

The efficacy of negative pressure wound therapy for diabetic foot ulcers: A systematised review

Matthew Wynn*, Samantha Freeman

University of Manchester, Oxford Road, Manchester, M13 9PL, UK



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ABSTRACT

Aim: This review investigated the current state of knowledge on negative pressure wound therapy (NPWT) used to treat diabetic foot ulceration (DFU), its clinical effectiveness and any current issues in the research. NICE have recommended research into the clinical effectiveness of different dressing types for DFUs since 2015.

Methods: A systematic search of the British Nursing Index, CINAHL, Cochrane Central and PubMed was undertaken. Only primary studies were included and studies investigating a combination of NPWT and other therapies were excluded. All the included studies were published in English between 2008 and 2018 and were peer reviewed.

Results: The search yielded seven studies for inclusion in the qualitative analysis. The studies included a variety of methodologies specifically; 3 randomized controlled trials, 2 case series, 1 non-controlled trial and 1 randomized case-control study. Three main themes were identified and formed the focus of the qualitative synthesis.

Discussion: All the included studies reported that NPWT led to better clinical outcomes when compared to standard treatment. However, the studies had numerous methodological flaws such as the absence of validated tools for the measurement of outcomes such as wound area and depth; a lack of statistical power calculations to determine adequate sample sizes or the significance of outcome measures. Additionally, there was little consistency in the pressures used for the NPWT devices. Finally, many of the controlled trials did not conform to the standard of reporting trials stipulated by the CONSORT statement.

1. Introduction

According to the National Diabetic Foot Care Audit Report 2014–2016 [1], more than 60,000 people with diabetes in England are estimated to have foot ulcers at any given time. This represents a huge cost to the NHS and society with an estimated £1 billion spent on diabetic foot related disease in 2014–15 [1]. The cost is also high for the patients who often suffer a reduction in physical, psychological and social wellbeing due to their ulcers [2]. Around 12% of patients with diabetes undergo amputations each year in England, and only half of those undergoing an amputation survive for 2 years post-amputation [1]. Most patients with diabetic foot ulcers in the UK are type 2 diabetics (87%), male (70%), white (92%) and on average 67 years old [1]. Diabetes prevalence is increasing and expected to reach 4.9 million people in England by 2035 and almost 1 million people are currently thought to be un-diagnosed but suffering from diabetes in England [3].

This clearly demonstrates the importance of effective, evidence-based and timely treatment of DFU in diabetic patients, in order to reduce the financial and psychosocial burden of the disease, which is

expected to increase in the coming years.

1.1. What are the current standard treatments for diabetic foot ulcers?

Overall treatment of diabetic foot ulcers relies on a combination of approaches including:

- Effective control of diabetes
- Effective wound care
- Pressure relieving strategy
- Restoration of pulsatile blood flow

[4].

The selection of dressings is varied, and no single type or combination of dressings is recommended for DFUs, due in part to the varied aetiologies of the wounds and their anatomical locations [5]. Currently, there is very little high-quality evidence supporting the use of any particular dressing for DFUs and as such, dressing selection should be based on a clinical assessment of the wound site as well as patient preferences [6].

* Corresponding author.

E-mail addresses: matthew.wynn@mft.nhs.uk (M. Wynn), Samantha.freeman@manchester.ac.uk (S. Freeman).

1.2. What is NPWT?

NPWT is a biophysical agent consisting of a mechanical unit attached to a dressing through a plastic tube which, when connected to a suction device, enables the creation of sub atmospheric pressure at the site of a wound [7]. It is thought to encourage wound healing via removal of exudate, mechanically contracting wound edges and promoting angiogenesis (European Pressure Ulcer Advisory Panel 2009).

