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SCIENTIFIC REVIEW

The Efficacy of Prophylactic Negative Pressure Wound Therapy for Closed Incisions in Breast Surgery: A Systematic Review and Meta-Analysis

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Abstract

Background Negative pressure wound therapy (NPWT) is a promising advance in the management of closed surgical incisions. NPWT application induces several effects locally within the wound including reduced lateral tension and improving lymphatic drainage. As a result, NPWT may improve wound healing and reduce surgical site complications. We aim to evaluate the efficacy of prophylactic application of NPWT in preventing surgical site complications for closed incisions in breast surgery.

Methods This systematic review was reported according to PRISMA guidelines. The protocol was published in PROSPERO (CRD42018114625). Medline, Embase, CINAHL and Cochrane Library databases were searched for studies which compare the efficacy of NPWT versus non-NPWT dressings for closed incisions in breast surgery. Specific outcomes of interest were total wound complications, surgical site infection (SSI), seroma, haematoma, wound dehiscence and necrosis.

Results Seven studies (1500 breast incisions in 904 patients) met the inclusion criteria. NPWT was associated with a significantly lower rate of total wound complications [odds ratio (OR) 0.36; 95% CI 0.19–069; $P = 0.002$], SSI (OR 0.45; 95% CI 0.24–0.86; $P = 0.015$), seroma (OR 0.28; 95% CI 0.13–0.59; $P = 0.001$), wound dehiscence (OR 0.49; 95% CI 0.32–0.72; $P < 0.001$) and wound necrosis (OR 0.38; 95% CI 0.19–0.78; $P = 0.008$). There was no significant difference in haematoma rate (OR 0.8; 95% CI 0.19–3.2; $P = 0.75$). Statistically significant heterogeneity existed for total wound complications, but no other outcomes.

Conclusion Compared with conventional non-NPWT dressings, prophylactic application of NPWT is associated with significantly fewer surgical site complications including SSI, seroma, wound dehiscence and wound necrosis for closed breast incisions.

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Introduction

Wound healing complications following surgery are a major cause of morbidity for patients and incur a significant cost burden for healthcare providers [1–5]. Frequently occurring complications include surgical site infection

(SSI), wound dehiscence, skin necrosis, haematoma and seroma formation. An estimated 20–36% of nosocomial infections occurring in the USA each year are SSI-related [6]. Zimlichman et al. estimated that healthcare-associated infections in the USA cost $9.8 billion dollars annually with SSI making up 33.7% of this total cost [6].

Prophylactic negative pressure wound therapy (NPWT) has recently emerged as a promising advance in the prevention of surgical site complications [7-10]. There is a growing body of evidence demonstrating a significant reduction in surgical site complications when NPWT is compared to conventional dressings. This effect appears to be uniform across a range of surgical disciplines involving both clean and contaminated wounds [11-15]. There is also evidence to suggest that prophylactic use of NPWT may be a cost-saving intervention when compared to standard dressings particularly in the higher-risk patient [16, 17].

The incidence of SSI in patients undergoing breast surgery varies depending on the type of procedure being undertaken [18]. In their retrospective analysis of 18,696 mastectomies, Olsen et al. reported an SSI rate of 5% in patients undergoing mastectomy alone rising to 10.3% in patients undergoing mastectomy plus implant [19]. In a separate study, the same authors calculated the cost of SSI per patient undergoing breast surgery to be $4,091 after adjusting for type of surgical procedure and other variables [3]. These figures suggest a need for further infection control interventions in order to improve both patient outcomes and treatment-associated costs. This is of particular relevance in breast cancer patients as surgical site complications can delay the initiation of adjuvant treatment and may impact negatively both recurrence risk and overall survival [20, 21].

NPWT consists of the continuous delivery of negative pressure to the wound bed via a vacuum device. Commercially available devices at present have the capability of generating −80 mm Hg to −150 mm Hg of negative pressure, depending on the device, which is then applied to the wound. As a result, the negative pressure environment leads to a reduction in lateral wound tension, improved lymphatic drainage and propagation of local wound factors required for wound bed granulation [14]. It was initially utilised to expedite the healing of open or chronic wounds, but its indications have expanded in recent times to encompass the prevention of wound healing complications in closed surgical incisions [9, 22, 23].

