REVIEW ARTICLE

Negative Pressure Wound Therapy

A Vacuum of Evidence?

Sven Gregor, MD; Marc Maegele, MD; Stefan Sauerland, MD, MPH; Jan F. Krahn, MD; Frank Peinemann, MD; Stefan Lange, MD, PhD

Objective: To systematically examine the clinical effectiveness and safety of negative pressure wound therapy (NPWT) compared with conventional wound therapy.

Data Sources: MEDLINE, EMBASE, CINAHL, and the Cochrane Library were searched. Manufacturers were contacted, and trial registries were screened.

Study Selection: Randomized controlled trials (RCTs) and non-RCTs comparing NPWT and conventional therapy for acute or chronic wounds were included in this review. The main outcomes of interest were wound-healing variables. After screening 255 full-text articles, 17 studies remained. In addition, 19 unpublished trials were found, of which 5 had been prematurely terminated.

Data Extraction: Two reviewers independently extracted data and assessed methodologic quality in a standardized manner.

Data Synthesis: Seven RCTs (n=324) and 10 non-RCTs (n=278) met the inclusion criteria. The overall methodologic quality of the trials was poor. Significant differences in favor of NPWT for time to wound closure or incidence of wound closure were shown in 2 of 5 RCTs and 2 of 4 non-RCTs. A meta-analysis of changes in wound size that included 4 RCTs and 2 non-RCTs favored NPWT (standardized mean difference: RCTs, −0.57; non-RCTs, −1.30).

Conclusions: Although there is some indication that NPWT may improve wound healing, the body of evidence available is insufficient to clearly prove an additional clinical benefit of NPWT. The large number of prematurely terminated and unpublished trials is reason for concern.

Arch Surg. 2008;143(2):189-196

Author Affiliations: Departments of Abdominal, Vascular, and Transplantation Surgery (Dr Gregor) and Trauma/Orthopedic Surgery (Dr Maegele) and Institute for Research in Operative Medicine (Drs Sauerland and Krahn), University of Witten/Herdecke, and Institute for Quality and Efficiency in Health Care (Drs Peinemann and Lange), Cologne; and Department of Abdominal, Thoracic, and Vascular Surgery, Regional Hospital Gummersbach, (Dr Gregor), Gummersbach, Germany.

ACUTE AND CHRONIC WOUNDS affect at least 1% of the population.[1] Regardless of etiology, wounds are difficult to treat if coexisting factors (eg, infection or diabetes mellitus) prevent regular wound healing. Wounds represent a significant risk factor for hospitalization, amputation, sepsis, and even death, and from the patient's perspective, wound therapy is often uncomfortable or painful. Modern wound-healing concepts include different types of moist dressings and topical agents, although only a few of these treatments have convincingly been shown to give higher wound closure rates compared with traditional wet gauze dressings.[2-4]

Negative pressure wound therapy (NPWT), developed at Wake Forest University (Winston-Salem, North Carolina) in the early 1990s,[5,6] consists of an open-cell foam dressing covered with an adhesive drape. The dressing is connected to a vacuum pump that creates and maintains a subatmospheric pressure (intermittent or continuous). Positive effects of NPWT on wound healing have been demonstrated in basic science studies,[6,7] and many case reports and case series document broad use of NPWT in various clinical settings. Several thousand NPWT applications are performed each day worldwide, mostly in the United States. The most commonly used NPWT device is the vacuum-assisted closure device (Kinetic Concepts Inc [KCI], San Antonio, Texas). From 2003 to 2004, revenue for vacuum-assisted closure increased by 45% to $700 million.[8]

Clinical knowledge about the management of difficult-to-treat wounds is still limited owing to the lack of high-quality evidence.[9-12] During the past few years, many clinical trials have been initiated, and first results have been reported in leading journals. The aim of the present systematic review is to assess the clinical effectiveness and safety of NPWT vs conventional wound therapy regarding wound-healing variables, such as time to wound closure and other patient-relevant outcomes.

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 05/26/2016

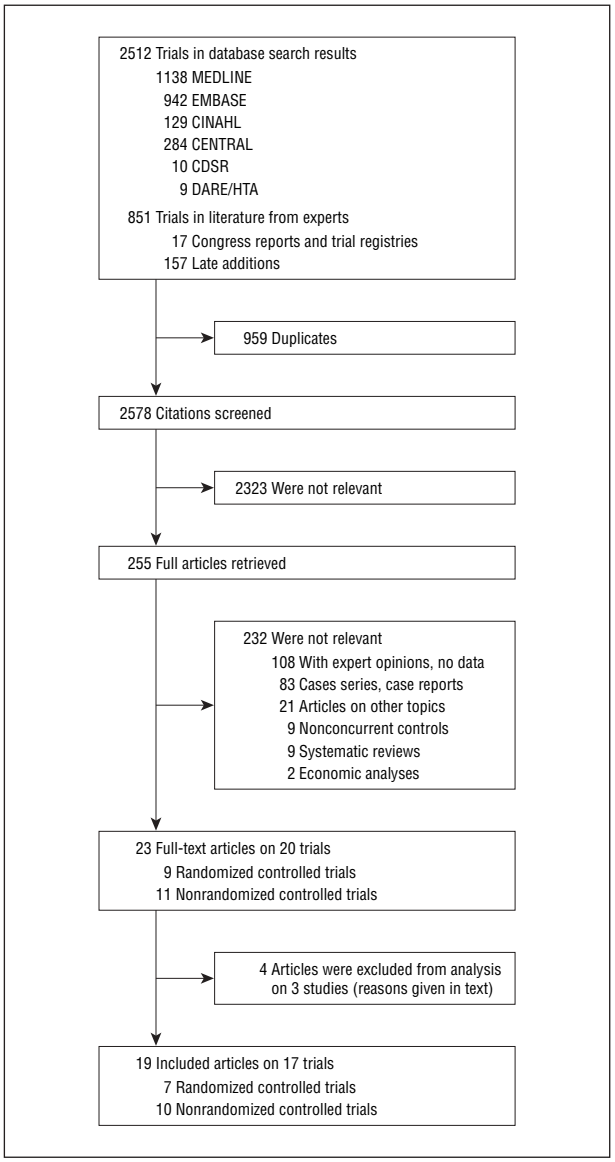

Figure 1. Flow diagram of trial selection. CDSR indicates Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; and HTA, Health Technology Assessment Database.