1.3. Negative pressure wound therapy in clinical practice

NPWT is a treatment recommendation as per [6] guidelines for the treatment of DFUs and considered following surgical debridement. Despite this, since 2015 NICE have been recommending further research into NPWT for DFUs as well as several other treatments (total contact casting, hyperbaric oxygen therapy and surgical debridement respectively) due to the lack of evidence supporting these therapies. The Cochrane Collaboration [8] published an overview of NPWT concluding that the current dearth of high quality evidence is creating political issues regarding funding for the use NPWT devices in healthcare facilities across Europe. In 2010 the Institute for Quality and Efficiency in Health Care (IQWiG) produced reports concluding that there is no convincing evidence in favour of NPWT. Consequently, the Federal Joint Committee stopped reimbursing for NPWT in German ambulatory care and it is possible for this removal of financial support for NPWT to recur in other European countries [9].

2. Methods

2.1. Search strategy

A systematic search of databases selected based on their relevance to wound care and peer reviewed status was conducted; specifically, CINAHL, Cochrane CENTRAL, PubMed and the British Nursing Index were searched (Table 1).

No specific comparison was used due to the vast number of alternative treatment options for diabetic foot ulcers; these include off-loading, topical growth factors, bio-engineered skin substitutes and advanced moist wound therapy which are often used in combination [10]. For the purpose of this review studies focused on NPWT used in conjunction with other treatments were not used as this will make it difficult to determine the impact NPWT has on ulcer healing. Medical sub headings (MeSH) were used in the PubMed search to improve the relevance of studies (Fig. 1 and Table 2).

3. Results

3.1. Emerging themes from the literature

Three main themes were identified from the qualitative analysis. There are a multitude of tools available to assess the quality of research,

Table 1
PICO formulation.

PICO	Search Terms
Population	Diabet* AND (foot OR heal) AND (ulcer OR wound)
Intervention	Negative pressure* therapy OR vac
Comparison	Any alternative treatment or no alternative treatment
Outcome	Heal* OR improve* OR reduc*
Overall:	BNI, CINAHL, COCHRANE CENTRAL: (Diabet* AND foot OR heel) AND (ulcer OR wound) AND (negative pressure* therapy OR vac) AND (heal* OR improve OR reduc*) PubMed: (Diabetes [MeSH] AND foot OR heel) AND (ulcer [MeSH] OR wound) AND (negative pressure* therapy OR vac) AND (heal* OR improve OR reduc*)

and at present, there is no consensus as to which tools are the most effective for appraisal of any given research methodology [17]. Critique of the included studies was largely based on criteria identified in the critical appraisal skills programme [18] as well as other sources including the principles of the CONSORT statement (2010) and studies investigating the specific research issues in wound care in order to produce the qualitative analysis.

3.1.1. NPWT association with reduction in amputation incidences

Amputations secondary to diabetic foot ulcers are a common occurrence with approximately 12% of diabetics undergoing a minor (below level of the ankle) or major (above the level of the ankle) amputation every year in England due to ulceration [1,19]. Amputation incidences are a commonly used metric to determine the quality of wound care due to their potential to be avoided. Amputations are associated with a poorer quality and shorter length of life as well as with worsening wound outcomes leading to a vicious cycle [20].

Three of the seven studies [11,15,16] reported a statistically significant reduction in amputations in patients receiving NPWT, and the study [15] reported a 0% incidence of amputation when NPWT was used. The only study to differentiate between the incidence of major and minor amputations. Notably, the incidence of major amputations was reportedly higher than minor amputations when advanced moist wound therapy was used. None of the studies provided an explanation for the lower incidence of amputations associated with NPWT.

To determine the relevance of these findings, analysis of the statistical power and sampling methods is necessary to determine if the results represent statistically and/or clinically relevant evidence that NPWT reduced amputations [21].

[11] had the largest sample size (n = 342) whereas the other two studies had significantly smaller samples, n = 23 (Kazemzadeh et al., 2014) and n = 56 [16] respectively [11]. and Kazemzadeh et al. (2014) included a sample size based on a power calculation which is essential to reduce the chance of an alpha or beta error (falsely attributing a relationship or lack thereof between the therapy and clinical outcomes) which may impact the conclusions and subsequently negatively impact clinical effectiveness [22]. The power calculations included were not specifically powered to detect differences in amputation rates. The other two studies used samples from a single healthcare facility without any statistical measures to ensure the results were significant. This reduces the validity and generalisability of the results obtained from these two studies as the patients are unlikely to be representative of the wider patient population [21].

