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Negative pressure wound therapy for burn patients: A meta-analysis and systematic review

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Abstract

Negative pressure wound therapy (NPWT), which has been applied in various medical specialties to accelerate wound healing, has been the object of a few investigations. We explored the effectiveness of NPWT and the possibility of its inclusion in burn management guidelines. Randomised controlled trials comparing NPWT with non-NPWT treatments for burn wounds were extracted from PubMed. For the risk of bias analysis, all included studies were evaluated according to the Cochrane risk of bias tool and the approaches outlined in the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) Handbook. Outcomes such as graft take rate in the first week, infection rate, and overall complication rate were analysed. Six studies that included a total of 701 patients met our inclusion criteria. Qualitative analysis revealed that the NPWT group had a significantly better overall graft rate in the first week ($P = 0.001$) and a significantly lower infection rate ($P = 0.04$). No significant difference in the overall complication rate was found. Our results indicate that NPWT is a safe method for stimulating healing and lowering the infection rate of burn wounds. NPWT can be part of general burn management, and its incorporation into burn treatment guidelines is recommended.

1 | INTRODUCTION

Burns is one of the leading causes of loss in terms of disability-adjusted life years and accounts for an estimated 180 000 deaths annually in lower- and middle-income countries.[1] Burn survivors may experience lifelong physical and emotional complications that place a heavy financial burden on society.[2]

Although burn wounds have various classifications, the basics of wound healing and care are the same.[3] The depth to which a burn has injured tissue determines the healing potential and the need for surgical grafting. Deep partial-thickness burns take more than 3 weeks to heal even if no infection occurs.[4] Delayed wound closure triggers scar formation and contracture, which can be prevented if excision and grafting are performed within the first few days of an injury.[5] Various methods have been applied to optimise skin graft take, and much pioneering work has focused on improving grafting outcomes.[6-8] Surgical interventions using split- and full-thickness skin grafting has proven effective for burn wounds and were reported in the literature as early as 1817.[9]

Negative pressure wound therapy (NPWT), a non-invasive therapy that uses negative pressure in a closed system, can be applied to wounds of diverse aetiology to

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promote healing.[10] The use of negative pressure in wound treatment dates back to the Roman era; Roman soldiers were each assigned an individual to perform oral suctioning of wounds.[11] NPWT began gaining popularity in 1997, following the publication of two articles[12,13] on the use of vacuum-assisted closure.[14] NPWT is now applied in many surgical specialties. Because it has been shown to accelerate both acute and chronic wound healing and reduce the length of hospital stay, NPWT is a popular method for treating soft-tissue defects.[15,16] NPWT creates a moist healing environment while decreasing tissue oedema, promotes blood flow to the wound, increases granulation tissue formation, and stimulates angiogenesis, thereby reducing wound surface area.[15] Although the mechanism by which NPWT promotes wound healing is not fully understood, some researchers believe that NPWT may contribute to removing inflammatory exudate from the donor site and reduce exposure to pathogens.[17] In addition, Chen et al noted that wound stiffness during healing may positively affect cell migration, in which NPWT plays an important role, thereby accelerating wound healing.[18]

To the best of our knowledge, only one series of reviews has evaluated the effectiveness of NPWT for burn wounds in adults, and no meta-analysis has been conducted on the topic; due to the limited number of completed randomised controlled trials (RCTs), conclusions regarding the treatment's merits have not been drawn.[19,20] In recent years, with NPWT's growing popularity and increased clinical use, more RCTs studying the correlation between its effectiveness in burn wound healing and graft take have been published. To evaluate the possibility of including NPWT in burn management guidelines, we conducted this systematic review. Our objectives were 3-fold: first, to conduct a systematic review of the available evidence for the use of NPWT; second, to assess the quality of the available evidence; and third, to conduct a meta-analysis to quantify the effectiveness of NPWT for improving burn wound healing.

Key Messages

- we explored the effectiveness of NPWT and the possibility of its inclusion in burn management guidelines
- six studies that included a total of 701 patients met our inclusion criteria
- NPWT group had a significantly better overall graft rate in the first week ($P = 0.001$) and a significantly lower infection rate ($P = 0.04$)
- no significant difference in the overall complication rate was found

2 | MATERIALS AND METHODS

This study, comprising a systematic review and meta-analysis, was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[21]

2.1 | Search strategy

Two reviewers (DZL and YCK) independently performed a systematic search of the PubMed database to identify relevant studies published from the inception of the database until May 16, 2020, using the following keywords: “NPWT” OR “negative pressure” AND “burn.” Only results in English and Chinese were included.

2.2 | Selection criteria

Two reviewers (DZL and YCK) systematically and independently performed the initial search, removed duplicate records, screened the titles and abstracts for relevance, and classified studies as included, excluded, or uncertain. Any disagreements regarding inclusion or exclusion were resolved by a third investigator (CC).

RCT inclusion was based on the following criteria: (a) the included population was patients with burn wounds, (b) the applied intervention was NPWT, (c) NPWT was compared with other therapies for burn wounds, and (d) at least one quantitative outcome was reported. Studies that were not in English or Chinese, used non-human experimental groups or evaluated unrelated outcomes were excluded. Case reports, case series, and retrospective data analyses were also excluded.