METHODS

SEARCH STRATEGY

Full-text articles relating to NPWT were searched for in MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials. Trial registries (http://clinicaltrials.gov and http://www.nrr.nhs.uk) were screened for ongoing trials. Search strategies were adapted and broadened according to the specific structure of each database to completely detect nonrandomized trials. In addition, systematic reviews were identified in the Cochrane Library by searching the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. All searches were last updated in October 2005. Furthermore, the US Food and Drug Administration (FDA), other health agencies, clinical experts, and the manufacturers of NPWT devices (KCI and Blue Sky Medical, La Costa, California) were asked to provide published and unpublished data. Detailed information about the search strategies is available on the Web site of the Institute for Quality and Efficiency in Health Care (http://www.iqwig.de).

SELECTION CRITERIA

Studies were considered eligible if they evaluated the effect of NPWT vs conventional wound therapy on wound healing. We included randomized controlled trials (RCTs) and non-RCTs if they had a concurrent control group. All abstracts were screened independently by 2 reviewers (S.G. and J.F.K.). Abstracts were excluded only if both investigators classified them as clearly not relevant or if they were not available as full-text articles. All languages were included. Potentially relevant articles in Chinese[13,14] and Russian[15] were translated by medically trained native speakers. Subsequently, all retrieved full-text articles were independently examined by 5 reviewers (all the authors except J.F.K.).

QUALITY ASSESSMENT AND DATA EXTRACTION

Eligible trials were assessed for their quality using standardized methods.[16] We evaluated each study regarding trial design (eg, allocation concealment, blinding of outcome evaluators, definition of primary end point, and sample size calculation) and trial conduct (eg, sample size included, withdrawals, quality of statistical analyses, and reporting of adverse effects). In addition, we determined the presence of any industrial sponsorship for each study. Data from the trials included were extracted using standardized forms and were summarized independently in tabular format by 2 reviewers (S.S. and F.P.). The authors of some publications were contacted to clarify inconsistencies in trial data, and when possible, the respective replies were included in this analysis.

STATISTICS

Meta-analyses for all primary outcomes were planned, but owing to the nature of the primary data, a meta-analysis was possible only for changes in wound size. We used a statistical software program (Review Manager 4.2; Cochrane Collaboration, Oxford, England) to summarize primary data from RCTs and non-RCTs. As a measure of effect, we calculated the standardized mean difference (SMD) from the difference in means divided by the pooled standard deviation. A random-effects model was used to pool data into a common estimate of SMD with 95% confidence intervals (95% CIs). Heterogeneity was quantified by I^2 in the 0% to 100% range. A formal analysis of publication bias was planned, but it later turned out to be impossible owing to the small number of studies available.

RESULTS

LITERATURE SEARCH

The literature search identified 2578 unique and potentially relevant citations (**Figure 1**). Of the 255 potentially relevant full articles, 23 (which described 20 trials) formed the primary focus. Three studies were excluded from further evaluation: in 1 RCT, incisional wounds after ankle surgery were studied, although such wounds can be sutured,[17] and in 2 studies, co-interventions (eg, use of bioartificial skin[18] or the technique of fracture fixation[19]) were different between treatment groups. Of the remaining studies, 7 (reported in 8 articles) were RCTs[20-27] and 10 were non-RCTs.[28-37]

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 05/26/2016

Table 1. Characteristics of Ongoing and Prematurely Terminated Randomized Controlled Trials