Additionally, the duration of these studies was relatively short or unclear. The study lengths were 112 days [11], 56 days [16] and unknown (Kazemzadeh et al., 2014) respectively. This may represent a limitation of these studies. In a recent multicentre prospective observational study conducted [23] focusing on the prognosis of infected diabetic foot ulcers they determined that over a 12-month period only 44.5% of infected DFUs were healed, 14.4% underwent amputations and 15.1% had died. These statistics correlate with older prognostic studies conducted [24] and Jeffcoate et al. (2006) who reported 77% and 68.3% healing at 12 months respectively although these were studies were focused on patients with non-infected DFUs and thus better healing outcomes are to be expected [25] and this is indeed reflected in the variance in healing statistics. This suggests that the duration of studies included in this review were not sufficient to determine improved clinical outcomes in the long-term when NPWT was used, especially in patients whose wounds had not fully healed by the end of the trials. It is possible that NPWT may have postponed but not prevented amputations. It is clear longer studies are required in order to determine whether NPWT leads to long term benefits over standard therapy and prevent the risk of clinicians indicating to patients that NPWT may reduce the chance of amputation when this may be false.

Ultimately the clinical significance of the findings of the aforementioned studies with regard to amputation rates and its association

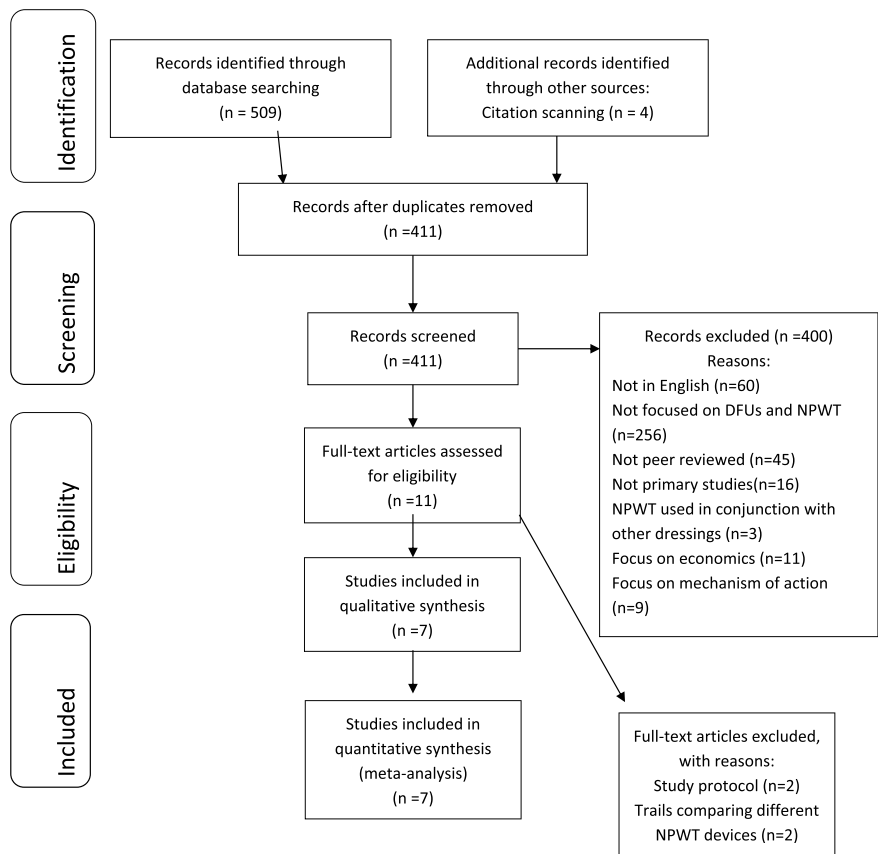


Fig. 1. PRISMA [58] Flow Diagram showing the search process and results.

Table 2
Inclusion and Exclusion criteria.

Inclusion	Exclusion
• -Published in English • -Published 2008–2018 • -Focus on DFU's and NPWT • -Peer reviewed • -Primary studies	• -NPWT used with other dressings • -Focus on economics of NPWT • -Focus on mechanism of action of NPWT • -Studies on animal tissue

with NPWT is unclear.

