Negative Pressure Wound Therapy

A Vacuum of Evidence?

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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 In addition, 19 unpublished trials were found, of which 5 had been prematurely terminated.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 The large number of prematurely terminated and unpublished trials is reason for concern.

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A CUTE 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.
### 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).

### QUALITY ASSESSMENT AND DATA EXTRACTION

Eligible trials were assessed for their quality using standardized methods. 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

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, and in 2 studies, co-interventions (eg, use of bioartificial skin or the technique of fracture fixation) were different between treatment groups. Of the remaining studies, 7 (reported in 8 articles) were RCTs and 10 were non-RCTs.28-37

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**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.
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 (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 allocation, 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.  

<table>
<thead>
<tr>
<th>Source, Year of Trial Start, KCI ID</th>
<th>Type of Wounds</th>
<th>Control Treatment</th>
<th>Planned Sample Size, No.</th>
<th>Active Treatment Phase</th>
<th>Observation Period</th>
<th>Planned Publication Date</th>
<th>Current Status of Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams et al, 1999²</td>
<td>Split-thickness skin graft donor sites</td>
<td>Moist wound therapy</td>
<td>Initially 206, later 338</td>
<td>112 d</td>
<td>NA</td>
<td>December 2007</td>
<td>Ongoing, abstract on 46 patients published³</td>
</tr>
<tr>
<td>Armstrong et al, 2001, VAC 2001-08</td>
<td>Diabetic foot ulcers</td>
<td>Moist wound therapy</td>
<td>Initially 206, later 338</td>
<td>112 d</td>
<td>NA</td>
<td>October 2007</td>
<td>Ongoing, abstract on 46 patients published³</td>
</tr>
<tr>
<td>Bayer et al, 2002, VAC 2002-09</td>
<td>Sternal wound infection</td>
<td>Moist wound therapy</td>
<td>116</td>
<td>84 d</td>
<td>NA</td>
<td>February 2009</td>
<td>Terminated early, unpublished Status unknown</td>
</tr>
<tr>
<td>Foo et al</td>
<td>Diabetic foot ulcers</td>
<td>Moist wound therapy</td>
<td>116</td>
<td>84 d</td>
<td>NA</td>
<td>November 2009</td>
<td>Terminated early, unpublished</td>
</tr>
<tr>
<td>Fryer et al, 2000</td>
<td>Pressure ulcers</td>
<td>Saline wet-to-moist dressings</td>
<td>120</td>
<td>Not given</td>
<td>NA</td>
<td>November 2000</td>
<td>Enrollment planned to end in 2001, unpublished</td>
</tr>
<tr>
<td>Greer et al, 1998</td>
<td>Pressure ulcers</td>
<td>Wet-to-moist dressings</td>
<td>160</td>
<td>NA 1 y</td>
<td>NA</td>
<td>Terminated after enrollment of 16 patients, unpublished</td>
<td></td>
</tr>
<tr>
<td>Gupta et al, 2001</td>
<td>Chronic infected wounds</td>
<td>Not given</td>
<td>NA</td>
<td>NA 7 d</td>
<td>90 d</td>
<td>NA</td>
<td>Status unknown</td>
</tr>
<tr>
<td>Lantis et al</td>
<td>Split-thickness skin grafts</td>
<td>Moist wound therapy</td>
<td>NA</td>
<td>Not given</td>
<td>214</td>
<td>Not given</td>
<td>Enrollment planned to end in 2005, unpublished</td>
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<tr>
<td>McCarthy J, et al, 2005²</td>
<td>Leg fasciotomy</td>
<td>Moist wound therapy</td>
<td>NA</td>
<td>NA 7 d</td>
<td>90 d</td>
<td>NA</td>
<td>Status unknown</td>
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<tr>
<td>McCarthy M, et al, 2005⁶</td>
<td>Ischemic leg ulcers</td>
<td>Moist wound therapy</td>
<td>NA</td>
<td>NA 7 d</td>
<td>90 d</td>
<td>NA</td>
<td>Status unknown</td>
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<tr>
<td>Niezgoda et al, 2001, VAC 2001-01</td>
<td>Pressure ulcers</td>
<td>Moist wound therapy</td>
<td>Initially 258, later 330</td>
<td>84 d</td>
<td>NA</td>
<td>April 2008</td>
<td>Ongoing, abstract on 97 patients published</td>
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<tr>
<td>Orgill et al, 2002, VAC 2002-10</td>
<td>Open abdominal wounds</td>
<td>Moist wound therapy</td>
<td>116</td>
<td>84 d</td>
<td>NA</td>
<td>March 2006</td>
<td>Terminated early, abstract on 30 patients published⁶</td>
</tr>
<tr>
<td>Stannard et al, 2001, VAC 2001-00</td>
<td>Hematoma</td>
<td>Pressure dressings</td>
<td>258</td>
<td>10 d</td>
<td>NA</td>
<td>August 2007</td>
<td>Ongoing, abstract on 59 patients published</td>
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<tr>
<td>Stannard et al, 2001, VAC 2001-05</td>
<td>Open fractures</td>
<td>Saline-soaked fine mesh gauze</td>
<td>300</td>
<td>Until completed wound healing</td>
<td>Until wound closure or infection</td>
<td>December 2007</td>
<td>Terminated early, abstract on 27 patients published</td>
</tr>
<tr>
<td>Vuerstaek et al, 2001, VAC 2001-05</td>
<td>Chronic leg ulcers</td>
<td>Standard wound drainage (Medinorm)</td>
<td>48</td>
<td>Until completed wound healing</td>
<td>Until wound closure or infection</td>
<td>July 2006</td>
<td>Ongoing, abstract on 60 patients published</td>
</tr>
</tbody>
</table>