Source, Year of Trial Start, KCI ID	Type of Wounds	Control Treatment	Planned Sample Size, No.	Active Treatment Phase	Observation Period	Planned Publication Date	Current Status of Trial
Anonymous, 2001, VAC 2001-02	Venous stasis ulcers	Moist wound therapy	214	112 d	NA	June 2007[a]	Terminated early, unpublished
Adams et al, 1999[b]	Split-thickness skin graft donor sites	Semipermeable membrane dressings	NA	NA	NA	NA	Enrollment planned to end in 2002, unpublished
Armstrong et al, 2001, VAC 2001-08	Diabetic foot ulcers	Moist wound therapy	Initially 206, later 338	112 d	NA	December 2007	Ongoing, abstract on 46 patients published[c]
Bayer et al, 2002, VAC 2002-09	Sternal wound infection	Moist wound therapy	116	84 d	NA	February 2009[a]	Terminated early, unpublished
Foo et al	Diabetic foot ulcers	Moist gauze dressing	NA	Not given	NA	NA	Status unknown
Fryer et al, 2000	Pressure ulcers	Saline wet-to-moist dressings	120	Not given	NA	NA	Enrollment planned to end in 2001, unpublished
Greer et al, 1998	Pressure ulcers	Wet-to-moist dressings	160	NA	1 y	NA	Terminated after enrollment of 16 patients, unpublished
Gupta et al, 2001	Chronic infected wounds	Not given	NA	NA	NA	NA	Status unknown
Lantis et al	Split-thickness skin grafts	Moist wound therapy	NA	7 d	90 d	NA	Abstract on 12 patients published
McCarthy J, et al, 2005[d]	Leg fasciotomy	Wet-to-dry dressings	30	NA	NA	NA	Status unknown, unpublished
McCarthy M, et al, 2005[b]	Ischemic leg ulcers	Not given	NA	NA	NA	NA	Enrollment planned to end in 2006, unpublished
Molnar et al, 2001, VAC 2001-00	Hand burns	Silver sulfadiazine	50	48 h	NA	December 2005[a]	Ongoing, abstract on 23 patients published[c]
Niezgoda et al, 2001, VAC 2001-01[d]	Pressure ulcers	Moist wound therapy	Initially 258, later 330	84 d	NA	April 2008	Ongoing, abstract on 97 patients published[c]
Orgill et al, 2002, VAC 2002-10	Open abdominal wounds	Moist wound therapy	116	84 d	NA	March 2006[a]	Terminated early, abstract on 30 patients published[d]
Stannard et al, 2001, VAC 2001-04[e]	Hematoma	Pressure dressings	258	10 d	NA	August 2007[a]	Ongoing, abstract on 59 patients published[c]
Stannard et al, 2001, VAC 2001-05[e]	High-risk fractures	Standard postoperative dressings	348	NA	Until drainage volume reduced	December 2007	Ongoing, abstract on 90 patients published[c]
Stannard et al, 2001, VAC 2001-06	Open fractures	Saline-soaked fine mesh gauze	300	Until completed wound healing	Until wound closure or infection	December 2007	Terminated early, abstract on 27 patients published[c]
Vuerstaek et al, VAC 2001-2005	Chronic leg ulcers	Conventional wound care	60	Until completed wound healing	1 y	July 2006	Ongoing, abstract on 60 patients published[c]
Walker et al, 1998[b]	NA	Standard wound drainage (Medinorm)	48	NA	NA	NA	Enrollment planned to end in 2000, unpublished

Abbreviation: KCI, Kinetic Concepts Inc; NA, not available.
[a] Estimated date of publication at the start of the trial.
[b] Registered at the UK National Research Register (N0084029434 for Walker, N02345095365 for Adams, and N0123138623 for McCarthy).
[c] Abstract presented at the Second World Union Wound Healing Societies' Meeting; July 8-13, 2004; Paris, France.
[d] Registered at ClinicalTrials.gov (Identifiers NCT00121537 for McCarthy and NCT00234559 for Niezgoda).
[e] Preliminary results of these trials have now been published.[38]

According to information from study registries, authors of publications, and the manufacturer (KCI), a further 19 trials were currently ongoing (n=7), completed but not published (n=3), or prematurely terminated (n=5); the status of 4 trials was unknown[38] (**Table 1**). Reasons for premature termination of trials included slow enrollment, high attrition rates, changes in clinical practice, and design flaws (KCI, written communication, August 19, 2005); none of the results of these 5 trials have been published to date.

Results were reported for 667 wounds in 602 patients (324 in RCTs and 278 in non-RCTs (**Table 2**). The overall methodologic quality of the trials was poor. Only 1 of the RCTs clearly described concealment of al-

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 05/26/2016

Table 2. Characteristics of Included Trials

Source	Design	Centers, No.	Type of Wounds	No. of Patients/ Wounds	Observation Period[a]	Blinding (Evaluator)	Sample Size Calculation, ITT	Dropouts, No.
			Randomized Controlled Trials (n = 7)					
Armstrong and Lavery,[20] 2005	Parallel	18	Diabetic foot amputations	162/162	16 wk	No	Yes, unclear	38
Eginton et al,[21] 2003	Crossover	2	Chronic diabetic wounds	10/11	2 wk[b]	Yes	No, no	4
Ford et al,[22] 2002	Parallel	1	Pressure ulcers	28/41	3-10 mo	Yes	No, no	6
Joseph et al,[26] 2000	Parallel	1	Chronic wounds	24/36	Up to 10 wk	Yes	No, unclear	Unclear
Moisidis et al,[25] 2004	Parallel, intraindividual	1	Skin grafts	22/22	2 wk	Yes	No, no	2
Mouës et al,[23] 2004	Parallel	1	Open wounds	54/54	Up to 1 mo	No	Unclear, no	26
Wanner et al,[27] 2003	Parallel	1	Pressure ulcers	24/24	Up to 8 wk	No	No, no	2
			Nonrandomized Controlled Trials (n = 10)					
Doss et al,[28] 2002	Parallel, retrospective	1	Infected sternotomy	42/42	5 wk[c]	No	NA, no	0
Etöz et al,[37] 2004	Parallel, pseudorandomized, prospective	1	Chronic diabetic wounds	24/24	4-24 d	No	NA, yes	0
Genecov et al,[29] 1998	Parallel, intraindividual, prospective	1	Skin graft donor sites	15/30	1 wk	Yes	NA, no	5
Kamolz et al,[30] 2004	Parallel, intraindividual, prospective	1	Acute burns	7/14	3 d	No	NA, yes	0
McCallon et al,[36] 2000	Parallel, pseudorandomized, prospective	1	Chronic diabetic wounds	10/10	1-13 wk	No	NA, yes	0
Page et al,[31] 2004	Parallel, retrospective	1	Foot wounds	47/47	1 y	No	NA, no	Unclear
Scherer et al,[32] 2002	Parallel, retrospective	1	Skin grafts	61/61	1-13 wk	No	NA, no	0
Schrank et al,[33] 2004	Parallel, intraindividual, prospective	1	Acute burns	11/22	Unknown	No	NA, unclear	0
Stone et al,[34] 2004	Parallel, retrospective	1	Skin grafts	40/46	5-41 d	No	NA, unclear	Unclear
Wild et al,[35] 2004	Parallel, retrospective	1	Open abdomen	21/21	42-65 d	No	NA, unclear	0

Abbreviations: ITT, intention to treat; NA, not applicable.
[a] Time for treatment and follow-up. If different times were reported, specification as range.
[b] Per sequence.
[c] Information provided by study authors.

location.[39] Blinding of outcome evaluation was performed in 5 studies.[21,22,25,26,29] Intention-to-treat analyses were explicitly described in 3 studies[30,36,37] and could be assumed in 6 further studies.[20,23,26,33-35] Sample size calculation was reported in only 1 trial.[20] In that trial, the primary end point was changed to comply with FDA recommendations. In 3 trials,[21,22,26] data originating from different wounds in the same patient were analyzed using standard statistics without controlling for the dependence between wounds. Study duration varied from 3 days to 1 year.

