Negative-pressure therapy versus conventional therapy on split-thickness skin graft: A systematic review and meta-analysis

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Title Page

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Negative-pressure Therapy versus Conventional Therapy on Split-thickness Skin Graft: a systematic review and meta-analysis

Abstract:

Objective: To compare the clinical outcomes of negative-pressure wound therapy (NPWT) versus conventional therapy on split-thickness skin after grafting surgery.

Design: Meta-analysis

Background: Split-thickness skin grafts are widely used in reconstruction of large skin defects. Conventional therapy causes pain during dressing changing. NPWT is an alternative method to cover the wound bed.

Methods: The Pubmed, Embase, and Cochrane databases were searched for randomized controlled trials (RCTs) or cohort studies for articles published between 1993 and April 2017 comparing NPWT to conventional wound therapy for split-thickness skin grafts. The rate of graft take was the primary outcome of this meta-analysis. Wound infection and reoperation rate of the wound were secondary outcomes. Data analysis was conducted using the Review Manager 5.3 software.

Results: Five cohort studies and seven RCTs including 653 patients were eligible for inclusion. Patients treated with NPWT had a significantly higher rate of graft take compared to those treated with conventional therapy [MD=7.02, (95% CI 3.74, 10.31)] (P=0.00). NPWT was associated with a reduction in reoperation [RR=0.28, (95% CI 0.14, 0.55)] (P=0.00). The reduction in wound infection was not significant [RR=0.63, (95% CI 0.31, 1.27)] (P=0.20).

Conclusion: Compared with conventional therapy, NPWT significantly increases the rate of graft take and reduces the rate of reoperation when applied to cover the wound bed with split-thickness skin graft. No significant impact on wound infection was found in this study.

Keywords: negative-pressure therapy; conventional therapy; split-thickness skin; meta-analysis

1. Introduction:

Soft tissue coverage for skin defect wounds remains a challenging therapeutic problem for patients sustaining traumatic injuries and burns. Postoperative complications can prolong the hospital stay, increase hospital expense and lead a lower quality of life.(1) Hence, the method of wound coverage has become increasingly important, especially in orthopaedic surgery.(2) Split-thickness skin grafting is a fundamental technique widely used in the reconstruction of large skin defects. It is very important to explore the most efficient way to cover the grafted skin and maximize the rate of graft take. The grafted skin has to go through three stages to survive: serum imbibition, revascularization, and maturation.(3) Revascularization is the most critical and is easily influenced by external factors. The determinants of skin-graft take include the thickness of graft, the soft tissue bed and the coverage technique. The common causes of skin graft loss are the result of the formation of hematoma under the graft, infection of the grafted skin and shear forces of the interface. If the grafted skin has a large area loss, then a second surgery is needed to remedy the wound bed.

Conventional postoperative recipient site care therapy usually refers to a protective layer of petroleum gauze and cotton gauze combined with tie-over dressing technique. The disadvantages of conventional techniques of skin grafting includes suboptimal graft take due to hematoma under the grafted skin and shearing of the interface, which would hinder the skin survival in the bed. To achieve drainage of the hematoma and immobilization, conventional dressings are used with the cotton gauze and tie-over technique. However, this conventional method of covering and stabilizing the skin graft is unwieldy and ineffective. To maintain a moist condition for the grafts to take, saline-moistened gauze and petroleum gauze need to be changed frequently. Replacement of the dressings can cause pain in patients and increase the workload of medical staff.

The technique of negative-pressure wound therapy (NPWT) has been reported as a good alternative to conventional dressing for the split-thickness grafts. The efficacy of NPWT was initially described by Morykwas and Argenta in the United States.(4) In addition, NPWT also has been used to prepare wound beds for the grafting of flap closure.(5, 6) The negative pressure closure is based on the use of Vacuum Assisted Closure (VAC) that places negative pressure over the wound surface, producing compression in soft tissues and improving its irrigation. Several studies have been reported the usage of NPWT over grafted skin, and some of these studies have shown encouraging results.(3, 7-12) However, there was no meta-analysis incorporating all these studies to compare the NPWT with the conventional dressing technique. The present study was performed to fill this blank and to provide evidence-supported answers to the questions about the cover of split-thickness graft skin.