While the body of evidence continues to grow regarding NPWT, its overall efficacy for closed incisions in breast surgery when compared with standard dressings remains unclear. Therefore, the aim of this systematic review and meta-analysis is to assess the efficacy of prophylactic NPWT versus non-NPWT dressings in closed breast incisions.

Methods

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (https://www.prisma-statement.org/) (Appendix 1).

Eligibility criteria

Any study which met all of the following inclusion criteria was included in the analysis: (1) published full-text studies in English language (either randomised or non-randomised) which directly compared NPWT with non-NPWT dressings; (2) studies involving only closed incisions in breast surgery; and (3) studies which report any of the following outcomes (total wound complications, surgical site infection (SSI), seroma, haematoma, wound dehiscence and necrosis).

Studies which examined the effect of NPWT on closed axillary or autologous donor site incisions were excluded.

Search strategy

PubMed, Embase, CINAHL and Cochrane Library databases were searched without any language restrictions, using the following combination of medical subject heading terms: “breast surgery” OR “breast reconstruction” OR “breast reduction” OR “mastectomy” OR “breast augmentation” AND “PICO” OR “VAC” OR “PREVENA” OR “negative pressure wound therapy” OR “negative pressure dressings” (Appendix 2). The search was performed from 1 to 31 October 2018. All potentially relevant titles and abstracts found were individually reviewed by two investigators (DC and LS), and full texts of relevant studies were examined. Any disagreement regarding publications was resolved by discussion, and if the question remained unsettled, the opinion of a third investigator (POL) was sought. Reference tracking from retrieved studies was further searched for additional studies which meet the inclusion criteria.

Data analysis

The following data were extracted from the included studies—authors, journal, year of publication, sample size, type of NPWT, duration of treatment, SSI rate, seroma rate, dehiscence rate, haematoma rate, wound necrosis rate, time to drain removal and length of follow-up.

Meta-analysis was performed if there were three or more studies providing the outcome data. The unit of analysis is the breast itself, and not the individual participant. The pooled relative risks were calculated using a Mantel–Haenszel random effects model (DerSimonian and Laird

method) [24]. A random effects model was used in expectation of clinical heterogeneity, irrespective of statistical heterogeneity. Pooled results were expressed according to odds ratios (OR) with the associated 95% confidence intervals (CIs). The absolute risk reduction (ARR)/absolute risk increase (ARI)/absolute risk difference and the associated number needed to treat (NNT) will be calculated if the OR was statistically significant. The ARR or ARI are weighted estimates of the difference in event rates [24]. Heterogeneity assessment was assessed using the I^2 index test. In the event of significant heterogeneity for an outcome, data were re-analysed following exclusion of relevant trial(s). The risk of bias within studies was assessed using the Cochrane Collaboration tool. Review authors' judgements about each risk of bias item were assessed and presented as overall summary and percentages across all included studies [25]. A two-sided P value of <0.05 was considered as statistically significant. Calculations were performed using RevMan version 5.3 and STATA version 14.2.

Results

A total of seven studies, which included 904 patients with 1500 closed breast incisions were analysed. There were five prospective and two retrospective studies with a total of 681 and 819 incisions in the NPWT and non-NPWT dressing groups, respectively. A flow diagram of the selection process is summarised in Appendix 3.

All patients included in the analysis were female. The mean age of participants from those studies which provided this information was 43.7 years. Ferrando et al. [26] did not report the mean age of their cohort. All included studies were published between 2014 and 2018 (Table 1).

Two of the included studies were performed comparing NPWT to standard non-NPWT dressing [27, 28] by randomising either right or left breast to NPWT (Table 1). Tanaydin et al. [28] compared a single-use PICO^{TM} (Smith and Nephew) NPWT dressing set at −80 mm Hg for up to 7 days with fixation strips (Steri-Strip^{TM} (3 M)). Galiano et al. [27] also used the PICO^{TM} set to −80 mm Hg, but it could be used for up to 14 days. In their case series of twenty-four patients undergoing oncoplastic procedures, Holt et al. [29] also utilised the PICO^{TM} dressing set to −80 mm Hg for 6 days, but made no mention of their comparator. The study by Pellino et al. [30] included a mixture of colorectal (50%) and breast (50%) procedures. The investigators applied a PICO^{TM} dressing at −80 mm Hg to the incisions in the NPWT group. Only the results from the breast group in this study were included in our meta-analysis. Gabriel et al. [31] utilised the PREVENA^{TM} (KCI) NPWT system set to −125 mm Hg for 7 days in their retrospective study. In their prospective study, Ferrando et al. [26] also used the PREVENA^{TM} system set to −125 mm Hg for 7 days.