2.3 | Data extraction

Data extraction was performed independently by two reviewers (DZL and YCK) and checked by a third investigator (CC). Any disagreements regarding the collected data were resolved through discussion. The following data were extracted: patient demographic details, including the degree of the burn wound and mean total body surface area (TBSA; Table 1), and data related to outcomes, including graft take rate and complication rates (Table 2).

TABLE 1 Characteristics of trials included in the systematic review

Authors/ Country	Study design and Sample size (M: Male number) / m: Overall mean age±SD Burn Characteristics and Follow-up time	No. of NPWT wounds (M: Male number) / m: Mean age±SD	No. of control wounds (M: Male number) / m: Mean age±SD	Experimental protocol and Follow up	Control protocol	Exclusion criteria	Risk of Bias Summary: Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (attrition bias)	Other bias
Bloemen et al. [2012] / The Netherlands (26)	Multicenter RCT N= 86 (M: 49) Deep dermal or full-thickness burns TBSA(%)± SD (1) DS-TNP= 8.0 ± 5.8 (2) DS= 9.6 ± 8.1 (3) TNP= 10.0 ± 11.9 (4) ST= 7.7 ± 7.4 Follow-up: daily until discharge; weekly at OPD	(1) DS-TNP= 21 (M: 11) / m: 44 ± 17.0 (2) TNP= 22 (M: 12) / m: 49 ± 13.3	(1) DS= 23 (M: 12) / m: 48 ± 19.4 (2) ST= 20 (M: 14) / m: 53 ± 18.3	(1) DS-TNP: NPWT + DS + STSG (2) TNP: NPWT + STSG Negative pressure: -125 mmHg. NPWT system keep 3-5 days. Soaking the substitute NaCl 0.9% and placed on the wound. Thin STSG meshed ratio were 1 : 1.5. Grafts were positioned on top of the substitute, covered with a nonadhesive dressing. After 4-7 days, wounds were dressed with nonadhesive wound dressings and supplemented with an adequate local antiseptic treatment if necessary.	(1) DS: DS + STSG (2) ST: STSG Wounds were covered with gauzes. Dressings were supplemented with an antibacterial substance if determined necessary. After 4-7 days, dressed with nonadhesive wound dressings and supplemented with an adequate local antiseptic treatment if necessary.	1. age<18 y 2. psychiatrics 3. TBSA>15% 4. wound surface too small or large 5. immunocompromised 6. pts in other trials or refusion	+	+	−	−	−	+	?
Hsiao et al. [2016] / Taiwan (27)	Prospective RCT N= 28 (M: 27) Partial or full-thickness dermal defect Follow-up: Postop day 7, 21; OPD follow up 3 mo	14 / m: 51.9	14 / m: 52.0	STSG + NPWT NPWT system keep 7 days. The skin grafts were 0.15-0.20mm thick and meshed at a 1.5:1. A closed wound drainage tube placing over the skin graft. A 12-mm silicone drain was wrapped around the surgical drain. To prevent air leakage from the system, they applied DuoDERM Extra Thin and Stomadhesive paste around before the transparent film was placed. Lastly, covered with a gauze pad and elastic bandage.	STSG The skin grafts were taken from the anterior thigh. The thickness of skin grafts were 0.15-0.20mm and meshed at a 1.5:1 ratio. Indirect wet gauze (petroleum and wet gauze) was applied to dress the wounds.	1. ESRD, coagulopathy, severe anemia 2. immunodeficiency or receive RT/chemotherapy 3. chronic wounds, dermatologic conditions, or necrotizing disorders 4. allergic to investigational products 5. physical/mental conditions 6. pregnancy 7. refusion	+	−	−	?	+	+	?
Ibrahim et al. [2019] / Egypt (28)	RCT N= 45 (M: 24) Partial-thickness thermal burns TBSA(%) ± SD (1)NPWT: 31.3 ± 3.3 (2)MES: 30.6 ± 3.8 (3)control: 31.9 ± 4.3 (p=0.634) Follow-up: Preop 72hr; Postop day 10, 21	(1)NPWT= 15 / m: 27.2 ± 3.6 (2)MES= 15 / m: 26.5 ± 4.2	15 / m: 26.2 ± 3.8	(1) NPWT (2) MES Negative pressure: -125 mmHg. NPWT system: intermittent suction, 5 mins on and 2 mins off over period of 24 hrs for a total of 3 wks. The system consisted of a non-adherent sponge dressing, a film to cover, and a drainage tube. Treatment was stopped when sufficient granulation tissue covered the wound. The wound was then covered in a thin layer of antibiotic cream and dressed with petroleum gauze and a dry gauze for 3 weeks or until the wound closed.	Conventional treatment Patients received standard wound care only.	1. had a cardiac pacemaker or metal implants 2. pregnancy 3. recently received steroid therapy 4. DM 5. blood problems	+	?	?	+	+	+	?
Liu et al. [2016] / China (29)	RCT N= 52 (M:17; 32 pts) / m: 34 ± 3 (range: 18-59) / Second to third-degree limbs burns TBSA(%) ± SD (1) NPWT: 2.4 ± 1.2 (2) NPWT+ADM: 2.6 ± 1.1 (3) ADM: 2.7 ± 0.8 (4) total: 2.5 ± 1 (range: 0.5-5.0) Follow-up: Postop day 7, 14, 21	(1)NPWT= 18 / m: 34 ± 4 (2)NPWT+ADM= 23 / m: 33 ± 4	ADM= 11 / m: 35 ± 3	(1) NPWT (2) NPWT + DS (porcine ADM) Negative pressure: -16.6 kPa (about -124.5 mmHg). NPWT system: intermittent suction, sustain 10 mins on and 2 mins off over period of 24 hrs. Using a 2 cm gauze to cover the edge, covering the wound by trimed polyvinyl alcohol medical sponge (built-in drainage tube), disinfecting with ethanol and sealed. The external drainage tube is connected to a negative pressure drainage machine and changed the dressing per 3-4 days. Placing the trimed porcine ADM (aperture 2 mm, hole spacing 1 cm), covering with multi-layer steriled gauzes, and fixing with pressure bandage in the NPWT + ADM group. The gauzes were changed daily, and dressing was changed every 3- 4 days.	DS (porcine ADM) Placing the trimed porcine ADM (aperture 2 mm, hole spacing 1 cm), covering with multi-layer steriled gauzes, and fixing with pressure bandage. The gauzes were changed daily, and dressing was changed every 3- 4 days.	1. DM 2. severe heart, liver, kidney, hematopoietic system dysfunction 3. psychiatrics, seizure 4. pregnancy or breast-feeding 5. immunodeficiency or receive RT/chemotherapy	+	−	−	?	+	+	?
Petkar et al. [2011] / India (30)	Prospective RCT N= 40 (M: 14; 30 pts) Mean wound size (cm2) (1)NPWT: 244 (range: 16-1200) (2)control: 183 (range: 16-1000) Follow-up: Postop day 4, 9; total 3 wks	21 /m: 32 (range: 7-68)	19 / m: 28.5 (range: 7-60)	NPWT Negative pressure: -80 mmHg. NPWT system keep 4 days. Vaseline gauze was placed. A 1.5 inch low-density polyurethane foam was then placed. A flexible transparent plastic tube of 5mm inner diameter and 1 m length was perforated. Splinting and/or elevation of the grafted part was done when deemed necessary.	Conventional treatment Vaseline gauze, cotton pads and cotton or elastic adhesive bandage were applied. Splinting and/or elevation of the grafted part was done when deemed necessary.	1. known bleeding tendencies 2. areas where NPWT would be not possible	+	−	−	−	+	+	?
Wen et al. [2017] / China (31)	RCT N= 450 (M:222) Follow-up: Postop day 5	225 (M:110) / m: 29.2 ± 3.5	225 (M:112) / m: 30.5 ± 3.8	NPWT + DS (porcine ADM) Negative pressure: -9.30 kPa (about -70 mmHg). NPWT system keep 5 days. Cleansing the burn wounds with normal saline and sterilizing the wound by 1% benzalkonium bromide for 3 times, then covering the porcine ADM which immersed in the sterilized solution on it. Following, placing the drainage tube and connecting the single suction pump.	Conventional treatment The control group underwent the conventional dressing therapy.	Not mentioned	+	−	−	?	?	+	?