CLINICAL RESULTS

Wound closure (secondary healing or surgical closure) was described as the incidence of complete wound closure in 2 studies[20,22] and as the time to wound closure (complete or incomplete) in 7 studies[23,26-28,31,36,37] (**Table 3**). Only 2 of the 5 RCTs[20,26] and 2 of the 4 non-RCTs[28,37] reported a significant advantage in favor of NPWT. Owing to the heterogeneity of results and the different outcome definitions used, no meta-analysis was performed.

Eight studies[21-23,26-28,36,37] (5 RCTs and 3 non-RCTs) analyzed changes in wound size, measured as either wound volume or wound area (**Table 4**). Two of these studies had to be excluded from the meta-analysis: 1 non-RCT[28] failed to report measures of variability, and an RCT[21] had a crossover design. Pooled data showed a significant reduction in wound size in favor of NPWT (RCTs: SMD, –0.57; 95% CI, –0.94 to –0.20; non-RCTs: SMD, –1.30; 95% CI, –2.07 to –0.54) (**Figure 2**). Heterogeneity, as quantified using the I^2 statistic, was 0%. One RCT[20] presented detailed information on the generation of granulation tissue and reported a significantly faster rate in patients treated with NPWT.

All 3 studies[25,29,32] on the use of NPWT in patients with skin grafts found similar take rates. Repeated operations after skin grafting were reported significantly less often in the NPWT group in 1 non-RCT.[32] Of the 4 studies[22,30,36,37] reporting methods of surgical wound clo-

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 05/26/2016

Table 3. Incidence of Wound Closure and Time to Wound Closure

Source	Definition of Outcome Criterion (Unit)	NPWT, Mean (SD/Sample Size)	Control, Mean (SD/Sample Size)	Significance Reported
	Randomized Controlled Trials (n = 5)			
Armstrong and Lavery,[20] 2005	Complete or surgical closure within 16 wk (No. of patients)	43 (NA/77)	33 (NA/85)	.04
	Complete nonsurgical closure within 16 wk (No. of patients)	31 (NA/77)	25 (NA/85)	NA[a]
Ford et al,[22] 2002	Successful secondary wound healing within 6 wk (No. of patients)	2 (NA/20)	2 (NA/15)	NA
	Surgical closure with flap surgery (No. of patients)	6 (NA/20)	6 (NA/15)	NA
Joseph et al,[26] 2000	Time to 90% change of wound volume as estimated from the Kaplan-Meier curve (days)	45 (NA/18)[b]	56 (NA/18)[b]	.04
Mouës et al,[23] 2004	Time to possibility of surgical closure in Kaplan-Meier analysis (days)	6 (NA/29)[b,c]	7 (NA/25)[b,c]	.19
Wanner et al,[27] 2003	Time to 50% reduction of wound volume (days)	27 (10/11)	28 (7/11)	"No time benefit"
	Nonrandomized Controlled Trials (n = 4)			
Doss et al,[28] 2002	Time to surgical closure (days)	17.2 (5.8/20)	22.9 (10.8/22)	.009
Etöz et al,[37] 2004	Time to surgical closure (days)	11.25 (5.5/12)	15.75 (2.5/12)	.05
McCallon et al,[36] 2000	Time to surgical closure or secondary wound healing (days)	22.8 (17.4/5)	42.8 (32.5/5)	No data
Page et al,[31] 2004	Time to secondary wound healing in Kaplan-Meier analysis (days)	110[b] (79-184[d]/22)	124[b] (105-284[d]/25)	"Not significant"

Abbreviations: NPWT, negative pressure wound therapy; NA, not available or not applicable.
[a] Difference is not significant, with $P = .19$ in the Fisher exact test (own calculation).
[b] Data are medians.
[c] Data were derived from Figure 1 of the cited article. We assumed that figure legends had been interchanged because the text of the article suggests an advantage for NPWT.
[d] Data on variation are 95% confidence intervals.

Table 4. Changes in Wound Size

Source	Definition of Outcome Criterion and Time of Measurement (Unit)	Blinded Assessment	NPWT, Mean (SD/Sample Size)	Control, Mean (SD/Sample Size)	Significance Reported
	Randomized Controlled Trials (n = 5)				
Eginton et al,[21] 2003	Relative change in wound volume after 2 wk	Yes	−59.0% (9.7/7)	−0.1% (14.7/7)	.005
	Relative change in wound area after 2 wk	Yes	−16.4% (6.2/7)	5.9% (17.4/7)	"Not significant"
Ford et al,[22] 2002	Relative change in wound volume after 6 wk	Yes	−51.8% (38/20)[a]	−42.1% (38/15)[a]	.46
Joseph et al,[26] 2000	Relative change in wound volume after 6 wk	Yes	−78%[b] (72/18)[a]	−30%[b] (61/18)[a]	.04
Mouës et al,[23] 2004	Relative change in wound area per day	No	−3.8% (1.9/15)	−1.7% (2.2/13)	<.05
Wanner et al,[27] 2003	Relative change in wound volume after 2 wk	No	−25% (26/11)[c]	−14% (30/11)[c]	Not given
	Nonrandomized Controlled Trials (n = 3)				
Doss et al,[28] 2002	Change in wound area per day (cm^2)	No	−4.6 (No data/20)	−3.2 (No data/22)	Not given
Etöz et al,[37] 2004	Change in wound area until surgical closure (cm^2)	No	−20.5 (11.9/12)[d]	−9.5 (4.1/12)	.03
McCallon et al,[36] 2000	Relative change in wound area until surgical closure or hospital discharge	No	−28.4% (24.3/5)	9.5% (16.9/5)	Not given