Apart from the study by Tanaydin et al.[28], data on total wound complications were available in all included studies (1,436 incisions). NPWT was associated with a statistically significant lower rate of total wound complications compared to non-NPWT dressings [pooled odds ratio (OR) 0.36; 95% CI 0.19–069; P = 0.002] (Fig. 1). The number needed to treat (NNT) to prevent one wound complication was 6. Heterogeneity amongst included studies was statistically significant (τ23 = 0.35; P = 0.0006; I^2 = 69%) (Fig. 1).

Four studies provided data on SSI (1,341 incisions) (Fig. 2). NPWT was associated with a statistically significant lower rate of SSI compared to non-NPWT dressings (pooled OR 0.45; 95% CI 0.24–0.86; P = 0.015, NNT = 50) (Fig. 2).

NPWT was associated with a statistically significantly lower rate of seroma formation compared to non-NPWT dressings in the four studies for which data were included (990 incisions) (pooled OR 0.28; 95% CI 0.13–0.59; P = 0.001, NNT = 20) (Fig. 3).

Data on wound dehiscence were included in four studies (1,175 incisions), and there was a statistically significant difference in favour of NPWT (pooled OR 0.49; 95% CI 0.32–0.72; P = 0.000, NNT = 13) (Fig. 4). Three studies provided data on wound necrosis (940 incisions). NPWT was associated with a statistically significant lower rate of necrosis compared to non-NPWT dressings (pooled OR 0.38; 95% CI 0.19–0.78; P = 0.008, NNT = 9) (Fig. 5).

Data on haematoma were included in three studies (940 incisions), but we found there to be no statistically significant difference between NPWT and non-NPWT dressings (pooled OR 0.8; 95% CI 0.19–3.2; P = 0.75) (Fig. 6).

There was no significant statistical evidence of heterogeneity for all secondary outcomes. Test for funnel plot asymmetry was not performed because its power is too low to distinguish chance from real asymmetry, since there were less than ten studies with available data for analysis.

Discussion

This study demonstrates that prophylactic use of NPWT for closed incisions in breast surgery is associated with a reduced risk of total wound complications, SSI, wound dehiscence, wound necrosis and seroma formation when compared to conventional non-NPWT dressings. There was no significant difference in rates of haematoma between the two groups. Overall, the prophylactic use of NPWT was associated with improved wound outcomes in patients with closed incisions undergoing breast surgery.

Table 1 Characteristics of the included studies

Source/country/study type	Sample size	No. breasts NPWT/control groups	Relevant outcome (time measured)	Details of NPWT	Comparator	Type of procedure	Antibiotic therapy	Follow-up (days)
Ferrando et al./Italy/prospective	37	25/22	Infection, haematoma, seroma, skin necrosis	PREVENA™ (set to −125 mm Hg) for 7 days	Steri-Strip™ for 14 days	All elective oncological	IV Pre-op and oral till drain removal (no further details)	365
Galiano et al./USA/RCT	199	199/199	Infection, dehiscence, delayed healing (90 days)	PICO™ (set to −80 mm Hg) for 14 days	Steri-Strip™ and dry gauze/non-adherent dressing	All elective reduction mammoplasty	94.5% received prophylactic (no further details)	90
Tanaydin et al./Netherlands/RCT	32	32/32	Surgical site complication (within 21 days)	PICO™ (set to −80 mm Hg for 7 days)	Steri-Strip™	All elective reduction mammoplasty	Not mentioned	365
Holt et al./UK/prospective	24	24/24	Delayed healing, wound dehiscence	PICO™ (set to −80 mm Hg for 6 days)	Not mentioned	All elective oncoplastic reconstruction	Not mentioned	70
Kim et al./South Korea/retrospective	206	45/183	Necrosis, infection, seroma, haematoma	Model not specified (set to −125 mm Hg) for 3 days	Polyurethane foam and Antibacterial ointment	All elective immediate expander-based reconstruction	Peri-op IV continued until drain removal	30
Pellino et al./Italy/RCT	50	25/25	SSI, Seroma	PICO™ (set to −80 mm Hg for 7 days)	Wound contact absorbent dressing	Not mentioned	Peri-op IV (no further details)	90
Gabriel et al./Canada/retrospective	356	331/334	Total wound complication, SSI, dehiscence, necrosis, Seroma, haematoma	PREVENA™ (set to −125 mm Hg) for 7 days	Steri-Strip™	All elective mastectomy and expander/implant reconstruction	Not mentioned	90