Note. RCT= randomized controlled trial; N= number of patients; M= male; F= female; pts= patients; NPWT= negative pressure wound therapy; TNP= topical negative pressure; DS= dermal substitute; STSG= split-thickness skin graft; ST= standard treatment; ADM= acellular dermal matrix; MES= microcurrent electrical stimulation; TBSA= total body surface area ;ESRD= end stage renal disease; DM= diabetes mellitus; RT= radiotherapy.

TABLE 2 Outcomes of trials included in the systematic review

Authors/Country	Graft Take Rate	Infection Rate	Overall Complication Rate	Major Complications
Bloemen et al (2012)/ The Netherlands[22]	Day 5	None of the wounds were infected, pre- or postoperatively	Patients with complications (n, %)	1. Contaminated wounds pre-/post-op:
	(1) DS-TNP = 94.8%		(1) DS-TNP = 7 (33)	(1) DS-TNP = 10/21 (48%)/ 10/14 (71%)
	(2) DS = 92.4%		(2) DS = 7 (30)	(2) TNP = 5/21 (24%)/6/17 (35%)
	(3) TNP = 94.2%		(3) TNP = 5 (23)	(3) DS = 10/22 (45%)/13/17 (76%)
	(4) ST = 96.1%		(4) ST = 2 (10)	(4) ST = 8/18 (44%)/7/9 (78%)
				2. Patients re-op (n, %):
				(1) DS-TNP = 2 (10), (2) TNP = 1 (5), (3) DS = 3 (13), (4) ST = 1 (5)
				3. Hematoma and graft loss: (1) DS-TNP = 1, (2) TNP = 0, (3) DS = 2, (4) ST = 0
				4. Graft shift: (1) DS-TNP = 2, (2) TNP = 2, (3) DS = 0, (4) ST = 0
				5. Graft loss (5%-100%) (1) DS-TNP = 2, (2) TNP = 3, (3) DS = 5, (4) ST = 2
				6. Postop bleeding: (1) DS-TNP = 1, (2) TNP = 0, (3) DS = 0, (4) ST = 0
Hsiao et al (2016)/ Taiwan[23]	Week 1 NPWT: 71.4% control: 85.7%	No wound infection was noted in any patients	Itching (%) NPWT: 0 control: 7.1	No unwanted event (such as seroma formation) and no formation of hypertrophic scar
Ibrahim et al (2019)/ Egypt[24]	Wound surface area Percentage change ± SD (%) NPWT/MES/control (1) Pre-treatment—Day 10: 27.8 ± 6.6/47.2 ± 7.2/15.7 ± 5.7 (2) Pre-treatment—Day 21: 74.7 ± 16.4/85.4 ± 10.6/37.2 ± 10.4			
Liu et al (2016)/China[25]	Day 7/14/21 (%) NPWT: 40.6 ± 1.0/60.9 ± 1.5/90.6 ± 5.1 NPWT + ADM: 39.8 ± 1.2/77.1 ± 2.3/98.7 ± 1.7 ADM: 10.6 ± 0.3/55.9 ± 1.4/75.0 ± 1.8	Infected wounds/total wounds at day 21 NPW: 2/18 (0.11%) NPWT+ADM: 2/23 (0.08%) ADM: 8/11 (0.72%)	Infected wounds/total wounds at day 21 NPW: 2/18 (0.11%) NPWT+ADM: 2/23 (0.08%) ADM: 8/11 (0.72%)	
Petkar et al (2011)/India[26]	Day 9 Percentage ± SD NPWT: 96.67% ± 3.554			1. Air leak: 5 in NPWT group