2. Materials and Methods:

This meta-analysis was performed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (13) reporting guidelines for the conduct of meta-analysis of intervention trials.

2.1 Literature Search Strategy

Pubmed, Embase and Cochrane Library were searched for comparative studies published before April 2017 involving VAC in the management of split-thickness skin grafts. The search terms were as follows: “vacuum assisted closure” or “negative pressure” or “subatmospheric pressure” “suction dressing” or “topical negative pressure” or “VAC” or “vacuum therapy” AND “gauze suction” or “conventional gauze therapy” or “conventional treatment” or “conventional dressing” or “wound therapy” or “standard wound care” AND “skin transplantation” or “dermatoplasty” or “skin grafts” or “skin grafting”.

2.2 Inclusion criteria and study selection

We identified randomized controlled trials (RCTs) or clinical cohort studies comparing NPWT versus the conventional method on split-thickness skin grafts. Only English-language articles were included by us. Studies included reported at least one of the following factors: rate of graft take, wound infection, and reoperation. Those studies without the outcome measures of interest were excluded. Systematic reviews, letters, editorials, comments and guidelines were also excluded. When included articles had the same patient cohort, only the article with the longest follow-up period was selected. Reference lists of all eligible studies and relevant reviews were manually searched for any additional studies.

2.3 Data abstraction and quality assessment

Two authors (Y.C.Y and R.P.Z) independently reviewed all titles and abstracts of studies identified by the above searches. Full texts of any potentially useful studies were reviewed, and disagreements were resolved by discussion. General data of the studies, including first author, year of publication, study design, mean age of the patients, mean wound size, details of the treatment were extracted in duplicate by the two authors, using a standardized form. The quality of evidence of outcomes was judged according to the Newcastle Ottawa Scale. Newcastle Ottawa Scale scores ranges from 0 to 9, with higher scores indicating better quality.