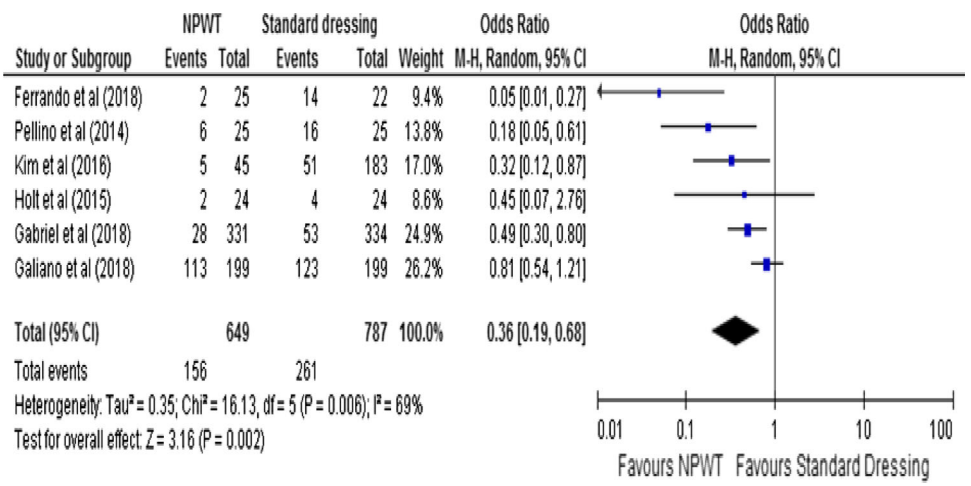


Fig. 1 Forest plot of NPWT versus non-NPWT dressings for total wound complications

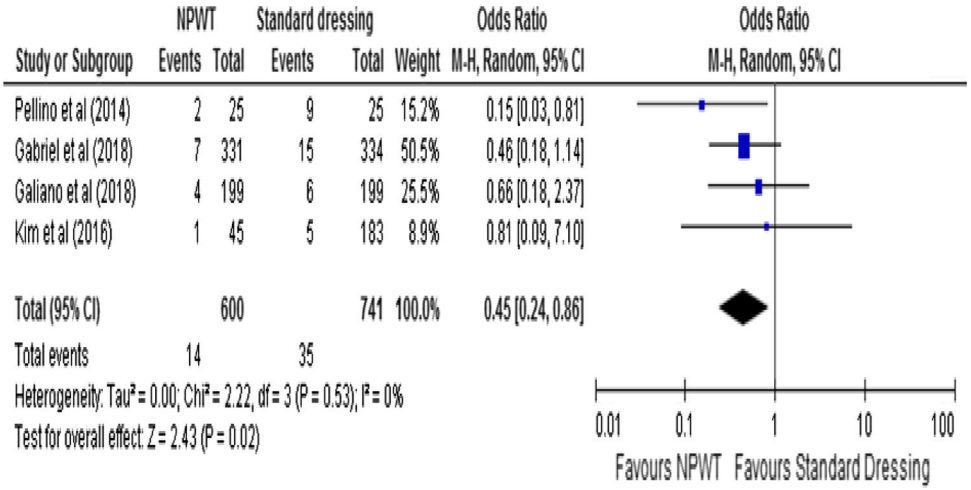


Fig. 2 Forest plot of NPWT versus conventional dressings for surgical site infection