3.1.2. NPWT association with greater rate of formation of granulation tissue

Wound healing is widely considered to be a four-phase process including ‘haemostasis’, ‘Inflammation’, ‘proliferation’ and ‘maturation’ [5] (see Table 3). In patients with chronic wounds such as diabetic foot ulcers, these four stages are interrupted ultimately giving the ulcers their chronicity [25]. In the case of diabetic foot ulcers, the inflammation stage is typically prolonged due to the hypoxic environments in DFUs, which contain inflammatory oxygen radicals; this is due to arterial disease secondary to diabetes [26]. Metalloprotease enzymes in chronic wound fluid can be up to 60 times higher than in acute wounds. These increased MMP levels contribute to tissue destruction and further prolongs inflammation and slows normal repair processes [27]. These are two examples of a plethora of issues preventing normal wound healing in DFUs [25].

Granulation tissue is formed during the ‘proliferation’ phase of wound healing, following inflammation, and consists of a fibrin matrix, fibronectin collagens, proteoglycans and glycoproteins [28]. This ultimately lays the foundation for new epithelial tissue and represents the

overcoming of physiological hurdles to wound healing laid down by pathology associated with diabetes. It is not uncommon to see the presence or increase of granulation used as a metric for wound healing in wound research due to its synonymy with wound healing progression; as such, four out of the seven studies [7,11,15,16] in this review include granulation measurements as outcomes. The other three studies cite other works relating to the mechanism of action of NPWT and its impact on granulation tissue or, simply state that NPWT increases the rate of granulation tissue formation without including any original data on the matter. All of the studies that included granulation as an outcome reported that granulation was present more often and developed more quickly in wounds treated with NPWT.

The studies that included granulation tissue presence, or rate of growth, did so as a secondary measure [7,15,16]. These studies included notable methodological flaws. The studies [11,15] included no description of how the quantity of granulation tissue had been measured, only [11] considered the presence of granulation tissue at baseline within the randomization process.

[7,16] respectively estimated the quantity of granulation tissue in wounds. This is a subjective measure at high risk of bias, however, this is currently the widely accepted method to determine the quantity of granulation tissue present in a wound [5]. The measurement of wounds in wound care research is essential for determining clinical effectiveness of wound therapies [5]. At present no specific tools are recommended by NICE to measure the area and constituent tissues present in a wound in clinical practice. A validated tool for the assessment of wounds including the quantity of granulation tissue does exist, specifically the Pressure Ulcer Scale for Healing or PUSH tool [30]. The tool consists of a chart which tracks a numerical score calculated by identifying the presence of different tissue types within a wound as well as the surface area and levels of exudate present which allows wound healing to be tracked quantitatively. Although it has been validated for

Table 3
Summary of studies.