Abbreviation: KCI, Kinetic Concepts Inc; NA, not available.
¹ Estimated date of publication at the start of the trial.
² Registered at the UK National Research Register (N0084029434 for Walker, N02345095365 for Adams, and N0123138623 for McCarthy).
³ Abstract presented at the Second World Union Wound Healing Societies’ Meeting, July 8-13, 2004; Paris, France.
⁴ Registered at ClinicalTrials.gov (Identifiers NCT00121537 for McCarthy and NCT00234559 for Niezgoda).
⁵ Preliminary results of these trials have now been published.⁶
location. Blinding of outcome evaluation was performed in 5 studies. Intention-to-treat analyses were explicitly described in 3 studies and could be assumed in 6 further studies. Sample size calculation was reported in only 1 trial. In that trial, the primary end point was changed to comply with FDA recommendations. In 3 trials, 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 and as the time to wound closure (complete or incomplete) in 7 studies. Only 2 of the 5 RCTs and 2 of the 4 non-RCTs 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 (5 RCTs and 3 non-RCTs) analyzed changes in wound size, measured as either wound volume or wound area. Two of these studies had to be excluded from the meta-analysis: 1 non-RCT failed to report measures of variability, and an RCT 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 presented detailed information on the generation of granulation tissue and reported a significantly faster rate in patients treated with NPWT. All 3 studies 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. Of the 4 studies reporting methods of surgical wound clo-
sure, none found closure to be easier in the NPWT group. The only study\(^\text{20}\) to analyze differences between treatment groups for repeated amputation rates noted a (non-significant) reduction in favor of NPWT. Adverse event rates were similar between NPWT and conventional therapy in 7 studies,\(^\text{20-22,25,29,34,37}\) whereas 2 studies\(^\text{20,31}\) reported fewer complications when using NPWT. In 1 RCT,\(^\text{35}\) infections were more common in patients treated
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 in patients with an open abdomen. Hospital stay was shortened by NPWT in 1 non-RCT but was similar in 4 other non-RCTs. An economic analysis was performed in 1 RCT, yielding similar overall costs for NPWT and conventional therapy.

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.” 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. Furthermore, a recent RCT (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 indicate 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 patients recruited into RCTs is so low. The FDA noted that a “consensus definition of allocation, sufficiently detailed reasons for losses to follow-up, and definition of outcome criteria” is “not fully established.” The FDA also noted that a “clinical benefit of incremental wound size changes has not been established.” 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.” Furthermore, a recent RCT (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.

COMMENT

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, the potential for publication bias is high. Our decision not to include abstract publications and confidential study reports complies with current recommendations.

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.
been changed during recruitment to comply with FDA recommendations. 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. 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. 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. 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 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. 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, 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.

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REFERENCES

6. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W. Vacuum-assisted clo-