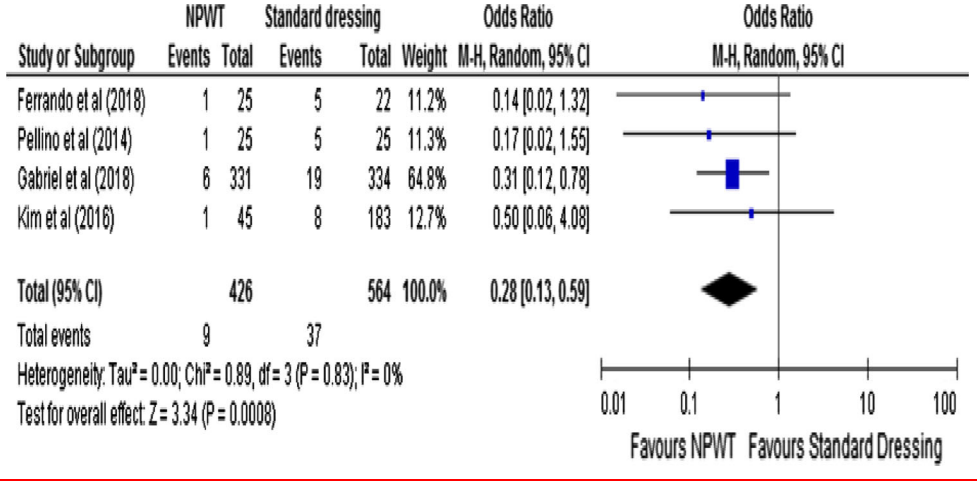


Fig. 3 Forest plot of NPWT versus conventional dressings for wound seroma

The use of NPWT on surgical wounds remains controversial. A 2014 Cochrane review concluded that there was no clear benefit from using NPWT in closed incisions [32]. This review included nine randomised control trials, three of which included patients undergoing split skin grafting. Of the six trials that looked at closed surgical incisions,