Title and author(s)	Primary aims	Sample	Design	Pressure used	Results	Strengths/limitations
[11]. Comparison of Negative Pressure Wound Therapy Using Vacuum-Assisted Closure with Advanced Moist Wound Therapy in the Treatment of Diabetic Foot Ulcers.	Evaluate safety and clinical efficacy of NPWT compared to advanced moist wound therapy for DFUs.	N = 342	RCT	50–200 mmHg	43.2% of ulcers fully healed with NPWT 28.9% ulcers fully healed with AMWT	Strengths: - Large sample - Multi-centre - Excluded any additional treatments which may impact wound healing (internally valid) - statistically significant primary outcome (healing) Limitations: - No blinding of wound assessors - Potential pharmaceutical bias from research sponsors - Used outdated wound classification system (Wagner scale)
[12]. Clinical experience of a new NPWT system in diabetic foot ulcers and post-amputation wounds.	Determine the reduction in wound depth and area achieved by use of NPWT in DFU and post amputation wound.	N = 16	Prospective, open non-controlled clinical trial	120 mmHg Continuous	- Wound area showed reduction of –41% - General trend of reduction in depth from baseline	Strengths: - Wound area assessed using digital planimeter. Limitations: - Small sample - Only one patient with DFU included in sample - Subjective measures used to determine improvement - significant intra-patient variance between study visits - potential pharmaceutical bias - Pain severity and ease of device use measured using non-validated tools - weak statistical analysis
[13]. Effectiveness of Vacuum-assisted Closure (VAC) Therapy in the Healing of Chronic Diabetic Foot Ulcers	Determine changes in wound dimension and presence of granulation tissue due to	N = 11	Case Series	125 mmHg continuous or intermittent or 75–100 mmHg if bleeding	- Average reduction in area of 24.9% - not considered statistically significant	Strengths: - Sample demographics well described - Wounds photographed throughout the study with a ruler, leaving an audit trail. Limitations: - All wounds studied were infected at the start of the trial which may alter wound healing - unclear how many DFUs were included in the trial and atypical ulcer aetiologies described in participants - outdated wound classification system used (Wagner scale) - inconsistent/unclear pressure used during therapy - small sample
[7]. Role of Negative Wound Therapy in Healing of Diabetic Foot Ulcers	Complete healing of ulcers	N = 30	RCT	50–125 mmHg intermittent	- Statistically significant increased rate of appearance of granulation tissue in NPWT group compared to control group. - 80% of NPWT fully healed compared to 60% in control group	Strengths: - Treatment and control groups showed no significant difference in demographics - No obvious pharmaceutical industry involvement Limitations: - Small sample size - No description given on how wound area, quantity of granulation tissue, or wound

(continued on next page)

Table 3 (continued)

Title and author(s)	Primary aims	Sample	Design	Pressure used	Results	Strengths/limitations
[14] Use of Indigenously Made Negative-Pressure Wound Therapy System for Patients with Diabetic Foot	Time for ulcer to be ready for secondary closure	N = 11	Case series	Unknown pressure	- mean time for preparation for surgery 7 days	discharge was measured. (unclear validity of tools) Strengths: - no pharmaceutical bias - hospital stay length recorded for participants Limitations: - unknown pressure used - small sample - inappropriate conclusion that NPWT is more effective than standard care considering lack of control group - subjective measures used to record wound progress
[15] Comparison of Vacuum-assisted closure and moist wound dressing in the treatment of diabetic foot ulcers	Size and depth of ulcers	N = 23	RCT	125 mmHg	- Significant reduction in depth of ulcers in NPWT group - Significant reduction in wound area in NPWT group - 70% of NPWT formed granulation tissue over the 2-week period compared to 50% in control group	Strengths: - validated software (SPSS) used for statistical analysis Limitations: - Used outdated wound classification system (Wagner scale) - Unclear length of study - Unclear treatment used in control group - non-validated Vernier callipers used to determine wound area - Small sample size
[16] Vacuum-assisted closure versus conventional dressings in the management of diabetic foot ulcers: a prospective case-control study	Time to prepare ulcer for closure spontaneously or by surgery	N = 56	case control study	80–125 mmHg	- Faster formation of granulation tissue in NPWT group compared to control - Greater satisfaction achieved in NPWT group - Fewer amputations in NPWT group - Fewer positive blood culture cultures in NPWT group	Strengths: - validated software (SPSS) used for statistical analysis - no statistically significant demographic difference between groups - well described findings of bacterial cultures between groups Limitations: - Unclear length of follow up - Use of outdated (Wagner) ulcer classification system - Unclear methods used to determine the quantity of granulation tissue and patient satisfaction - area of wounds not controlled between groups

Table 4
[29] The four stages of wound healing.

Phase	Timeframe	Cells Involved	Function	Cellular and Biophysical Events
Haemostasis	Instant	Platelets	Clotting to prevent blood loss	● Vascular constriction ● Platelet aggregation, degranulation and thrombus formation
Inflammation	1–4 Days	Monocytes Lymphocytes Neutrophils Macrophages	Phagocytosis	● Neutrophil infiltration ● Monocyte infiltration ● Lymphocyte infiltration
Proliferation	4–12 Days	Lymphocytes Macrophages Angiocytes Neutrophils Fibroblasts Keratinocytes	- Re-establishment of skin function - Wound bed filling - Wound closure	● Re-epithelialisation ● Angiogenesis ● Collagen synthesis
Maturation	21 + Days	Fibrocytes	Develop tensile strength	● Collagen remodeling ● Vascular maturation and regression

research and also specifically for the assessment of diabetic foot ulcers [31], this tool still relies on subjective assessment regarding the presence of particular tissue types in a wound. It is unclear why this tool was not used in the studies reviewed as its validation for research pre-dates these studies [7,15,16]. The use of a validated tool such as PUSH would have improved the reproducibility of results and help reduce information bias [22].