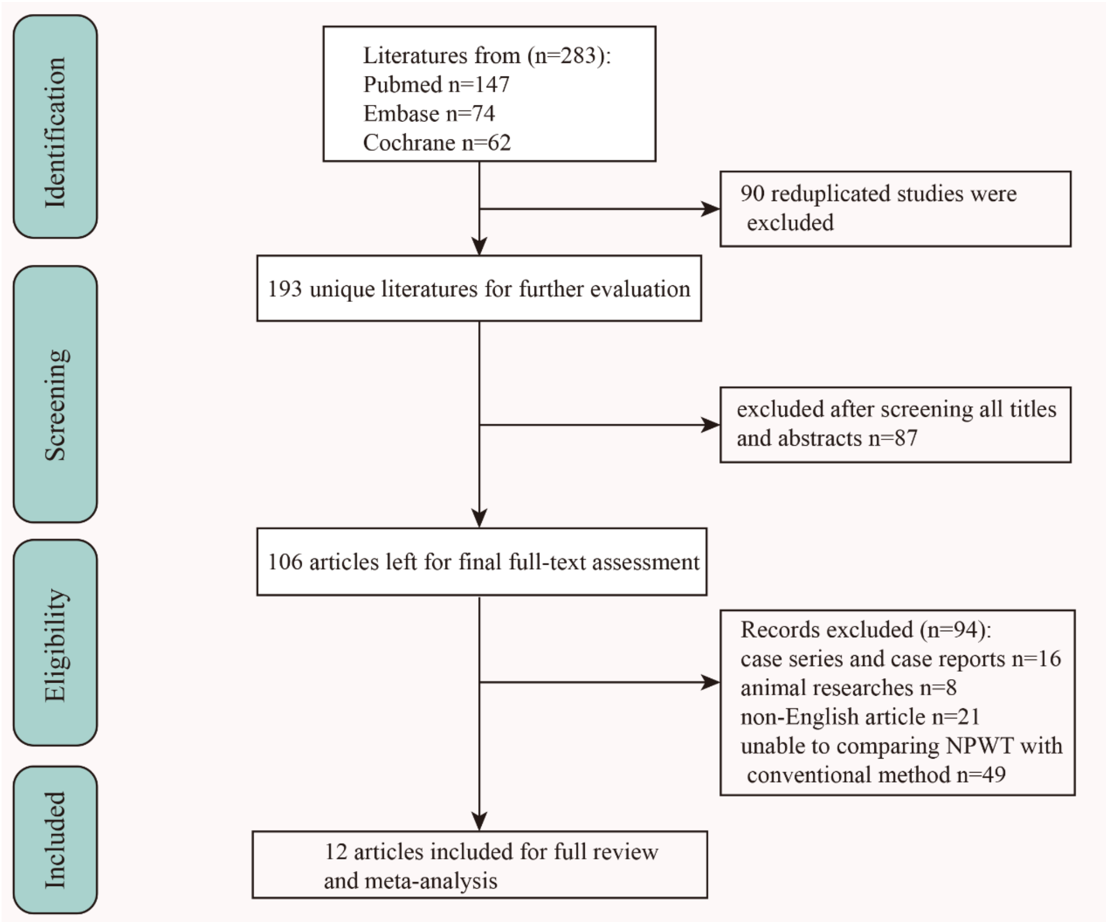
2.4 Statistical analysis

Y.C.Y conducted all the calculations using Cochrane Collaboration's Revman 5.3 software. Pooled mean difference (MD) with a 95% confidence interval (95% CI) was calculated for the continuous data, and risk ratios (RR) and a 95% CI were calculated for the dichotomous data. A *Z*-test was performed to determine the overall effects. Heterogeneity among studies was estimated using I^2, and substantial heterogeneity was represented by an I^2 value > 50%. A fixed effects model was used if the heterogeneity test did not reveal statistical significance ($I^2 < 50\%$, $P > 0.1$). Otherwise, we adopted a random effects model. $P < 0.05$ was considered to be statistically significant. Sensitivity analysis was performed to explore the impact of an individual study by deleting one study at a time. Funnel plot analysis was applied to determine publication bias.

3. Results:

3.1 Search results

The initial search yielded 283 citations, of which 90 were excluded due to duplication. After screening the titles and abstracts, 106 studies were excluded based on the inclusion criteria, and 94 studies were excluded after reading the full texts for the following reasons: case reports, animal studies, non-English article, or inability to compare NPWT with the conventional therapy. Finally, seven RCTs (3, 7-12) and five cohort studies (14-18) involving 653 patients were eligible for data extraction and meta-analysis (Fig. 1).



3.2 Study characteristics and quality assessment

The characteristics of all the included studies are presented in Table 1. The studies were published between 2002 and 2016. A total of 653 split-thickness skin graft patients were performed in the seven RCTs and five cohort studies. The sample size of these studies ranged from 20 to 142 patients. All studies compared NPWT with conventional therapy only. Outcomes of graft take rate, wound infection and reoperation were extracted and pooled. As a random effect model was used, the publication bias risk for graft take rate of split-thickness skin was analyzed by funnel plot and shown in Fig. 2. The quality assessment score was high in most of cases, ranging from 6 to 8 points (Table 1). No studies scored 9 points, because it is impossible to carry out a double-blind study for clinical therapy.