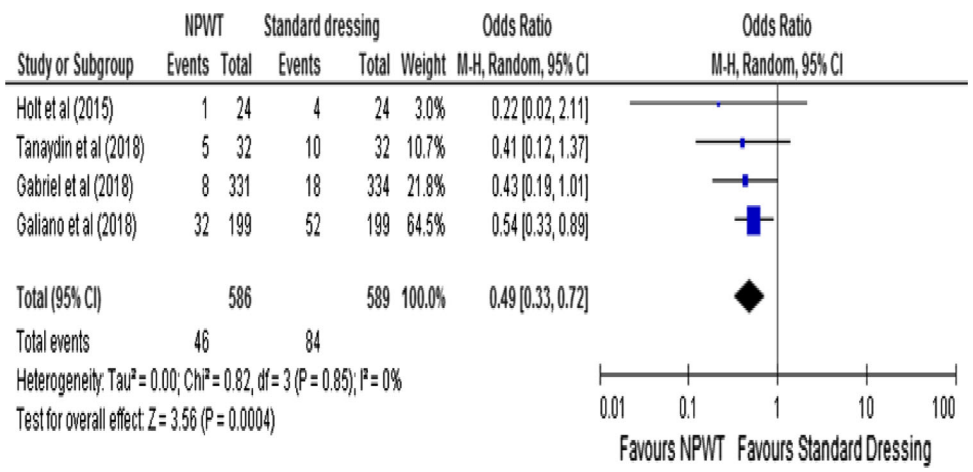


Fig. 4 Forest plot of NPWT versus conventional dressings for wound dehiscence

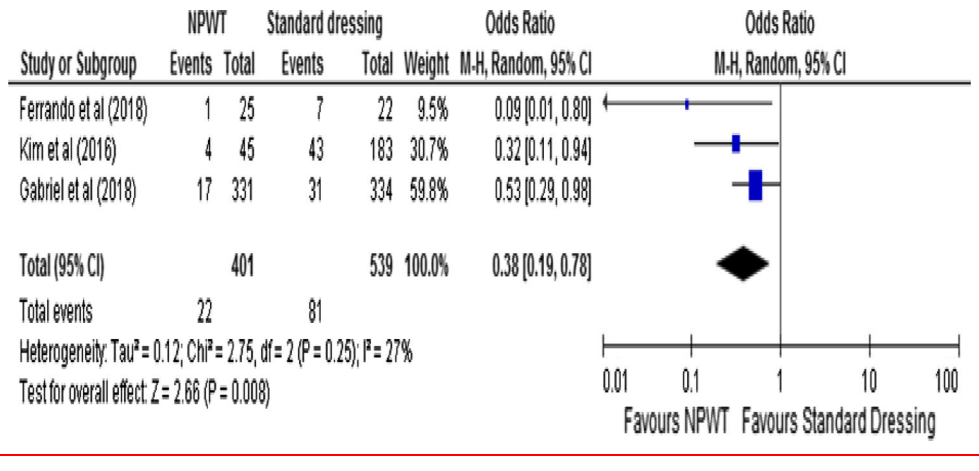


Fig. 5 Forest plot of NPWT versus conventional dressings for wound necrosis

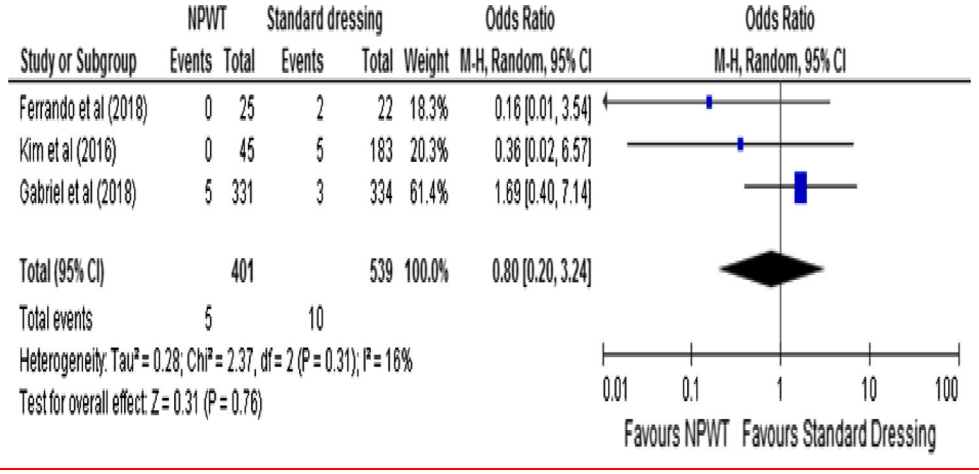


Fig. 6 Forest plot of NPWT versus conventional dressings for haematoma

four used the VAC® (KCI) negative pressure vacuum-assisted closure device, one used the PREVENA^{TM} system and the other used a homemade negative pressure device. None of those trials included patients undergoing breast surgery. The availability of newer devices specifically designed for closed surgical incisions such as PICO^{TM} has

prompted further interval research which lays the foundation for this study. In 2016, the World Health Organization published their Global Guidelines for the Prevention of SSI [33]. In the development of these guidelines, De Vries et al. [12] conducted a meta-analysis which showed that NPWT caused a significant reduction in SSI, but concluded that the overall quality of evidence was low. However, high-quality evidence continues to emerge that shows that wound complications can be prevented in both clean and clean–contaminated wounds with prophylactic application of NPWT [11, 34]. At present, the evidence for NPWT in breast surgery largely consists of small- to moderate-sized observational studies. The results of our study provide support for NPWT in the management of closed surgical incisions on the breast. Further research should be performed to determine which patients are likely to benefit most from these interventions.

Our understanding of NPWT and the role it can play in the management of both closed and open wounds is continually growing. Animal studies have shown demonstratable changes in microvascular blood flow around wounds that is dependent on the pressure applied, the distance from the wound edge and the tissue type [35]. There is uncertainty as to the optimum level of negative pressure to enhance this phenomenon, but it appears to be inhibited at values below −400 mm Hg with two studies by Kairinos et al., demonstrating that lower levels of negative pressure may reduce tissue perfusion and compromise vascularity. These findings suggest that NPWT application to already ischaemic tissue may further compromise their blood supply particularly in cases when it is applied circumferentially [36, 37]. Further studies have also shown increased rates of granulation tissue formation and reduced tissue bacterial counts with the application of NPWT [38]. There also appears to be a reduction in the level of tissue oedema which likely relates to improved lymphatic drainage, thus further enhancing the conditions for wound healing [10, 39, 40]. At a cellular level, this appears to translate into a modulation of cytokines to an anti-inflammatory profile with increased expression of signal proteins such as vascular endothelial growth factor, platelet-derived growth factor and fibroblast growth factor 2, leading to angiogenesis, extracellular matrix remodelling and deposition of granulation tissue [41].

NPWT devices such as PICO^{TM} are now available as a single-use battery-powered device and an easy-to-apply wound dressing with or without a small portable canister to collect the absorbed fluid. Patients can be easily taught about the device and be discharged home with it in place. Cost–benefit was not reported by any of our included studies; therefore, we have made no attempt to address it in this review. Nherera et al. suggest that the reduction in surgical site complications brought about by NPWT makes it a suitably cost-effective alternative to conventional dressings [16, 17]. Heard et al. [42] estimated that a 15% reduction in SSI would make NPWT cost-effective. Our results suggest that SSI can be reduced by more than 50% in breast incisions with NPWT use. This is a fast-moving and exciting development in wound management, and further studies regarding mechanism of action and cost-effectiveness will only provide further support for its widespread adaptation in clinical practice.