The difficulty of differentiating different tissues within a wound such as granulation, necrosis or slough, which can exist simultaneously in a wound bed [32], is currently the subject of much research. Notably, digital analysis tools have shown to be effective in assessing wounds in studies [33,34]. However, these tools are not widely available and have not yet been validated. It is necessary for future research into NPWT to include the use of validated assessment tools in the monitoring of wounds in order to reduce bias in determining wound healing.

Granulation formation is widely considered a primary goal for wound bed preparation allowing for wound closure by secondary intent or surgery [35]. A study into granulation tissue in chronic pressure ulcers found that the presence of granulation tissue did not predict wound closure, it instead found that it represents a wound that is ready to close but not necessarily actively progressing towards closure [36]. These findings have been challenged recently in a randomized controlled trial [37]. They found that granulation formation in advanced DFUs did predict positive wound outcomes. There is little evidence at present to support the assertion that granulation is a predictor of healing outcomes. This creates difficulty interpreting the included studies when extrapolating any potential increase in granulation tissue found in the wounds to longer term healing outcomes; and, ultimately, the efficacy of NPWT in healing DFUs independent of other interventions. The length of the studies included in this review were too short or unknown, thus determining which of these potential outcomes is more likely is impossible as the wounds were not always followed to full closure. In one paper [16] patients that underwent amputation were excluded from statistical analysis regarding the presence of granulation. This makes it difficult to assess whether the presence of granulation is

evidence of reduced risk for amputation also.

Finally, the sample sizes of the studies including a statistical analysis on differences in the presence of granulation tissue between groups [7,16] were small ($N = 56$ and $N = 30$ respectively) and only one study (Bajaj et al., 2013) was powered to detect differences in granulation formation.

Ultimately it is unclear what the impact of NPWT is on wound granulation. The included studies lack adequate detail on how granulation tissue was measured and did not provide powerful statistical evidence of its increased presence in wounds treated with NPWT. It is not clear whether the presence of granulation is a valid predictor of positive wound outcomes.

3.1.3. NPWT association with reduced wound area and depth

The changing dimensions of wounds are a commonly used indicator of healing and were used in all of the studies in this review as an outcome measure, except one [14], focused on time until surgery and length of hospital stay rather than wound dimensions. The percentage decrease in wound area within the first 4 weeks of treatment has been shown to be an effective indicator of wound healing at 12 weeks [38] these findings were later supported [39]. This makes wound area statistics a potentially reliable source of information on the efficacy of NPWT as data to indicate improved healing outcomes can be obtained in a relatively short study, which many of the studies in this review were. The studies yielded varying results using different data collection tools. Due to the variation, the results and methods used they have been summarised in Table (5) below.

As can be seen in Table 4 only 2 out of the 6 studies investigating wound area included a description of the tools used to gather data. The study [12] was the only one to use a digital planimetry tool to measure wound area which is considered to be the 'gold standard' of wound measurement, [40]. Specifically, they describe the use of an instrument validated for this purpose (KP-90 N, Sokkia) citing [41] as evidence for validation. The cited paper did not provide evidence for validation of this tool but instead investigated the validity of a different tool entirely.

Table 5
Methods and findings of wound area assessments.

Study	Measurement tool(s)	Results
[11]	Unknown	Statistically significant reduction in DFU area in NPWT group.
[12]	Digital Planimeter (KP-90 N, Sokkia)	Statistically significant reduction in DFU area and depth
	Wound depth measured using standard practice at participating centers	
[13]	Unknown	No statistically significant change in wound area with NPWT over course of study (98 days)
[7]	Unknown	Statistically significant reduction in wound area when NPWT used
[15]	Vernier Caliper used to measure depth	Statistically significant reduction in wound area in NPWT group
	Tool used to measure area unknown	
[16]	Unknown	Reduction in wound area in NPWT group

The author could find no evidence for the validation of the KP-90N Socknia tool for medical use. The author could also find no evidence that Vernier calipers are a validated tool for measuring wound depth as used [15].

