



TITLE: Negative Pressure Therapy for Patients Infected Wounds: A Review of the Clinical and Cost-Effectiveness Evidence and Recommendations for Use

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CONTEXT AND POLICY ISSUES:

Topical negative pressure (TNP) therapy is the application of negative pressure across a wound to aid wound healing.¹ An open-cell foam insert (sponge) is cut to fit the open wound and then secured under a clear, vapor permeable, plastic dressing.¹ Tubing extends from the sponge to a disposable collection canister.¹ A portable pump applies controlled suction to the system.¹ TNP is also known as negative pressure wound therapy (NPWT) or vacuum-assisted closure (VAC).¹ One example of a VAC system is a device manufactured by KCI (San Antonio, Texas) that is simply referred to as VAC®.²

TNP has recently gained popularity in many wound care settings, with indications mostly derived from expert opinion.² TNP is thought to aid the drainage of excess fluid, reduce infection rates and increase localized blood flow.³ The putative mechanism for reducing infection rates is a reduction of bacterial load and the potential for bacterial colonization.³

This report will review the evidence of the comparative clinical- and cost-effectiveness, and recommended indications for use of topical negative pressure therapy versus traditional wound packing and dressing change therapy in treating infected wounds.

RESEARCH QUESTIONS:

1. What is the comparative clinical effectiveness of topical negative pressure therapy versus traditional wound packing and dressing change for patients with infected wounds in hospital, home care, and long-term care settings?
2. What is the comparative cost-effectiveness of topical negative pressure therapy versus traditional wound packing and dressing change for patients with infected wounds in hospital, home care, and long-term care settings?

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3. What are the recommended indications for negative-pressure therapy for infected wounds?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID Medline, PubMed, The Cochrane Library (Issue 6, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and June 16, 2010. No filters were applied to limit the retrieval by study type.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

SUMMARY OF FINDINGS:

The literature search identified four relevant systematic reviews and meta-analyses and one relevant randomized control trial (RCT). No relevant health technology assessments, economic evaluations, or evidence-based guidelines were identified. Non-randomized clinical trials or observational studies were not eligible for inclusion.

Systematic reviews and meta-analyses

Ubbink et al (2008)² conducted a systematic review of TNP therapy for acute and chronic wounds. A search of RCTs on TNP in adult patients with any wound type in all settings was undertaken in Medline, Embase, Cinahl (to October 2007) and the Cochrane Library (to issue 4, 2007). The search identified 15 publications from 13 unique RCTs that reported on patients with chronic wounds, diabetic wounds, pressure ulcers, skin grafts and acute wounds. Three of these 13 RCTs reported infection-related outcomes. Braakenburg et al. (2006) found an increase in bacterial load with VAC versus conventional therapy for mixed treatment wounds, although this was not statistically significant ($p=0.06$). At the end of treatment, bacterial contamination was present in 21 of 25 (84%) of the VAC-treated wounds versus in 11 of 19 (58%) of the conventionally treated wounds (odds ratio 3.82; 95% CI 0.94 to 15.55). Mouës et al. (2004) reported that the bacterial load in mixed wound groups treated with either VAC or conventional therapy averaged approximately 10^5 per gram of tissue in each treatment group. Armstrong et al (2005) reported that for patients with diabetic foot ulcers, 13 of 77 patients in the VAC group (17%) and 5 of 85 controls (6%) developed a wound infection (risk difference 0.11 (95% CI 0.01 to 0.21)). The systematic review noted that this 11% higher infection rate was only accompanied by a 17% higher rate of earlier wound healing, and thus while the number needed to treat was six (95% CI 3 to 50), the number needed to harm was nine (95% CI 5 to 100). The systematic review noted that there were few trials that reported bacterial counts, even though this is considered relevant to the mechanism of action of the TNP technique. The authors of the systematic review concluded that there was little overall evidence to support the use of TNP in the treatment of wounds, and noted that increased benefits (faster wound healing) were accompanied by increased harms (higher infection rates) in one RCT. The

University of York Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effects (DARE) has an appraisal⁴ of this systematic review, and it judged it to be generally well-conducted. The appraisal further stated that the authors' conclusion that there was little evidence to support the use of TNP was an accurate reflection of the evidence and was likely reliable.