There are some potential limitations to our review. Due to an underreporting of patient co-morbidities in the included studies, we were unable to perform a meaningful subgroup analysis to assess NPWT efficacy in higher- versus lower-risk patients undergoing breast surgery. Similarly, there was significant heterogeneity in the types of surgical procedures being undertaken between the included studies ranging from simple mastectomy to implant-based reconstruction. We did not perform a subgroup analysis of different surgical procedures as there was not three or more studies assessing the effect of NPWT in any one procedure. Most of the included studies are non-randomised and therefore subject to selection bias. Within-patient randomisation was performed by Tanaydin et al. and Galiano et al., but this is not without limitations [27, 28]. Given the visible nature of the treatment, it is not possible to blind patients or investigators, thereby further predisposing our results to performance and detection bias. There was also significant clinical heterogeneity. Three studies made no mention of prophylactic antibiotic use [28, 29, 31] despite two of those studies including patients undergoing implant reconstruction. Two studies only provided antibiotics at induction [27, 30], while the remaining studies continued antibiotics until at least drain removal [26, 43]. Similarly, differences were evident regarding the use of surgical drains. Three studies did not mention whether drains were utilised [28-30]. Galiano et al. [27] used drains at the discretion of the operating surgeon, and the remaining three studies all used surgical drains [26, 31, 43]. The NPWT device utilised also varied amongst the included studies along with the applied negative pressure setting and length of treatment. While Steri-Strip^{TM} were the most commonly investigated comparator, they were not utilised in all studies, thereby potentially further reducing the effect of our results. Despite this, our meta-analysis did not demonstrate any statistically significant heterogeneity for included studies apart from total wound complications.

Conclusions

Prophylactic negative pressure dressings applied to closed incisions in breast surgery are associated with a significant reduction in the total wound complications, SSI, seroma, wound dehiscence and wound necrosis. Widespread adaptation of NPWT in clinical practice is limited by its higher cost in comparison with conventional dressings. Further research evaluating the effect of NPWT on length of hospital stay and need for readmission or re-intervention in the event of surgical site complication will serve as a basis for calculating the long-term cost-saving potential of this technology.

Appendix 1

See Table 2.

Table 2 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes and study design (PICOS)	3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. Web address) and, if available, provide registration information including registration number	Prospero
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale	4
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	4
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review and, if applicable, included in the meta-analysis)	4
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	4,5
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made	4,5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level) and how this information is to be used in any data synthesis	5
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means)	4,5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^2) for each meta-analysis	4,5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies)	8
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	4,5
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	5

Table 2 continued

Section/topic	#	Checklist item	Reported on page #
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations	5, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12)	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	7, Forest Plots
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	
Additional analysis	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, meta-regression [see Item 16])	
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. healthcare providers, users and policy makers)	7
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias) and at review level (e.g. incomplete retrieval of identified research, reporting bias)	7, 8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research	7, 8
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review	None