Evaluating the results from wound dimension measurements in the included studies is difficult. The tools used to collect data were either unknown or not validated. The lack of description of how wounds were measured in the studies [7,11,13,16] respectively means these studies do not fulfill the criteria set out in the Consolidated Standards of Reporting Clinical Trials (CONSORT). Specifically, the standards state that trials should report on ‘Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed’ [42]. This deviation from widely accepted reporting standards represents a major issue when translating the findings of these studies into clinical practice. Inadequate reporting is associated with biased estimates of treatment effects [43]. The use of validated tools is recommended [44] and assists in comparison with other studies [45].

Finally, only one of the studies [11] controlled the initial wound area between treatment groups. One paper [15] controlled the pre-study duration of ulcers in patients in each treatment group but did not control initial wound area. This is significant as a recent study carried out by Barret et al. (2016) within which data on 13,266 DFUs was analysed, identified predictive factors for diabetic foot ulcer outcome which includes wound area and duration. Notably, wounds that are larger and longer standing typically take longer to heal. This indicates a clear need for the different treatment groups to have controls for this. If one group in a study was over-represented by patients with large long-standing wounds or smaller wounds of less duration, then the results (particularly statistics on complete wound healing or wound area) would be invalid due to the impact these independent variables are known to have on wound healing. It is unknown what impact this may have had on the studies in this review.

Based on these findings it appears inappropriate to promote the use of NPWT for the purpose of reducing wound area until further evidence with greater clarity with regards to the methods used to determine changes in wound area becomes available.

4. Discussion

Overall the quality of evidence supporting the use of NPWT in this review is low and earlier wider reviews of the evidence on NPWT have come to similar conclusions [6].

The methodologies used in the existing literature are varied as well as using varying methods for the application of NPWT and the collection of data. Different pressures for the NPWT were used and different controls on treatment groups existed between studies. In many cases, these methods may lead to the studies having a high internal validity at the cost of external validity and by extension utility in guiding real-world clinical decision making regarding treatment for DFUs by use of NPWT [46].

The differing pressures used were justified with a range of reasons, typically based on clinical indications such as bleeding, pain or exudate levels. These indications cannot be ignored; however, they do represent a challenge when determining the efficacy of NPWT due to the varying effects differing pressures may have on wound healing. The impact of different pressures on wound healing rates is not clear; at present the clinical standard is 125 mmHg [47] however, in multiple studies on porcine tissue a lower pressure of 80 mmHg has been suggested to be equally as effective at healing wounds and with less pain [47,48]. The effect of ‘macro-strain’ or ‘macro-deformation’, which draws wound edges together mechanically due to the vacuum created by the pressure, is a known phenomenon [49]; this may have a temporary impact on data collected regarding the wound area and consequently undermine statistical analysis comparing healing in patients using varying pressures. Patients receiving lower pressures may experience less macro-strain compared to those receiving higher pressures and may, therefore,

be recorded to be healing slower or not at all, despite this potentially not being true. There is no research at present detailing the exact impact that macro-strain can have on wound dimensions [50]. found that pressures up to 125 mmHg may cause an increase in angiogenesis which is associated with improved healing. It is clear more research is required specifically into the pressures used and at what point(s) they have the optimum therapeutic effect in human tissue. Despite speculation as to how the varying intended pressures may have impacted these trials, none of the trials reported calibration of the devices prior to treatment. Therefore, unclear as to what the pressures in any of the trials used was in reality.

The controls used, in the studies that included them [7,11,15] were generally consistent in baseline variables including age, gender, comorbidities and type, and quality of control of diabetes which are known to impact wound healing [5]. Characteristics such as initial wound area, presence of granulation tissue or infection was inconsistently controlled within the studies making it difficult to assess the true impact of NPWT.

