patients. Systematic random sampling was used to select 279 study participants. The mean age of the included patients was 59.8 ± 15.6 years and the average BMI was 29.5 kg/m^2.

In diabetic foot ulcer, ulceration is particularly likely to occur over the dorsal portion of the toes and on the plantar aspect of the metatarsal heads and the heel(**Otu et al.**, **2013**).

In the present systematic review and meta-analysis, calcaneal dorsal or plantar foot ulcer was the most common site of ulceration within the included studies.

In line with our findings, **Cervantes-García and Salazar-Schettino** (**2017**) performed a longitudinal, descriptive study from July, 2012 to August, 2015 on a sample composed of 100 patients with type 2 diabetes mellitus and infected diabetic foot ulcers. It was found that the most affected areas were the forefoot (48%) and the plantar region (55%) of the foot.

The determination of the healing rate of diabetic foot ulcers is a fundamental aspect of good clinical care; however, there has been some debate in the literature regarding the best methods for the calculation of healing rate. Historically, the methods that have been employed include measurement of wound length and width, surface area changes over time, and linear advancement of the wound edge (**Santamaria et al.**, **2012**).

In the present study, the overall effect estimates favoured NPWT over conventional care for complete healing of the ulcer (RR 1.38, 95% CI [1.21 – 1.58]; P <0.001), reduction of time healing (MD -8.07, 95% CI [-13.7 – -2.45]; P =0.005), reduction of ulcer depth (MD -40.83, 95% CI [-45.65 – -36]; P <0.001), and reduction of ulcer area (MD -12.19, 95% CI [-15.87 – -8.5]; P <0.001).

In concordance with our findings, **Liu and colleagues** (**2017**)performed an updated systematic review and meta-analysis to assess the clinical efficacy, safety, and cost-effectiveness of NPWT in the treatment of diabetic foot ulcers. The authors searched the Cochrane Library, MEDLINE, EMBASE, Ovid, and Chinese Biological Medicine databases up to June 30, 2016. A total of eleven randomized controlled trials, which included a total of 1,044 patients, were selected from 691 identified studies. Compared with standard dressing changes, NPWT had a higher rate of complete healing of ulcers (RR 1.48; 95% CI: 1.24–1.76; *P*<0.001), shorter healing time (*P*=0.005), greater reduction in ulcer area (*P*<0.00001), greater reduction in ulcer depth (*P*<0.00001).

Similarly, **Noble-Bell and Forbes** (**2008**) performed a systematic review to examine whether NPWT is effective in achieving wound healing in diabetes foot ulcers. A systematic literature review and tabulative synthesis of randomized controlled trials was performed. The review identified four RCTs of weak to moderate quality. The NPWT achieved 20% improvement in wound healing.

In addition, an 2018 Cochrane review was conducted to assess the effects of NPWT compared with standard care or other therapies in the treatment of foot wounds in people with DM in any care setting. In January 2018, the authors searched the Cochrane Wounds Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE; Ovid Embase and EBSCO CINAHL Plus. Eleven RCTs (972 participants) met the inclusion criteria. The number of healed wounds was higher in the NPWT group compared with the dressings group (RR 1.44, 95% CI 1.03 to 2.01)(**Z. Liu et al.**, **2018**).

The exact mechanism by which NPWT is effective in diabetic foot ulcer is not fully understood. Proposed mechanisms of its action at the tissue and cellular level include reduction of the edema, local blood flow improvement, granulation and angiogenesis induction, epithelialization of the wound borders, and facilitation of cell migration and proliferation. Macrostrain mechanisms of NPWT involve both union of wound edges and removal of exudates with infectious materials from the wound bed (**Borys et al.**, **2018**).

Diabetic foot wound, including diabetic foot ulcer and diabetic foot gangrene, is known to be the main cause of non-traumatic lower extremity amputation. Several studies have reported that diabetic patients have a 10–15 times risk of lower extremity amputation compared to patients without DM. It has been estimated that approximately 15% of all diabetic patients develop diabetic foot ulcer during their lifetime and 5% to 8% of diabetic foot ulcer will require major amputation within one year despite of aggressive wound management treatment and recent advanced revascularization techniques(**Kim et al., 2018**).