Abbreviation: NPWT, negative pressure wound therapy.
[a] The SD was calculated from the P value.
[b] Data were taken from the text of the cited article; data in Figure 5 are slightly different (NPWT vs control, 47% vs 39%).
[c] Data were taken from Figure 3 of the cited article; data in Figure 4 are slightly different (NPWT vs control, 27% vs 10%).
[d] Data were calculated from raw data shown in Table 1 of the cited article.

sure, none found closure to be easier in the NPWT group. The only study[20] to analyze differences between treatment groups for repeated amputation rates noted a (nonsignificant) reduction in favor of NPWT. Adverse event rates were similar between NPWT and conventional therapy in 7 studies,[20-22,29,32,34,37] whereas 2 studies[26,31] reported fewer complications when using NPWT. In 1 RCT,[20] infections were more common in patients treated

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 05/26/2016

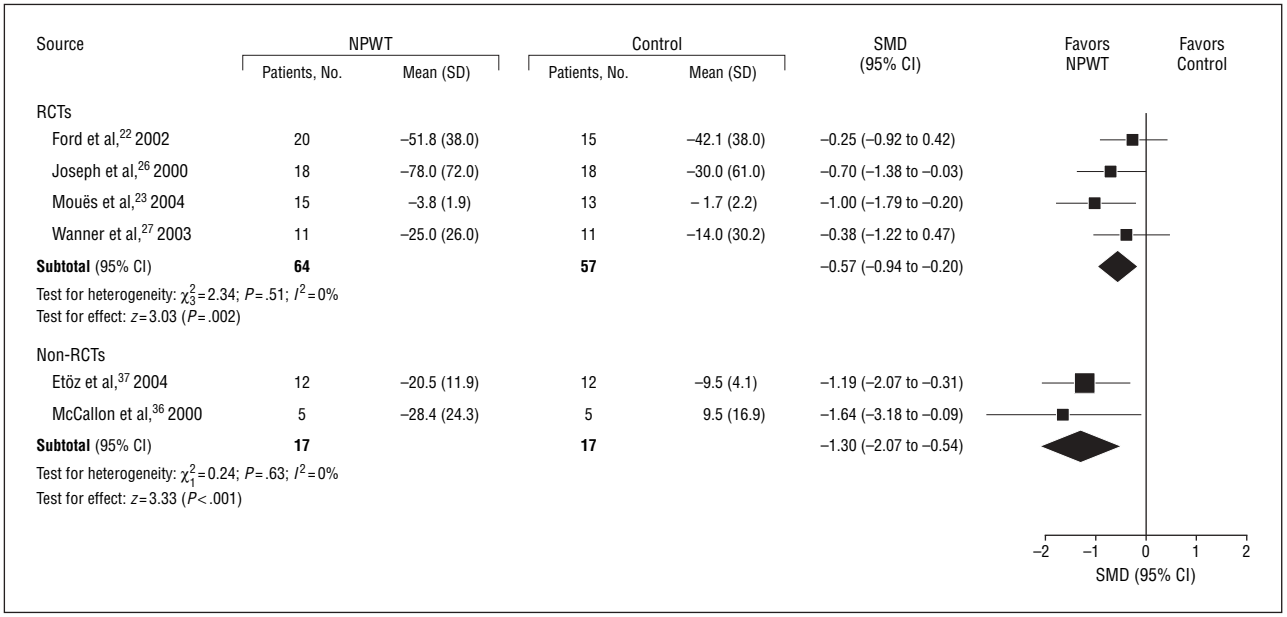

Figure 2. Effects of negative pressure wound therapy (NPWT) vs conventional wound therapy on changes in wound size: random-effects model of standardized mean differences (SMDs) (95% confidence intervals [CIs]). RCT indicates randomized controlled trial.

with NPWT. Pain was not measured in a standardized manner in any study. Mortality was reduced significantly in the NPWT group in 1 non-RCT[35] in patients with an open abdomen. Hospital stay was shortened by NPWT in 1 non-RCT[28] but was similar in 4 other non-RCTs.[31,32,34,35] An economic analysis was performed in 1 RCT,[24] yielding similar overall costs for NPWT and conventional therapy.

COMMENT

The results of this systematic review show that clinical evidence on NPWT consists of only a few small trials of insufficient methodologic quality. Results in favor of NPWT were seen for surrogate variables of wound healing, such as reduction in wound size and formation of granulation tissue. However, although this may facilitate surgical closure, according to the FDA, only "complete wound closure . . . is one of the most objective and clinically meaningful wound healing endpoints" and "the clinical benefit of incremental wound size changes has not been established."[37 (p12)] The FDA also noted that a claim of facilitation of surgical closure by an NPWT device should be supported by adequately designed trials to evaluate complete wound closure after application of the surgical graft.[40] Furthermore, a recent RCT[41] (published after completion of the literature search for this review) reported that NPWT did not result in significantly faster granulation or wound surface reduction compared with modern wound dressings.

Some patient-relevant outcomes, such as a reduction in repeated operations after skin grafting, also indicated a more favorable effect of NPWT. However, data were scarce, and these findings should be interpreted with caution owing to various methodologic flaws in the trials analyzed.