(Continues)

TABLE 2 (Continued)

Authors/Country	Graft Take Rate	Infection Rate	Overall Complication Rate	Major Complications
	control: 87.53% ± 8.733			
				2. Post-operative day when dressing was discontinued for self-massage with moisturiser was noted
				3. No serious adverse effects in either group
Wen et al (2017)/China[27]		Number/total NPWT: 6/225 (2.67%) control: 10/225 (4.44%)	Number/total NPWT: 18/225 (8%) control: 32/225 (14.22%)	

Abbreviations: ADM, acellular dermal matrix; DS, dermal substitute; MES, microcurrent electrical stimulation; NPWT, negative pressure wound therapy; ST, standard treatment; STSG, split-thickness skin graft; TNP, topical negative pressure.

2.4 | Statistical analysis

The analysis was performed using Review Manager (RevMan Version 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Categorical variables were reported as odds ratios (OR) and 95% confidence intervals (CIs). Data heterogeneity was assessed using the I^2 index. Statistical significance was set at $P < 0.05$.[28,29]

2.5 | Quality assessment

Two reviewers (DZL and YCK) independently assessed the studies' potential risk of bias after data collection. The Cochrane risk of bias tool[30] was used to assess the possibility of bias, which includes six domains for RCTs: (a) random sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessment, (e) incomplete outcome data, and (f) selective reporting. The reviewers ranked each category for each study as having a low, high, or plausible risk of bias. For the overall risk of bias, any differences between the assessments of the two reviewers were resolved by a third investigator (CC). We applied the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach[31] for rating the quality of evidence for each comparison, and we used GRADEpro GDT to summarise the GRADE results in a table.

3 | RESULTS

Six RCTs that included a total of 701 patients were selected for review. Data extracted from these studies formed the basis of this systematic review.[22-27] The flowchart of the literature search is provided in Figure 1.

3.1 | Characteristics of included studies

The included studies were published between 2011 and 2019 and investigated varying degrees and TBSA of burn wounds. Follow-up time ranged from 3 days preoperation to 3 months postoperation.

Among the studies, several types of NPWT interventions were used. Two studies applied the intermittent mode of NPWT,[24,25] in which negative pressure is repeatedly switched on and off over a period of 24 hours. In the remainder[22,23,26,27] of cases, negative pressure was maintained for three to 7 days. Regarding the magnitude of the pressure, three of the studies applied pressure of −125 mmHg,[22,24,25] whereas Petkar et al[26] and Wen,[27] respectively, used −80 mmHg[26] and −9.30 kPa (approximately −70 mmHg).

Moreover, the studies used different combinations of NPWT and control groups. Three studies compared the application of NPWT with a split-thickness skin graft (STSG) with the use of STSG alone.[22,23,26] One study evaluated STSG with or without NPWT and with or without a dermal substitute (DS)[22] with the combined use of STSG and DS. Two studies compared the combined application of NPWT and porcine acellular dermal matrix (ADM) with the use of ADM alone[25] or conventional dressing.[27] One study compared the application of NPWT with the use of ADM.[25]

3.2 | Effects of interventions

3.2.1 | Graft take rate in the first week

Five studies reported graft take rate in the first week,[22-26] of which four provided assessable data[22,24-26] that were analysed for experimental and control groups (Figure 2).