Ubbink et al. (2009)³ conducted a systematic review of TNP therapy specifically for chronic wounds. A search of RCTs in TNP in patients with chronic wounds was undertaken in Medline, Embase, Cinahl, and various Cochrane databases (to at least October 2007). Seven trials involving 205 participants were identified, but only one trial reported an infection-related outcome. This trial (Ford et al., 2002) reported that 22 patients with 35 wounds completed the study, that 13 out of 35 wounds were suspected to involve infection of bone or marrow (i.e., osteomyelitis) and that three wounds treated with TNP, compared with zero in the gel treatment group demonstrated an improvement of the osteomyelitis ($p=0.25$). The authors of the systematic review stated that this study failed to specify the number of wounds with osteomyelitis in each group, how osteomyelitis was diagnosed, or how improvement in osteomyelitis was defined, so the analysis could not be verified. The authors of the systematic review concluded that there was little high-level evidence to support the use of TNP in the treatment of chronic wounds, and that more rigorous evaluation is essential before TNP can become routine and reimbursed in clinical and outpatient care settings.

Van den Boogaard et al. (2008)⁵ carried out a systematic review of the effectiveness of TNP in the treatment of pressure ulcers. A search for RCTs involving TNP in pressure ulcers over the period 1992 to 2007 yielded five RCTs, including Braakenburg et al. (2006), which did not find a statistically significant difference in bacterial clearing ($p=0.06$) in 65 mixed wound patients, 19 of whom had pressure sores, treated with VAC versus conventional therapy. The authors also provided specific results for Mouës et al. (2004, 2005 and 2007), an RCT with three publications. Mouës et al. (2004) found no overall difference in bacterial load, but did report a reduction in non-fermenting Gram-negative rods ($p\leq 0.05$) and an increase in *Staphylococcus aureus* ($p\leq 0.05$) with VAC versus conventional therapy. This RCT included 54 patients, 20 of whom had pressure ulcers. The reviewers also reported that the quality of this RCT was low (three of nine Dutch Cochrane quality criteria were met). The overall conclusion of this review was that TNP has not proven to be more effective than various control interventions. The University of York Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effects (DARE) has an appraisal⁶ of this systematic review, and concluded that the reliability of its conclusions is limited by the sample sizes of included studies and the lack of information on participants, outcomes, study selection and data extraction.

Satat et al., (2008)⁷ conducted a meta-analysis of three RCTs that compared TNP with conventional treatment in patients with lower limb ulcers. Two of these RCTs (Armstrong et al., 2005; Vuerstaek et al., 2006) reported infection rates for randomized patients ($n=222$). The meta-analysis showed no differences in wound infection rates between the two groups, with a pooled odds ratio of 1.72 (95% CI 0.22 to 13.07), $p=0.5969$. There were too few studies to assess publication bias. The authors concluded that the evidence from this review suggests that TNP does not increase the risk of wound infection. The University of York Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effects (DARE) has an appraisal⁸ of this meta-analysis and concluded that in view of the limited data, poor reporting and methodological limitations of the review, the authors' conclusions may not be reliable.

Randomized controlled trials

Stannard et al., (2009)⁹ conducted an RCT in an academic trauma centre, to evaluate the impact of negative pressure wound therapy (NPWT) on deep wound infections after severe open fractures. Fifty-nine patients with 63 severe high-energy open fractures were enrolled in this study, with data available on 58 patients with 62 open fractures. Patients (n=23) with 25 fractures who were randomized to the control group underwent initial irrigation and debridement followed by standard fine mesh gauze dressing, with repeat irrigation and debridement every 36 to 72 hours until wound closure. Patients (n=35) with 37 fractures who were randomized to the NPWT group had identical treatment except that NPWT was applied to the wounds between irrigation and debridement procedures until closure using the VAC® system. Surgical irrigation and debridement was repeated every 36 to 72 hours until the wound was ready for closure or coverage. All patients received prophylactic intravenous antibiotics until 24 hours after closure or coverage of the wound. Patients who developed infections received antibiotics based on the sensitivity of their culture. The mean follow-up was 28 months (range 14 to 67 months). The main study outcome reported was the presence or absence of deep wound infection.