In clinical practice, NPWT has enormous importance, and it is therefore disappointing that the total number of studies, their sample size, and their quality are inadequate. The total number of patients included in this review was 602, which contrasts sharply with the thousands of NPWT applications performed each day worldwide. This problem of lack of research also affects many other wound therapies,[2,42,43] probably because wound healing represents a complex and heterogeneous scientific problem. Owing to the large number of still unpublished trials and especially the unreported early termination of trials, the potential for publication bias is high. Our decision not to include abstract publications and confidential study reports complies with current recommendations.[44,45]

Two comprehensive systematic reviews on NPWT were published in 2003 and 2004.[9,10] A strength of the present review lies in the substantial amount of further evidence that could be included, thus doubling the number of patients recruited into RCTs. Furthermore, we included non-RCTs to avoid overselective attention to RCTs. As a result of the highly sensitive search strategy, it seems unlikely that any pertinent article was missed. We excluded 1 of the trials included in the Cochrane 2001 review on NPWT[46] because this article[15] did not mention any specific elements of NPWT and apparently dealt with simple suction wound drainage.

Owing to its size (162 patients, which is similar to the total number of patients included in the other 6 RCTs) and high quality demands, the trial by Armstrong and Lavery[20] is of special importance. Although it was published in a journal that endorses the CONSORT statement,[47] the publication lacked a clear description of methodologic details, such as concealment of allocation, sufficiently detailed reasons for losses to follow-up, and definition of outcome criteria.[48] Only the first of these issues could be fully clarified by the authors.[39] We also received a written statement from KCI noting that the study's primary end point had

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 05/26/2016

been changed during recruitment to comply with FDA recommendations.[40] Different definitions of the primary end point (complete wound closure including or excluding surgical wound closure) affected the significance of the overall results.

The inclusion of non-RCTs in this review may be criticized. Although the existence of RCTs on wound-healing devices shows that these trials can be conducted, one must acknowledge that, for a variety of reasons, they are more difficult to implement than clinical drug trials. Some experts in the field of wound healing have emphasized that randomized trials on NPWT may be unnecessary and even unethical given the large effects observed in uncontrolled studies.[49] Our decision to include nonrandomized studies with a concurrent control group, therefore, strikes a fair balance between the scientifically sound evaluation of a therapy and the clinical problems of performing the studies necessary for such an evaluation. It seems unwarranted to include studies with nonconcurrent controls.[50] One should also note that NPWT may have striking benefits in some rare diseases (eg, complex reconstructions in plastic surgery), for which it may be impossible to conduct RCTs.

The clinical and economic importance of NPWT has increased tremendously in recent years because NPWT is an innovative and commercially successful concept for the management of difficult-to-treat wounds of nearly every etiology. In addition to worldwide marketing, the most important reasons for the success of NPWT are probably its assumed safety and the facilitation of wound care; for example, in patients with large or heavily secreting wounds.[51] In general, conventional dressings require more frequent changing, which may result in increases in nursing interventions, discomfort for patients, and length of hospital stay. A recent publication[41] that includes health economic data reported advantages of NPWT in wound care; NPWT yielded significantly lower nursing staff costs and less time involvement than treatment with modern wound dressings. The overall costs for treatment groups were similar. It was also noted that "many" patients reported that NPWT was more comfortable than previous dressings (eg, owing to fewer dressing changes and less odor), but detailed data were not provided.[41] The manufacturers of NPWT devices are currently emphasizing the safety and applicability of NPWT in ambulatory settings; however, the data identified in the present review are insufficient to make any statements on the use of NPWT in outpatients.

In summary, many patients have been treated with NPWT, but the present body of evidence is small and insufficient to clearly prove an additional clinical benefit of NPWT compared with conventional wound therapy. However, the absence of evidence does not prove the absence of effectiveness,[52] and there are signs of a clinical benefit of NPWT, which should be confirmed in well-designed trials. To date, industrial, medical, and governmental institutions have not initialized adequate and timely research to verify the assumed effects of NPWT. Therefore, physicians and health policymakers should reconsider the widespread use of NPWT outside the setting of clinical trials until better evidence is available.

Accepted for Publication: October 15, 2006.
Correspondence: Stefan Sauerland, MD, MPH, Institute for Research in Operative Medicine, University of Witten/Herdecke, Ostmerheimer Str 200, 51109 Cologne, Germany (Stefan.Sauerland@ifom-uni-wh.de).
Author Contributions: *Study concept and design:* Gregor, Sauerland, Peinemann, and Lange. *Acquisition of data:* Gregor, Sauerland, and Krahn. *Analysis and interpretation of data:* Gregor, Maegele, Sauerland, Krahn, Peinemann, and Lange. *Drafting of the manuscript:* Gregor and Sauerland. *Critical revision of the manuscript for important intellectual content:* Maegele, Krahn, Peinemann, and Lange. *Statistical analysis:* Gregor, Sauerland, and Krahn. *Administrative, technical, and material support:* Krahn, Peinemann, and Lange. *Study supervision:* Sauerland, Peinemann, and Lange.
Financial Disclosure: None reported.
Funding/Support: The work was supported by the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG]). The IQWiG is an independent nonprofit and nongovernment scientific institute that receives commissions from the Federal Joint Committee and the German Ministry of Health.
Role of the Sponsor: This work was commissioned by the German Federal Joint Committee (legislative institution of the German health care self-administration system) to support decision making on the reimbursement of NPWT by the German statutory health insurance funds.
Additional Information: The full report (in German) is available on the IQWiG Web site (http://www.iqwig.de). Since the acceptance of this article, 2 additional RCTs were published: Llanos S, Danilla S, Barraza C, et al. Effectiveness of negative pressure closure in the integration of split thickness skin grafts: a randomized, double-masked, controlled trial. *Ann Surg.* 2006;244(5):700-705; Vuerstaek JDD, Vainas T, Wuite J, Nelemans P, Neumann MHA, Veraart JCJM. State-of-the-art treatment of chronic leg ulcers: a randomized controlled trial comparing vacuum-assisted closure (VAC) with modern wound dressings. *J Vasc Surg.* 2006;44(5):1029-1037. In our view, however, the conclusions of this article remain unchanged.
Additional Contributions: Natalie McGauran provided skillful assistance in finalizing the manuscript.