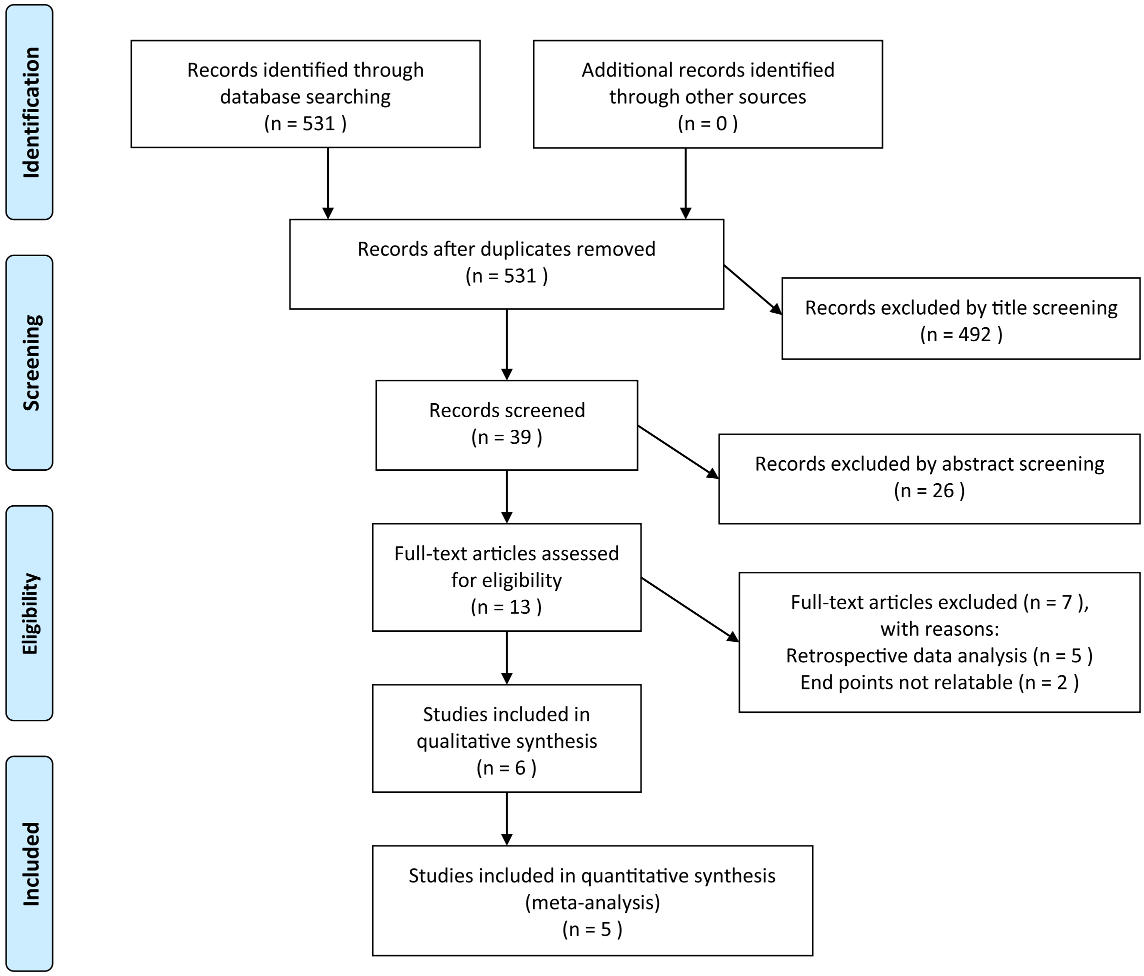

FIGURE 1 Flow chart of the study selection

The pooled analysis indicated an overall significantly improved graft take rate in the first week in the NPWT groups compared with control groups (standardised mean difference [SMD]: 2.62 [95% CI: 1.01, 4.22]; I^2: 94%, P = 0.001; Figure 2). Improved graft take rate at first week was noted in the following three subgroups: (a) NPWT and DS compared with DS (SMD: 5.93 [95% CI: 4.27, 7.60]; $P < 0.0001$; Figure 2.1.3), (b) NPWT compared with DS (SMD: 8.52 [95% CI: 6.05, 11.00]; $P < 0.00001$; Figure 2.1.4), and (c) NPWT to conventional dressing therapy alone (SMD: 1.91 [95% CI: 1.03, 2.79]; $P < 0.00001$; Figure 2.1.5). No significant difference in graft take rate at first week was observed between the experimental (NPWT, DS, and STSG) groups and the control (DS and STSG) groups (SMD: 0.2 [95% CI: −0.40, 0.79]; P = 0.65; Figure 2.1.1). No significant difference was found between the NPWT and STSG experimental groups and the control groups using STSG alone (SMD: 0.63 [95% CI: −0.86, 2.13]; I^2: 86%, P = 0.41; Figure 2.1.2).

3.3 | Complication rates

Complication rates, including infection rate and overall complication rate, are shown in Figure 3. The infection rate was reported in two studies.[25,27] The pooled analysis showed significantly lower odds compared with control groups (OR: 0.12 [95% CI: 0.02, 0.87]; I^2: 78%, P = 0.04; Figure 3.1.1). Bloemen et al[22] and Hsiao et al[23] observed a 0% infection rate across the experimental and control groups. The overall complication rate, which four studies reported,[22,23,25,27] showed no significant reduction of odds in the NPWT groups in the pooled analysis (OR: 0.59 [95% CI: 0.16, 2.17]; I^2: 78%, P = 0.42; Figure 3.1.2). Petkar et al[26] reported no serious adverse effects in either group.

4 | DISCUSSION

This systematic review and meta-analysis study summarised the available evidence on the effects associated with the application of NPWT for burn wounds.