First author, year	Study design	NPWT/Non-NPWT		Mean wound size(cm^2), NPWT/Non-NPWT	Skin thickness, meshed	Treatment	NPWT, negative pressure	Covering time	NOS
		Number of patients	Mean age						
Scherer, 2002(14)	CS	34 VS 27	33±23, 41±20	387±573, 984±996	0.012 inches, -	VAC VS 5% moisted cotton gauze dressing	125 mmHg	4 days	7
Moisidis, 2004(9)	RCT	20(12 men,8 women)	64(27-88)	128(35-450)	0.011 inches, 1:1.5	VAC VS standard bolster dressing	100 mmHg	5 days	6
Llanos, 2006(10)	RCT	30 VS 30	34(20-52), 34.5(19-58)	33.8(8.8-124.3), 31.2(5.5-179.7)	0.12 mm, 1:1.5	Negative pressure wound dressing VS polyurethane dressing	80 mmHg	4 days	8
Kim, 2007(11)	RCT	37 VS 10	54.5(22-73)	68.2(42-122)	0.012 inches, -	Negative pressure wound dressing VS conventional tie-over dressing	125 mmHg	5 days	6
Blume, 2010(16)	CS	87 VS 55	54.6±15.2, 58.4±11.9	45.4±9.69, 47.4±10.3	0.030-0.041 cm, -	VAC VS sterile compressive dressing	125 mmHg	5 days	8
Petkar, 2012	RCT	35 VS 36	34.08±16.75, 35.14±15.25	239.77±299.50, 269.06±336.74	-	VAC VS conventional cotton pads dressing	80 mmHg	4 days	7
Ho, 2013(12)	RCT	29 VS 19	61(54-71), 61(53-66)	-	-	Negative pressure wound dressing VS conventional tie-over dressing	125 mmHg	5 days	8
Lee, 2014(15)	CS	14 VS 12	56.86±8.09, 56.33±9.55	286.21±152.97, 257.83±133.49	0.008 inches, 1:1.5	VAC VS conventional tie-over dressing	125 mmHg	5 days	6
Zhang, 2015(7)	RCT	27 VS 54	45.59, 43.80	257.59, 294.87	-	Negative pressure wound dressing VS conventional gauze	125mmHg	5 days	7
Bach, 2015(17)	CS	16 VS 13	58(41-76), 55(42-71)	36.8±3.4, 33.9±3	0.2 mm for scalp and 0.4 mm for skin paddle harvesting, -	Negative pressure wound dressing VS stapled bolster dressing	125 mmHg	5 days	7
Wu, 2015(18)	CS	20 VS 20	56.7±13.6, 53.6±14.3	48.1±50.1, 55.4±61.1	-	Negative pressure wound dressing VS stapled bolster dressing	110 mmHg	5 days	6
Hsiao, 2016(3)	RCT	14 VS 14	51.9, 52.0	11 ≤120 cm^2 3＞120 cm^2, 9 ≤120 cm^2 5＞120 cm^2	0.15-0.20 mm, 1:1.5	Negative pressure wound dressing VS saline moisten gauze	-	7 days	8