Two of the studies included made use of the outdated [51] classification system to classify the wounds of patients in the study and measure outcomes. This includes the large scale RCT [11] and the controlled trial [15] respectively. The [51] scale has been criticized due to its inconsistency with regards to the inclusion of depth and presence of infection in wounds which are known to impact healing outcomes [25]. It is unclear why more up to date and validated tools were not used to classify wounds in these studies such as the Texas Classification system [52] or the SINBAD system [53]. Both of the more up to date classification systems were validated prior to the publication of the studies in this review so it is unclear why they selected the Wagner system. There is no evidence, to the authors knowledge, that the Wagner system is recommended specifically for research purposes [6]. guidelines specifically state not to use the Wagner system. More studies are required which use validated classification tools that consider all the factors affecting wound healing to minimise bias.

Other methodological issues included small sample sizes, inconsistent length of study and use of un-validated tools for collecting prognostic and clinical outcome data. This is in line with historical reviews of the evidence for NPWT with few robust prospective RCTs supporting its use [54]. It has been suggested that wound care research is commonly subject to ‘spin’ in which primary outcome measures are unclear and the reporting of results focuses mainly on positive effects of the wound care product giving a false impression of efficacy or, a lack of reporting of negative effects [55]. This is reflected in the literature in this review in which many neglect to report important information. Several studies reported NPWT to improve healing despite the fact surgical interventions were carried out after treatment with NPWT, giving the false impression in the abstracts that NPWT had been used exclusively to cause healing. Another indicator of spin is a lack of research recommendations [55], these recommendations were absent in all the studies in this review except one [12]. Nurses must be aware of this use of language in abstracts when appraising wound care research in order to make clinical decisions. Study results maybe inadvertently influenced by funders. The studies [11,12,15] respectively were all sponsored by pharmaceutical companies who may have an interest in the uptake of their products by healthcare professionals.

Methodological issues and the general lack of high quality evidence on NPWT has been attributed to current rules regarding medical devices within the European Union. NPWT is classed as a medical device and as such does not require research supporting its effectiveness for licensing and use in Europe [56]. This may limit motivation for researchers to conduct high quality phase 3 trials, however, this is unlikely to have impacted this review as only one of the studies included was conducted within the European Union. Further to this in April 2017 new regulations on medical devices were created and are due to come into effect in 2020, these new regulations include new rules on clinical evidence for medical devices including an EU wide coordinated procedure for

authorisation of multi-centre clinical trials [57].

At present, there are no specific NICE guidelines on the use of NPWT, no specific dressing(s) are recommended by NICE as standard practice for treatment of DFUs instead a holistic approach is recommended [6] with patient preference and practitioner discretion guiding dressing selection.

4.1. Limitations

The review was conducted by the main author however the work was overseen and guided by the second author. No formal quality assessment was conducted on the reviewed studies and literature unpublished by the pharmaceutical industry was not included due to pragmatic challenges in obtaining it.

5. Conclusion

This review has established, some three years after the publication of NICE recommendations for further research on this subject, that it remains unclear whether NPWT is more effective for the treatment of DFUs than any other dressing type. The studies in this review had common flaws including the non-use of validated tools for wound assessment and data collection, inadequate or absent power calculations to determine the statistical significance of outcomes and reporting standards that did not fulfil CONSORT criteria. Multiple different pressures were used within the reviewed trials as well as varying comparators and types of NPWT device. The devices were also potentially uncalibrated which may have undermined potential treatment effects, caused adverse effects and negatively impacted the reporting of the trials. This review highlights the on-going lack of compelling evidence for NPWT and recommends that more experimental studies are required meeting the widely accepted reporting standards and adopting research paradigms that are less conducive to multiple sources of bias. It is recommended that the current clinical standard of 125 mmHg should be adopted in NPWT investigations and calibration of NPWT devices should be included.

Due to the aforementioned flaws in methodology, it remains unclear as to whether NPWT has the potential to reduce amputation incidences, increase the rate of granulation formation, heal wounds faster or offer greater quality of life for patients with DFU. These issues should be the focus of future research.

Conflict of interest

None.

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