Study or Subgroup	NPWT Mean	NPWT SD	NPWT Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
2.1.1 [NPWT+DS+STSG] to [DS+STSG]									
Bloemen 2012 DS-TNP[26]	94.8	14.2796	21	92.4	9.4813	23	18.2%	0.20 [-0.40, 0.79]	2012
Subtotal (95% CI)			**21**			**23**	**18.2%**	**0.20 [-0.40, 0.79]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.65 (P = 0.52)									
2.1.2 [NPWT+STSG] to [STSG]									
Petkar 2011[30]	96.67	3.554	21	87.53	8.733	19	18.0%	1.37 [0.67, 2.07]	2011
Bloemen 2012 TNP[26]	94.2	12.8559	22	96.1	1.8105	6	17.6%	-0.16 [-1.06, 0.74]	2012
Subtotal (95% CI)			**43**			**25**	**35.7%**	**0.63 [-0.86, 2.13]**	
Heterogeneity: Tau² = 1.00; Chi² = 6.90, df = 1 (P = 0.009); I^2 = 86%									
Test for overall effect: Z = 0.83 (P = 0.41)									
2.1.3 [NPWT+DS] to [DS]									
Liu 2016 NPWT+ADM[29]	39.8	5.755	23	10.6	0.995	11	15.5%	5.93 [4.27, 7.60]	2016
Subtotal (95% CI)			**23**			**11**	**15.5%**	**5.93 [4.27, 7.60]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 6.99 (P < 0.00001)									
2.1.4 [NPWT] to [DS]									
Liu 2016 NPWT[29]	40.6	4.2426	18	10.6	0.995	11	12.9%	8.52 [6.05, 11.00]	2016
Subtotal (95% CI)			**18**			**11**	**12.9%**	**8.52 [6.05, 11.00]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 6.75 (P < 0.00001)									
2.1.5 [NPWT] to [Conventional dressing]									
Ibrahim 2019 NPWT[28]	27.8	6.6	15	15.7	5.7	15	17.7%	1.91 [1.03, 2.79]	2019
Subtotal (95% CI)			**15**			**15**	**17.7%**	**1.91 [1.03, 2.79]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 4.23 (P < 0.0001)									
Total (95% CI)			**120**			**85**	**100.0%**	**2.62 [1.01, 4.22]**	
Heterogeneity: Tau² = 3.58; Chi² = 87.06, df = 5 (P < 0.00001); I^2 = 94%									
Test for overall effect: Z = 3.20 (P = 0.001)									
Test for subgroup differences: Chi² = 78.38, df = 4 (P < 0.00001), I^2 = 94.9%									

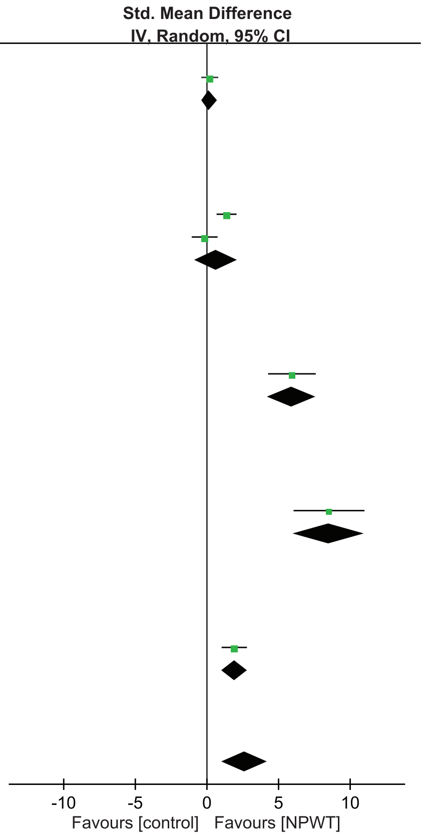

FIGURE 2 Forest plot and meta-analysis showing the standard mean difference of graft take rate at week one between NPWT (negative pressure wound treatment) and control groups

Study or Subgroup	NPWT Events	NPWT Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
3.1.1 Infection rate							
Liu 2016 NPWT[29]	2	18	8	11	30.5%	0.05 [0.01, 0.34]	2016
Liu 2016 NPWT+ADM[29]	2	23	8	11	30.6%	0.04 [0.01, 0.26]	2016
Wen 2017[31]	6	225	10	225	38.8%	0.59 [0.21, 1.65]	2017
Subtotal (95% CI)		**266**		**247**	**100.0%**	**0.12 [0.02, 0.87]**	
Total events	10		26				
Heterogeneity: Tau² = 2.46; Chi² = 9.13, df = 2 (P = 0.01); I^2 = 78%							
Test for overall effect: Z = 2.10 (P = 0.04)							
3.1.2 Overall complication rate							
Bloemen 2012 DS[26]	7	21	2	20	14.9%	4.50 [0.81, 25.12]	2012
Bloemen 2012 DS-TNP[26]	7	22	2	20	14.9%	4.20 [0.76, 23.32]	2012
Bloemen 2012 TNP[26]	5	23	2	20	14.7%	2.50 [0.43, 14.61]	2012
Hsiao 2016[27]	0	14	1	14	8.8%	0.31 [0.01, 8.29]	2016
Liu 2016 NPWT[29]	2	23	8	11	13.8%	0.04 [0.01, 0.26]	2016
Liu 2016 NPWT+ADM[29]	2	18	8	11	13.7%	0.05 [0.01, 0.34]	2016
Wen 2017[31]	18	225	32	225	19.2%	0.52 [0.29, 0.97]	2017
Subtotal (95% CI)		**346**		**321**	**100.0%**	**0.59 [0.16, 2.17]**	
Total events	41		55				
Heterogeneity: Tau² = 2.22; Chi² = 27.36, df = 6 (P = 0.0001); I^2 = 78%							
Test for overall effect: Z = 0.80 (P = 0.42)							