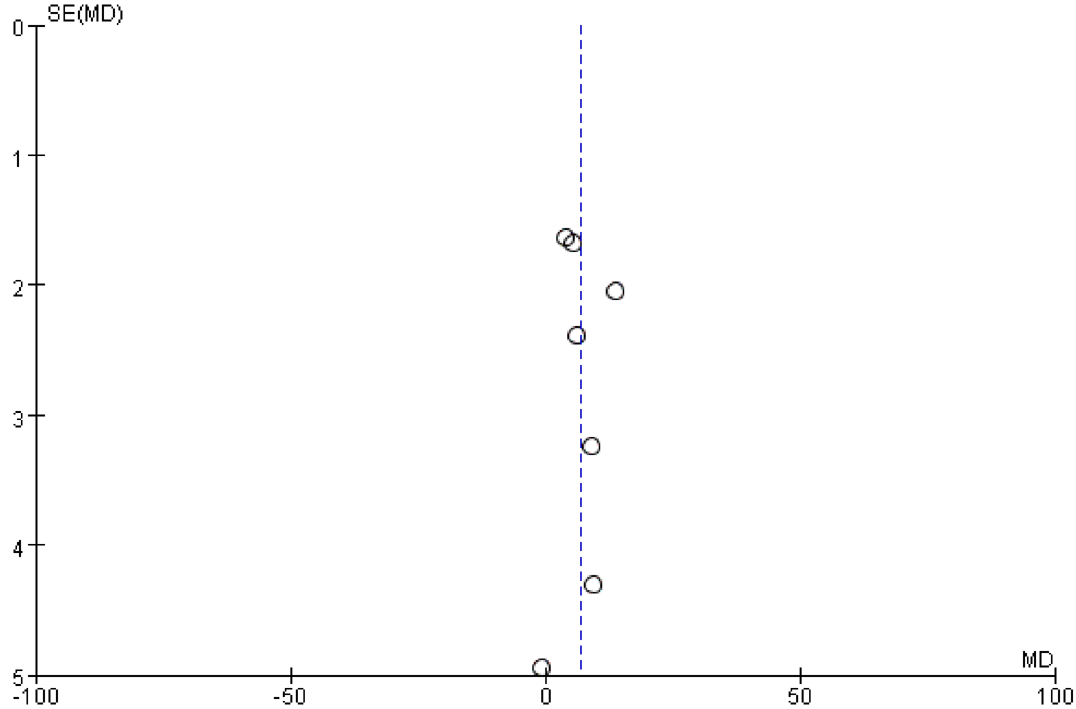
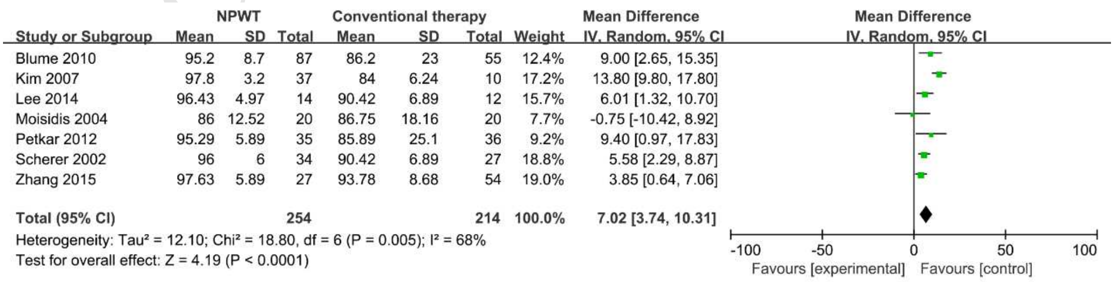


Fig. 2 Publication bias funnel plot for incidence of graft take rate of split-thickness skin

4. Results of the meta-analysis:

4.1 Rate of graft take

Seven studies provided data on the graft take rate of the split-thickness skin after treatment by NPWT or conventional therapy. Statistically significant heterogeneity was found between these two groups (P=0.005, I^2=68%). A random effects model was applied for meta-analysis (Fig. 3), which demonstrated that the graft take rate of split-thickness skin in the NPWT group was significantly higher than in the conventional therapy group (MD, 7.02; 95% CI, 3.74-10.31; P<0.0001).



	NPWT			Conventional therapy				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Blume 2010	95.2	8.7	87	86.2	23	55	12.4%	9.00 [2.65, 15.35]
Kim 2007	97.8	3.2	37	84	6.24	10	17.2%	13.80 [9.80, 17.80]
Lee 2014	96.43	4.97	14	90.42	6.89	12	15.7%	6.01 [1.32, 10.70]
Moisidis 2004	86	12.52	20	86.75	18.16	20	7.7%	-0.75 [-10.42, 8.92]
Petkar 2012	95.29	5.89	35	85.89	25.1	36	9.2%	9.40 [0.97, 17.83]
Scherer 2002	96	6	34	90.42	6.89	27	18.8%	5.58 [2.29, 8.87]
Zhang 2015	97.63	5.89	27	93.78	8.68	54	19.0%	3.85 [0.64, 7.06]
Total (95% CI)			**254**			**214**	**100.0%**	**7.02 [3.74, 10.31]**

Heterogeneity: Tau² = 12.10; Chi² = 18.80, df = 6 (P = 0.005); I² = 68%
Test for overall effect: Z = 4.19 (P < 0.0001)

Fig. 3 Forest plot of the mean difference of graft take rate between NPWT and conventional therapy

4.2 Wound infection

Six studies compared the wound infection of the split-thickness skin after treatment by NPWT or conventional therapy. Pooled analysis showed no difference in the wound infection rates between these two groups (RR, 0.63; 95% CI, 0.31-1.27; P=0.20). There was no significant heterogeneity between these studies (p=0.12; I^2=48%), and a fixed effects model was used for meta-analysis (Fig. 4).