Two control patients developed acute infections (8%) and five developed delayed infections (20%), for a total of seven deep infections (28%), whereas NPWT patients developed no acute infections, and two delayed infections (5.4%), for a total of two deep infections (5.4%). When acute and delayed infections were evaluated separately, the difference between the two groups was not significant. However, the difference in total infections was significant ($p=0.024$) and the relative risk ratio was 0.199 (95% confidence interval: 0.045 to 0.874), suggesting that patients treated with NPWT were approximately one-fifth as likely to have an infection compared with patients randomized to the control group. The difference in the rate of bacterial clearance between groups (20% of control wounds colonized compared with 8% in the NPWT group) was not statistically significant. The authors concluded that NPWT is an effective adjunct along with surgical debridement for severe open fractures after high-energy trauma.

The trial was powered to detect a $\geq 20\%$ difference between randomized treatment groups, assuming 25% of the control patients and 5% of the NPWT patients would require three or more surgical debridements, but this result was not reported. The mean number of irrigations and debridements was reported for both groups, and was lower for the control group (2.4) than for the NPWT group (2.7). As well, the mean number of days until wounds were ready for closure was reported, and was also lower for the control group (3.2) than for the NPWT group (4.0). Thus the overall impact of NPWT on open fracture wounds appears mixed. The timeframe for developing deep delayed infections after discharge was not reported for the NPWT group; in the control group these infections developed at a mean of 11 weeks after discharge. As NPWT was only used until the wound was determined to be ready for closure or coverage, it is unclear how NPWT versus control therapy would be expected to impact on delayed infections. If only acute infections are considered, the results were not statistically significant. The study was funded by KCI, the manufacturer of the VAC system. The interpretation of results is limited by a number of trial design factors: The study endpoint was not clearly specified, and the method of randomization and whether or not allocation was concealed were not reported. There was no mention of treatment blinding, but at least one systematic review² noted that the nature of the intervention (TNP) makes blinding of patients and healthcare workers impossible. Given these considerations, the authors' conclusions may not be reliable.

Economic evaluations

No economic evaluations were identified. Two RCTs with limitations identified in the previously summarized systematic reviews (Braakenburg et al., 2006; Mouës et al., 2005)^{9,10} reported that the costs of treatment were similar for VAC versus conventional therapy, but costs for patients with infected wounds were not reported separately, so no analysis is possible.

Limitations

There were no studies found that compared therapies specifically for patients with infected wounds, and few RCTs that reported infection-related outcomes for negative pressure therapy. None of the four systematic reviews identified RCTs that were considered good quality by the authors of the review. The one RCT not included in the systematic reviews and summarized in this report also had methodological issues that may limit the reliability of its conclusion. There were no economic evaluations or evidence-based guidelines identified, but one regulatory notice was identified.

The Federal Drug Administration (FDA) has issued an FDA Preliminary Public Health Notification: Serious Complications Associated with Negative Pressure Wound Therapy Systems (2009).¹¹ It states that 27 reports indicated infection from original open infected wounds or from retention of dressing pieces in the wound. The majority of these patients required wound debridement and treatment of wound dehiscence, as well as additional hospitalization and antibiotic therapy.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Evidence supporting the comparative clinical effectiveness of topical negative pressure (TNP) therapy versus traditional wound packing and dressing change for patients with infected wounds in hospital, home care, and long-term care settings was limited. None of the four systematic reviews concluded that the available RCT evidence supports TNP therapy. Further, there is some evidence that TNP therapy may be associated with an increased risk of infection.

No evidence was found regarding the comparative cost-effectiveness of topical negative pressure therapy for infected wounds, and there appear to be no evidence-based recommended indications for negative-pressure therapy involving infected wounds.

Given the lack of evidence to support the use of TNP therapy in infected wounds and the possible infection risk associated with this wound therapy, caution may be recommended using TNP therapy in infected wounds or wounds at risk of infection.

PREPARED BY:

Health Technology Inquiry Service

Email: htis@cadth.ca

Tel: 1-866-898-8439

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