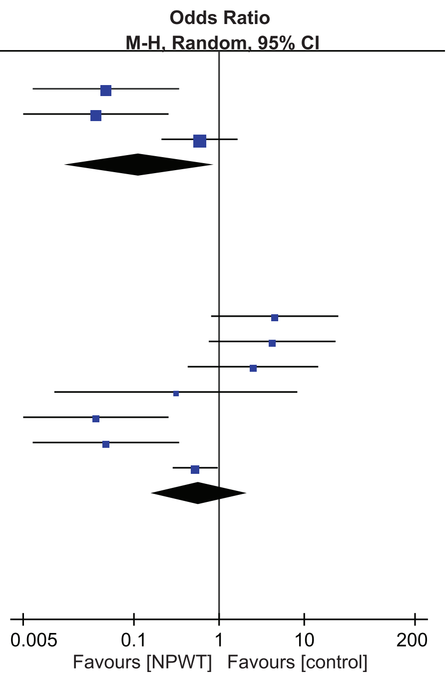

FIGURE 3 Forest plot and meta-analysis showing mean difference of complication rate between NPWT (negative pressure wound treatment) and control groups

Overall, the NPWT groups demonstrated more improvement in graft take rate in the first week and a lower infection rate compared with the other groups. Between-group differences in overall complication rates were not significant.

4.1 | Graft take rate

The overall graft take rate was significantly improved in the first week in the NPWT groups compared to the control groups. NPWT has better graft take comparing with dressing alone. No significant difference was found between the STSG group using NPWT and the group using STSG alone. Nevertheless, some reviews and meta-analyses comparing the use of NPWT versus other therapies on STSG have demonstrated that NPWT can improve graft take.[32-35] Therefore, NPWT may still have potential benefits for skin grafting of burn wounds. Blood filling of autochthonous graft capillaries usually occurs on day three. Through interconnections between the wound bed and skin grafts, skin microcirculation is almost completely restored by day five.[36] This may further explain our overall positive graft take rates in the first week. The removal of excess exudate through NPWT reduces the risk of hematoma formation and prevents the complications of graft shear or lift-off[37-39]; this is consistent with our graft take results.

In our study, two RCTs included DS as an adjunct to burn wound treatment.[22,25] However, the different interventions between the control groups preclude us from drawing any statistical conclusions. A limited benefit on graft take has been reported for the use of DS in burns.[40-42] DS was demonstrated to reduce and delay graft take due to vascular ingrowth on the DS surface; it can be improved through NPWT application, as reported by Bloemen et al[22] (an included study). NPWT can improve revascularisation through the induction of collagen transcription and angiogenesis, adhere to DS to the wound bed, and eventually improve skin graft take.[17,43] The benefits of applying NPWT to DS remain unclear, and larger trials are required before a conclusion can be reached.

In conclusion, it showed that among the overall significant better graft take in NPWT groups, first, it is better than conventional dressing therapy alone. Second, for the effects combining with DS or STSG, NPWT provides a better condition for DS to adhere, but little improvement with STSG in our study.

4.2 | Complications

Our infection rate outcomes indicated a significant risk reduction, which is consistent with findings from several past reviews.[17,39,43-47] It is suggested that NPWT decreases the infection rate due to the following reasons: For wound care management, the NPWT systems lower dressing frequency, the wound site would be exposed less.[17,48,49] For a wound healing environment, NPWT could provide a positive wound environment by removing the healing inhibitors such as metalloproteinases in the wound exudate and clear microorganisms,[50,51] promote better microvascular circulation to lower the bacterial colonisation.[17,43,45] However, others have found equivocal evidence.[35,37,42] The controversy may be due to the variation in patient inclusion and exclusion criteria and in methodology.

In our study, between-group differences in overall complication rates were not significant, but the rate in NPWT patients was improved. The studies we assessed reported various complications related to NPWT, leading to an inaccurate assessment. Nevertheless, their findings suggest that in general, patients receiving NPWT experienced improved wound healing with less discomfort.

4.3 | Burn guidelines and contraindications to NPWT

According to the World Health Organisation, full-thickness burns in the healing phase should undergo skin grafting after wound excision.[1] Regardless of this recommendation, NPWT remains excluded from current guidelines on burn wound treatment. We believe that NPWT has the potential to become standard for burn wound treatment.

Generally, NPWT is considered highly safe[44]; its most serious complication other than infection is bleeding.[52] However, to prevent haemorrhage from the affected vessels, NPWT is contraindicated for patients with arterial erosion, active massive haemorrhage, and necrosis.[53,54] Several of our included studies noted its contraindications for other groups, including patients with coagulopathy,[23-26] because untreated coagulopathy can cause bleeding and infection during NPWT.[55] However, NPWT is not contraindicated for patients receiving anticoagulant or platelet aggregation inhibitor therapy, provided its use is strictly monitored.[52,54,55] We believe that NPWT is beneficial in the majority of patients with burn wounds.