REFERENCES

1. Graham ID, Harrison MB, Nelson EA, Lorimer K, Fisher A. Prevalence of lower-limb ulceration: a systematic review of prevalence studies. *Adv Skin Wound Care.* 2003;16(6):305-316.
2. Vermeulen H, Ubbink DT, Goossens A, de Vos R, Legemate DA. Systematic review of dressings and topical agents for surgical wounds healing by secondary intention. *Br J Surg.* 2005;92(6):665-672.
3. Singh A, Halder S, Menon GR, et al. Meta-analysis of randomized controlled trials on hydrocolloid occlusive dressing versus conventional gauze dressing in the healing of chronic wounds. *Asian J Surg.* 2004;27(4):326-332.
4. Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. *Nature.* 1962;193:293-294.
5. Argenta LC, Morykwas MJ. Vacuum-assisted closure: a new method for wound control and treatment: clinical experience. *Ann Plast Surg.* 1997;38(6):563-577.
6. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W. Vacuum-assisted clo-

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 05/26/2016

sure: a new method for wound control and treatment: animal studies and basic foundation. *Ann Plast Surg*. 1997;38(6):553-562.
7. Morykwas MJ, Faler BJ, Pearce DJ, Argenta LC. Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine. *Ann Plast Surg*. 2001;47(5):547-551.
8. Kinetic Concepts Inc. Annual report 2004: changing the standard of healing. http://library.corporate-ir.net/library/64/645/64595/items/148610/KCIAnnualReport.pdf. Accessed September 27, 2006.
9. Samson DJ, Lefevre F, Aronson N. *Wound Healing Technologies: Low Level Laser and Vacuum-Assisted Closure*. Rockville, MD: Agency for Healthcare Research and Quality; 2004. AHRQ publication 05-E005-2.
10. Pham C, Middleton P, Maddern G. *Vacuum-Assisted Closure for the Management of Wounds: An Accelerated Systematic Review*. Adelaide: Australian Safety and Efficacy Register of New Interventional Procedures-Surgical; 2003. ASERNIP-S Report No. 37.
11. Fisher A, Brady B. Vacuum assisted wound closure therapy. *Issues Emerg Health Technol*. 2003;Mar(44):1-6.
12. Medical Advisory Secretariat; Ontario Health Technology Advisory Committee. *Vacuum Assisted Closure Therapy for Wound Closure*. Toronto, Ontario: Ontario Ministry of Health and Long-term Care; 2004.
13. Sun S, Yao Y, Li Y, Huang X, Ma X, Jinag Y. Mechanism and curative effect of vacuum sealing technique in treatment of wide chronic ulcer in the lower limbs in 24 cases [in Chinese]. *Zhongguo Linchiuang Kangfu*. 2003;7:577-578.
14. Yao YZ, Huang XK, Ma XL. Treatment of traumatic soft tissue defect by vacuum sealing [in Chinese]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2002;16(6):388-390.
15. Davydov YA, Abramov AY, Darichev AB. Regulation of wound process by the method of vacuum therapy in middle-aged and aged patients [in Russian]. *Khirurgiia (Mosk)*. 1994;(9):7-10.
16. IQWiG Steering Committee. Methods (version 1.0). http://www.iqwig.de/download/Methoden_IQWiG_V-1-0.pdf. Accessed September 27, 2006.
17. Buttenschön K, Fleischmann W, Haupt U, Kinzl L, Buttenschön DC. The influence of vacuum-assisted closure on inflammatory tissue reactions in the postoperative course of ankle fractures. *Foot Ankle Surg*. 2001;7:165-173.
18. Jeschke MG, Rose C, Angele P, Fuchtmeier B, Nerlich MN, Bolder U. Development of new reconstructive techniques: use of Integra in combination with fibrin glue and negative-pressure therapy for reconstruction of acute and chronic wounds. *Plast Reconstr Surg*. 2004;113(2):525-530.
19. Huang J, Yao YZ, Huang XK. Treatment of open fracture by vacuum sealing technique and internal fixation [in Chinese]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2003;17(6):456-458.
20. Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet*. 2005;366(9498):1704-1710.
21. Eginton MT, Brown KR, Seabrook GR, Towne JB, Cambria RA. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. *Ann Vasc Surg*. 2003;17(6):645-649.
22. Ford CN, Reinhard ER, Yeh D, et al. Interim analysis of a prospective, randomized trial of vacuum-assisted closure versus the healthpoint system in the management of pressure ulcers. *Ann Plast Surg*. 2002;49(1):55-61.
23. Mouës CM, Vos MC, van den Bemd GJ, Stijnen T, Hovius SE. Bacterial load in relation to vacuum-assisted closure wound therapy: a prospective randomized trial. *Wound Repair Regen*. 2004;12(1):11-17.
24. Mouës CM, van den Bemd GJ, Meerding WJ, Hovius SE. An economic evaluation of the use of TNP on full-thickness wounds. *J Wound Care*. 2005;14(5):224-227.
25. Moisidis E, Heath T, Boorer C, Ho K, Deva AK. A prospective, blinded, randomized, controlled clinical trial of topical negative pressure use in skin grafting. *Plast Reconstr Surg*. 2004;114(4):917-922.
26. Joseph E, Hamori CA, Bergman S, Roaf E, Swann NF, Anastasi GW. A prospective randomized trial of vacuum-assisted closure versus standard therapy of chronic nonhealing wounds. *Wounds*. 2000;12(3):60-67.