In the present systematic review and meta-analysis, six studies reported the rates of amputation. The overall effect estimates favoured NPWT over conventional care for amputation (RR 0.49, 95% CI [0.32 – 0.76]; P <0.001).

In agreement with our findings, **Peinemann and Sauerland (2011)** systematically searched the PubMed and Cochrane Library databases for randomized, controlled trials of NPWT for the treatment of acute or chronic wounds. The authors found reports of nine studies. Five of the nine trials involved NPWT systems that are not on the market. The frequency of amputation was stated in only 5 of the 9 new reports; a statistically significant effect in favor of NPWT was found.

Similarly, **Stansby and colleagues** (**2010**) conducted an observational study to assess the reduction in wound depth and area achieved NPWT system in diabetic patients with foot ulcers. Sixteen patients were enrolled into the study. There was a general trend in reduction in amputation rates.

During diabetic foot ulcer healing, the process of granulation tissue formation is pivotal as it constitutes a sort of living, temporary aggregate of cells and proteins, acting as a welding material until the tissue's continuity is restored(**Berlanga-Acosta et al.**, **2013**).

In the present study, four articles assessed the granulation tissue formation, but the evaluation results were not unified; therefore, we used descriptive analysis. **Armstrong et al** (**2005**) showed that the time during which 76%–100% of granulation tissue formed in the NPWT group, was shorter than that in the moist dressings change group. **Sepúlveda et al.**(**2009**) **and Vaidhya et al** (**2015**) provided the average time to reach 90% or over 90% of wound granulation tissue formation (18.8±6 days and 17.2±3.55 days, respectively) in the NPWT group; both time periods were shorter than corresponding times in the control group.

Diabetic foot syndrome is not only an important factor of mortality among patients with diabetes but also decreases quality of life (QoL). Indeed several trials showed that patents with foot ulceration have significantly decreased health related quality of life (HRQoL) compared to those without this complication (**Macioch et al.**, **2017**).

In the present systematic review and meta-analysis, **Karatepe et al** (**2011**) had patients fill out the 36-item short form health survey (SF-36 questionnaire at the beginning of treatment and in the follow-up month, to ascertain whether the patients' quality of life improved after treatment. The SF-36 questionnaire included two sections regarding the patient's physical and mental state. The results showed that the effect of the NPWT treatment was significantly positive for both mental (P=0.0287) and physical (P=0.004) health in comparison to treatment using conventional wound dressing.

Study's Strenghts and Limitations

The present systematic review and meta-analysis has some strenght points. We performed a comperehensive searhc of five electronic databases to comperehensively include all eligible studies. In addition, the risk of bias was low among the included studies. However, we acknowledge that the present study has some limitations. Some included studies were retrospective studies with inherent limitations of possible misclassification and ascertainment bias. In addition, most of the studies were a single-center experience and therefore the results cannot be generalized to the general population.

Conclusion

In conclusion, NPWT is safe and effective technique for chronic, resistant, diabetic foot ulcer. The present systematic review and meta-analysis showed that NPWT achieved higher healing rates and shorter time of healing than conventional treatment. In addition, the rate of amputation and serious complications was lower in patients receiving NPWT. These data draw attention to the importance of early identification of patients, at high risk of those complications. Nevertheless, further studies are still needed to confirm our findings and to identify patient factors that significantly increase the rate of healing after NPWT.

Recommendations and Limitations

- NPWT is safe and effective technique for chronic, resistant, diabetic foot ulcer. It is recommended to implement it in the algorithm of chronic wound healing strategy.
- Further studies are recommended to identify the importance of early identification of patients, at high risk of NPWT-related complications.
- Further studies are still needed to confirm our findings and to identify patient factors that significantly increase the rate of healing after NPWT.
- We acknowledge that the present study has some limitations. Some included studies were retrospective studies with inherent limitations of possible misclassification and ascertainment bias.

- In addition, most of the studies were a single-center experience and therefore the results cannot be generalized to the general population.

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