4.4 | Pressure settings for NPWT

The pressure settings in the included studies ranged from −70 to −125 mmHg, with three studies using −125 mmHg in their experimental groups.[22,24,25] We

TABLE 3 ĐRADE (grading of recommendations, assessment, development, and evaluation) assessment of the meta-analysis

Certainty Assessment							No of Patients		Effect			
No of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	NPWT	Conventional Treatment	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Graft take rate at week 1												
4	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	120	85	–	SMD 2.62 higher (1.01 higher to 4.22 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Complication rate – Infection rate												
2	Randomised trials	Serious[a]	Serious[b,c]	Not serious	Not serious	None	10/266 (3.8%)	26/247 (10.5%)	OR 0.12 (0.02-0.87)	91 fewer per 1000 (from 103 fewer to 12 fewer)	⊕⊕◦◦ LOW	CRITICAL
Complication rate – overall complication rate												
4	Randomised trials	Serious[d]	Serious[b,e]	Not serious	Not serious	None	41/346 (11.8%)	55/321 (17.1%)	OR 0.59 (0.16-2.17)	63 fewer per 1000 (from 139 fewer to 138 more)	⊕⊕◦◦ LOW	CRITICAL

Abbreviations: CI, confidence interval; OR, odds ratio; SMD, standardised mean difference.

[a]High risk of bias due to lack of blinding. None of them were able to blind the participants and personnel. Both RCTs' outcome assessors were not blinded for any outcomes.

[b]The variability is substantial, but differences are between small and large beneficial effects.

[c]Heterogeneity $P = 0.01$, $I\,\hat{}\,2 = 78\%$.

[d]High risk of bias due to a lack of blinding. None of them were able to blind the participants and personnel. 1 RCT's outcome assessors were not blinded for any outcomes while 3 RCTs were unclear on it.

[e]Heterogeneity $P = 0.0001$, $I\,\hat{}\,2 = 78\%$.

found that most studies on NPWT have used an optimal pressure of −125 mmHg. In an early study done on pigs, peak blood flow was −125 mmHg, which was four times higher than the baseline.[13] By contrast, another study on pigs observed a maximal net increase of blood flow in muscular tissue between −75 and − 100 mmHg.[56] The difference in optimal pressure setting can be explained by differences in wound sites and tissue components. The same researchers concluded in another study that for subcutaneous and muscular wounds, the optimal pressure is −75 and − 100 mmHg, respectively.[57] One study recommended adjusting the pressure from −70 to −125 mmHg after 72 hours of treatment and routinely placing paraffin gauze over the tissue to reduce adhesion and minimise trauma.[58] While further research on the optimal pressure settings of NPWT necessary for maximal wound healing is warranted, −125 mmHg is widely accepted pressure for NPWT so far.

Two studies included in our review used the intermittent mode of NPWT.[24,25] Studies comparing the differences between modes of NPWT are limited. Two studies have concluded that more granulation tissue may be formed in the non-continuous mode (intermittent or variable pressure modes) than in the continuous mode.[13,59] By contrast, a study by Lessing et al found no significant difference between continuous and non-continuous NPWT in any of the outcomes.[60] A recent study evaluating the clinical benefits of intermittent NPWT showed that it can improve local perfusion and oxygen supply to the wound.[61] Taking all the evidence into account, which NPWT mode should be used for optimal healing outcomes remains unclear. In summary, the settings of NPWT are most appropriated and most commonly used at −125 mmHg for both intermittent and continuous mode to date.

4.5 | Quality assessment

Table 1 illustrates the quality assessment results, which indicate several potential biases in some of the included studies. The Cochrane risk of bias tool was applied to RCTs, and with respect to allocation concealment, one study[22] had low risk, the risk was unclear in one,[24] and the remaining had high risk.[23,25-27] Because blinding of participants and personnel is inapplicable to NPWT, none of the studies were considered to be at low risk for it. Likewise, blinding of outcome assessment is inapplicable to NPWT; only one study[24] was at low risk of this. These concerns might have led to subjective judgement bias.

Based on the GRADE assessment (Table 3), the evidence assessed in graft take rate in the first week is of high certainty, evidence for infection rate (downgraded once for high risk of bias and once for inconsistency) is of low certainty, and evidence for the overall complication rate (downgraded once for high risk of bias and once for inconsistency) is of low certainty. According to the forward assessment, incorporating NPWT into burn management guidelines is worth considering.

5 | LIMITATIONS

This study has several limitations. First, the comparison variation was high, possibly contributing to the finding of varying degrees of effectiveness for NPWT. Second, the variation in application methods and duration of NPWT could have affected the outcomes. The limited number of RCTs and their relatively small sample sizes may also be considered limitations.

6 | CONCLUSIONS

NPWT is a safe method for accelerating healing and lowering the infection rate of burn wounds. Its use in burn wound treatment is recommended provided it is applied under appropriate circumstances. However, the optimal pressure settings of NPWT warrant further investigation, and further large-scale RCTs are required to provide more evidence of its effectiveness for treating burn wounds.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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