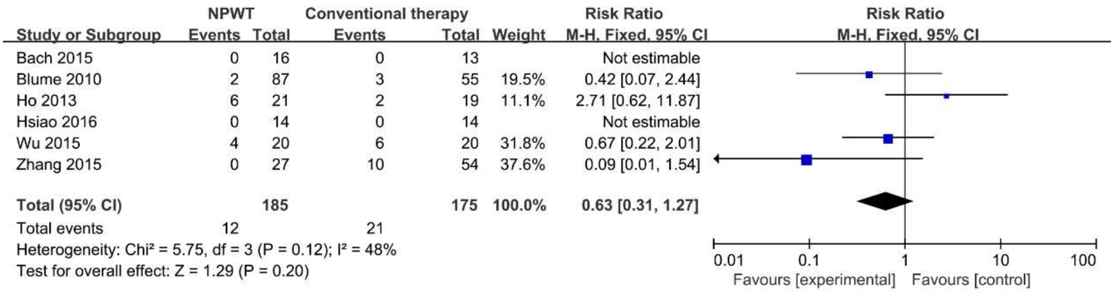


Fig. 4 Forest plot of the mean difference of wound infection for NPWT and conventional therapy

4.3 Reoperation

Four studies reported on the reoperation of split-thickness skin after treatment by NPWT or conventional therapy. Pooled analysis showed that patients treated by NPWT were less likely to undergo reoperation compared with patients treated with conventional therapy (RR, 0.28; 95% CI, 0.14-0.55, P=0.0002). No heterogeneity was detected between these two groups (I^2=0%), and a fixed effects model was applied (Fig. 5).

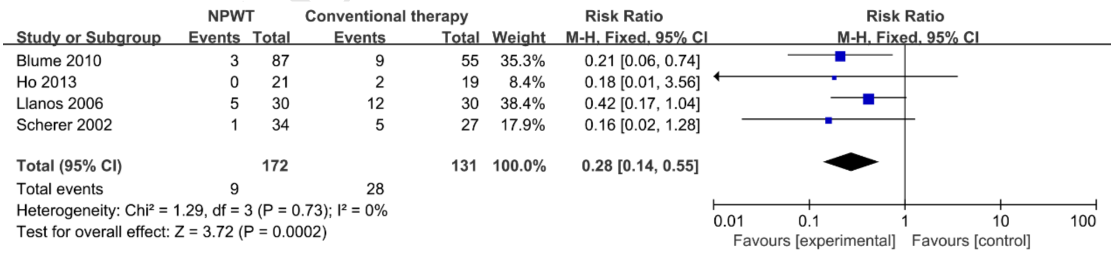


Fig. 5 Forest plot of mean difference of reoperation for NPWT and conventional therapy

4.4 Sensitivity analysis

Sensitivity analysis investigating the influence of a single study on the overall outcome was estimated by omitting 1 study in each turn. When removing the study conducted by Kim(11) and recalculating the remaining studies, heterogeneity changed from 68% to 0%.

5. Discussion:

This meta-analysis of five cohort studies and seven RCTs included a total of 653 patients. All relevant data from these studies were extracted and pooled. The funnel plot of the main outcome did not indicate significant bias. After several analyses, we demonstrated that NPWT seems to offer a significant benefit over conventional therapy for the treatment of split-thickness skin grafts. We found a significant benefit for both the rates of graft take and rate of reoperation compared with conventional therapy. However, there was no evidence that NPWT reduces the risk of wound infection.