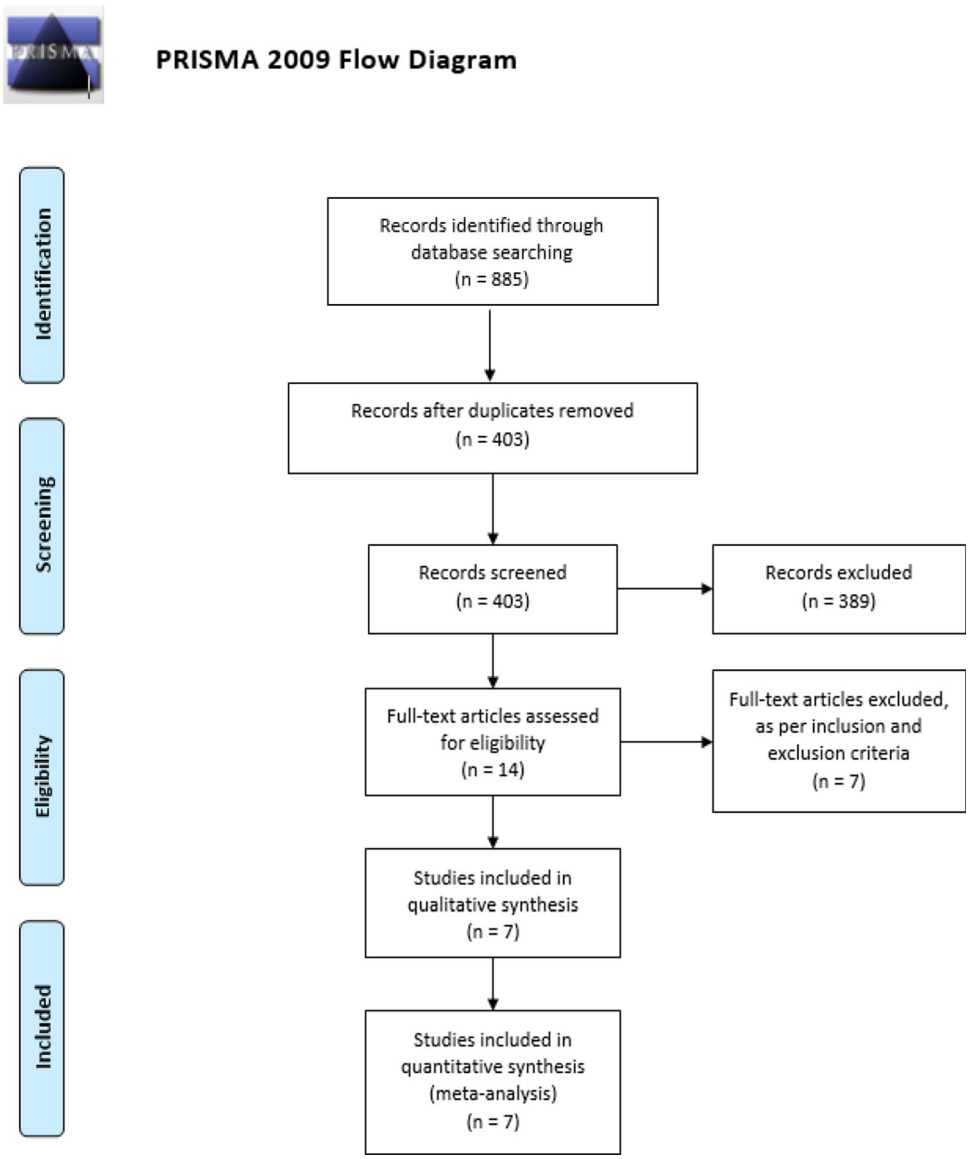
Appendix 2. PubMed search strategy

(((((negative[All Fields] AND ("pressure"[MeSH Terms] OR "pressure"[All Fields])) OR ("negative-pressure wound therapy"[MeSH Terms] OR ("negative-pressure"[All Fields] AND "wound"[All Fields] AND "therapy"[All Fields]) OR "negative-pressure wound therapy"[All Fields] OR ("negative"[All Fields] AND "pressure"[All Fields] AND "dressing"[All Fields]) OR "negative pressure dressing"[All Fields])) OR VAC[All Fields]) OR PICO[All Fields]) OR ("negative-pressure wound therapy"[MeSH Terms] OR ("negative-pressure"[All Fields] AND "wound"[All Fields] AND "therapy"[All Fields]) OR "negative-pressure wound therapy"[All Fields] OR ("negative"[All Fields] AND "pressure"[All Fields] AND "wound"[All Fields] AND "therapy"[All Fields]) OR "negative pressure wound therapy"[All Fields])) AND ((((((("breast"[MeSH Terms] OR "breast"[All Fields]) AND ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields])) OR ("mammaplasty"[MeSH Terms] OR "mammaplasty"[All Fields] OR ("breast"[All Fields] AND "reconstruction"[All Fields]) OR "breast reconstruction"[All Fields])) OR (("breast"[MeSH Terms] OR "breast"[All Fields]) AND augmentation[All Fields])) OR (("breast"[MeSH Terms] OR "breast"[All Fields]) AND reduction[All Fields])) OR ("mastectomy, simple"[MeSH Terms] OR ("mastectomy"[All Fields] AND "simple"[All Fields]) OR "simple mastectomy"[All Fields] OR "mastectomy"[All Fields] OR "mastectomy"[MeSH Terms])).

Appendix 3

See Fig. 7.

Fig. 7 PRISMA flow diagram



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