27. Wanner MB, Schwarzl F, Strub B, Zaech GA, Pierer G. Vacuum-assisted wound closure for cheaper and more comfortable healing of pressure sores: a prospective study. *Scand J Plast Reconstr Surg Hand Surg*. 2003;37(1):28-33.
28. Doss M, Martens S, Wood JP, Wolff JD, Baier C, Moritz A. Vacuum-assisted suction drainage versus conventional treatment in the management of poststernotomy osteomyelitis. *Eur J Cardiothorac Surg*. 2002;22(6):934-938.
29. Genecov DG, Schneider AM, Morykwas MJ, Parker D, White WL, Argenta LC. A controlled subatmospheric pressure dressing increases the rate of skin graft donor site reepithelialization. *Ann Plast Surg*. 1998;40(3):219-225.
30. Kamolz LP, Andel H, Haslik W, Winter W, Meissl G, Frey M. Use of subatmospheric pressure therapy to prevent burn wound progression in human: first experiences. *Burns*. 2004;30(3):253-258.
31. Page JC, Newswander B, Schwenke DC, Hansen M, Ferguson J. Retrospective analysis of negative pressure wound therapy in open foot wounds with significant soft tissue defects. *Adv Skin Wound Care*. 2004;17(7):354-364.
32. Scherer LA, Shiver S, Chang M, Meredith JW, Owings JT. The vacuum assisted closure device: a method of securing skin grafts and improving graft survival. *Arch Surg*. 2002;137(8):930-934.
33. Schrank C, Mayr M, Overesch M, et al. Results of vacuum therapy (V.A.C.) of superficial and deep dermal burns [in German]. *Zentralbl Chir*. 2004;129(suppl 1):S59-S61.
34. Stone P, Prigozen J, Hofeldt M, Hass S, DeLuca J, Flaherty S. Bolster versus negative pressure wound therapy for securing split-thickness skin grafts in trauma patients. *Wounds*. 2004;16(7):219-223.
35. Wild T, Stremitzer S, Budzanowski A, et al. "Abdominal dressing:" a new method of treatment for open abdomen following secondary peritonitis [in German]. *Zentralbl Chir*. 2004;129(suppl 1):S20-S23.
36. McCallon SK, Knight CA, Valiulus JP, Cunningham MW, McCulloch JM, Farinas LP. Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds. *Ostomy Wound Manage*. 2000;46(8):28-32, 34.
37. Etöz A, Özgenel Y, Özcan M. The use of negative pressure wound therapy on diabetic foot ulcers: a preliminary controlled trial. *Wounds*. 2004;16(8):264-269.
38. Stannard JP, Robinson JT, Anderson ER, McGwin G Jr, Volgas DA, Alonso JE. Negative pressure wound therapy to treat hematomas and surgical incisions following high-energy trauma. *J Trauma*. 2006;60(6):1301-1306.
39. Armstrong DG, Lavery LA. Negative pressure therapy in diabetic foot wounds [authors' reply]. *Lancet*. 2006;367(9512):726-727.
40. US Department of Health and Human Services; Food and Drug Administration, Center for Biologic Evaluation and Research (CBER), Center for Devices and Radiologic Health (CDRH), Center for Drug Evaluation and Research (CDER). Guidance for industry: chronic cutaneous ulcer and burn wounds: developing products for treatment. http://www.fda.gov/Cber/gdlns/ulcburn.htm. Accessed September 27, 2006.
41. Braakenburg A, Obdeijn MC, Feitz R, van Rooij IALM, van Griethuysen AJ, Klinkenbijl JHG. The clinical efficacy and cost effectiveness of the vacuum-assisted closure technique in the management of acute and chronic wounds: a randomized controlled trial. *Plast Reconstr Surg*. 2006;118(2):390-400.
42. Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention. *Health Technol Assess*. 2001;5(14):1-131.
43. Dinah F, Adhikari A. Gauze packing of open surgical wounds: empirical or evidence-based practice? *Ann R Coll Surg Engl*. 2006;88(1):33-36.
44. Cook DJ, Guyatt GH, Ryan G, et al. Should unpublished data be included in meta-analyses? current convictions and controversies. *JAMA*. 1993;269(21):2749-2753.
45. Eysenbach G, Tuische J, Diepgen TL. Evaluation of the usefulness of Internet searches to identify unpublished clinical trials for systematic reviews. *Med Inform Internet Med*. 2001;26(3):203-218.
46. Evans D, Land L. Topical negative pressure for treating chronic wounds. *Cochrane Database Syst Rev*. 2001;1(1):CD001898.
47. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA*. 2001;285(15):1987-1991.
48. Maegele M, Gregor S, Peinemann F, Sauerland S. Negative pressure therapy in diabetic foot wounds. *Lancet*. 2006;367(9512):725-726.
49. Willy C, ed. *Vacuum Therapy: Basics, Indications, Case Reports, Practical Hints* [in German]. Altusried-Krugzell, Germany: Kösel GmbH & Co KG; 2005.
50. Sacks H, Chalmers TC, Smith H Jr. Randomized versus historical controls for clinical trials. *Am J Med*. 1982;72(2):233-240.
51. Maegele M, Gregor S, Steinhausen E, et al. The long-distance tertiary air transfer and care of tsunami victims: injury pattern and microbiological and psychological aspects. *Crit Care Med*. 2005;33(5):1136-1140.
52. Altman DG, Bland JM. Absence of evidence is not evidence of absence. *BMJ*. 1995;311(7003):485.

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 05/26/2016