To our knowledge, this study is the first meta-analysis to evaluate NPWT and conventional therapy in patients treated with a split-thickness skin graft. The rate of graft take is an important index to evaluate the success of skin grafts. In this present meta-analysis, the primary outcome of this study was the rate of graft take. Of the twelve included studies, seven had reported the graft take rate of split-thickness skin. The merged mean difference (MD) showed that NPWT can improve the rate of graft take by 7% compared with conventional therapy. The heterogeneity was reduced from 68% to 0%, when removing the Kim study during the sensitivity analysis.(11) The patient number of the NPWT group was 3.7 times that of the control group, which may lead to increased heterogeneity of the reasons. Interconnections of capillaries between the wound bed and skin graft occurred at day 3, and complete restoration of microcirculation at day 5.(19) Most of the studies included in this meta-analysis uncovered the dressing and evaluated the rate of graft take at day 5. Hsiao et al. left the drainage system in place for 7 days after operation and then removed to evaluate the graft condition.(3)

The reasons for skin graft loss can be multifactorial. Wound infection is one of the most important factors, which influences the rate of skin graft take and prolongs the hospital stay. The continuous negative pressure environment provided by NPWT reduces the formation of a subcutaneous hematoma. Meanwhile, the negative pressure between the NPWT and the wound bed can hold the skin tightly and reduce shear force. However, this meta-analysis showed no difference between NPWT and conventional therapy. Three studies focused on the flap donor site care.(11, 12, 17) One of these studies was aimed at patients with perineal skin defects.(15) The remaining eight studies concentrated on the complex wound types, including burns, trauma, ulcers and fresh surgical wounds. The mean wound bed size was greater than 100 cm^2 in five studies,(7-9, 14, 15) the others was less than 100 cm^2. Accordingly, all these factors may impact the reliability of this meta-analysis finding. Previous microbiology studies demonstrated that NPWT could not decrease the bacterial load compared to conventional therapy.(20, 21) Moreover, a higher level of bacterial led by NPWT in both acute and chronic wounds, despite the foam was routinely changed.(22)

Reoperation is the remedial measures for the failure of the initial skin graft, whichprolongs hospital stays. The datafor this outcome were extracted from four studies. Pooled analysis showed that NPWT reduced the incidence of reoperation, compared with conventional therapy. Blume et al. conducted a 10-year review of 142 patients who accepted split-thickness skin graft surgery. The results indicated that the NPWT patients were less likely to undergo a second operation.(16) Scherer reported that the reoperation rate in the NPWT group was 16% smaller than in the conventional therapy group.(14) Ho et al. reported that the cost of a five day course of NPWT treatment was 400 dollars, and the reoperation cost was 1450 dollars.(12) This finding means using the NPWT appropriately according to the patient's condition can reduce patient hospitalization costs.

Some limitations of the present meta-analysis must be noted. First, systematic reviews of the literature and meta-analyses provide the strongest scientific evidence when they pool data from high-quality RCTs.(23) Unfortunately, this was not possible, so we had to rely on data extracted from cohort studies. Second, the included studies contained patients with different causes of injury and skin defects in parts. The nonstandard baseline and distribution of the wound bed which may have been a source of clinical heterogeneity.

Conclusions:

This systematic review and meta-analysis has demonstrated that NPWT increased the rate of graft take and reduced the reoperation rate. However, no difference was found between the NPWT group and the conventional therapy group regarding wound infection rate. Further studies of NPWT versus conventional therapy in a prospective, randomized design are warranted to provide better quality outcome measures.

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1. Split-thickness skin grafts are widely used in reconstruction of large skin defects.
2. Conventional postoperative skin recipient site care includes saline-moistened gauze with a protective layer of petroleum gauze and tie-over technique. However, this method causes pain while changing the dressing.
3. The technique of negative-pressure wound therapy (NPWT) has been claimed to be a good alternative for the conventional dressing for the split-thickness grafts.
4. The aim of this systematic review was to compare the clinical outcomes of negative-pressure wound therapy (NPWT) versus conventional therapy on split-thickness skin after grafting surgery.