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Negative Pressure Wound Therapy

An Evidence Update

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List of Abbreviations

AHRQ	Healthcare Research and Quality
CI	Confidence interval
HR	Hazard ratio
IQR	Inter-quartile range
ITT	Intention to treat
NPWT	Negative pressure wound therapy
RCT	Randomized controlled trial
SD	Standard deviation
VAC	Vacuum

Objective

The objective of this report is to review the results of randomized controlled trials (RCTs) on Negative Pressure Wound Therapy (NPWT) as an update to the report produced by the Medical Advisory Secretariat in 2006 (1) regarding efficacy and safety of this wound healing technique in the management of skin ulcers.

Evidence-Based Analysis: Update

Current Status of the Technology

In 2006, it was estimated that home care agencies use 40% of NPWT systems in Ontario, followed by long-term facilities (29%) and hospitals (27%) and it is anticipated that estimates have not changed dramatically since that time.

Regulatory Status

When the original analysis was published in July 2006, two manufacturers of NPWT were licensed by Health Canada: KCI USA Inc (V.A.C. therapy system) and BlueSky Medical Group Inc. (Versatile 1 Wound Vacuum System). (1) As of March 2010, the V.A.C. therapy system continues to be licensed by Health Canada, however the Versatile 1 Wound Vacuum System is no longer licensed by Health Canada (license expired July 2008 – Blue Sky Medical Group Inc. is now owned by Smith & Nephew, Inc.). Many other NPWT devices have recently been licensed by Health Canada and are listed below in Table 1.

Table 1: Negative Pressure Wound Therapy Devices Licensed by Health Canada

Manufacturer	**Device**	***(license number)***
KCI USA, Inc.	V.A.C. Therapy System Info V.A.C. Therapy Unit	*73155* *81959*
Medela	Medela Invia Liberty	*77005*
Genadyne Biotechnologies Inc.	Gendayne A4 Negative Pressure Wound Therapy System	*77445*
Smith & Nephew Inc.	EZCARE Wound Vacuum System RENASYS EZ Negative Pressure Wound Therapy RENASYS GO Negative Pressure Wound Therapy	*74703* *78488* *79008*
ATMOS Medizintechnik GMBH & Co	ATMOS S 041 Wound System	*80608*
Talley Group Ltd.	*Venturi Advanced Vacuum System for Negative Pressure Wound Therapy*	*78713*

Methods

Research Methods

Literature Search

Search Strategy

Literature search was performed on February 23, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2006 until February 14, 2010. Abstracts of the citations were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established. The search strategy is detailed in Appendix I.

Research Questions

- Is NPWT effective for healing wounds compared with standard care?
- Is NPWT safe?
- If NPWT is effective, is it cost-effective compared with standard care?

Inclusion Criteria

- RCTS published between 2000 and 2010
- Sample size >=30
- Inclusion of homogenous type of wounds
- Commercially marketed NPWT systems
- Human subjects
- English language

Exclusion Criteria

- Non-RCTs
- Sample size <30
- Studies included a variety of wound types
- Studies used home-made negative pressure systems
- Studies included patients with abdominal wall loss
- Studies on open fractures/high energy trauma
- Studies on wounds at the donor site of the graft

Outcomes of Interest

Primary Outcomes

- Proportion of patients with complete (100%) wound closure
- Time to complete wound closure

- Reduction in wound area over time
- Area loss of skin graft (if grafted)
- Graft survival (if grafted)

Secondary Outcomes

- Proportion of patients with granulation tissue formation/wound bed preparation
- Time to granulation tissue formation/wound bed preparation
- Rate of secondary amputation and other adverse events

Statistical Analysis

Quality of Evidence

Quality of Studies

PEDro Scale was used to determine the quality of the RCTs on NPWT in terms of how these trials were conducted. This scale offers a comprehensive measure of methodological quality of the studies taking into account all important elements of quality such as blinding, concealment, and intention to treat analysis. The scale has an additional criterion that measures the external validity (generalizability). This criterion is not used to calculate the PEDro scores for internal validity of the studies.

Quality of Body of Evidence

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (2) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Results of Evidence-Based Analysis

The search identified 247 citations including several existing systematic reviews and health technology assessments. A systematic review by the Agency for Healthcare Research and Quality (AHRQ) (3) included published studies from 2000 to 2008. The primary objective of the AHRQ review was to examine the comparative effectiveness of different NPWT systems and their components as well as the complication rates of different NPWT systems. Of the 40 studies included in the AHRQ review, 9 studies were RCTs. The sample sizes ranged from 22 patients to 342 patients. The majority of studies examined chronic wounds. Two studies investigated the effectiveness of NPWT in skin grafts.

Studies included in the AHRQ review were very heterogeneous in regards to the patient population and wound type, primary outcomes, and method of outcome measurement. Thus, any quantitative synthesis of the data was not possible.

Adverse events were reported in 37 of the 40 studies comparing NPWT to other treatments. Seven studies described NPWT as a safe treatment. Nineteen studies reported fewer complications in patients receiving NPWT compared to standard care while eight studies reported that the two groups had similar adverse events.

The AHRQ review concluded that *"at this time the available evidence cannot be used to determine a significant therapeutic distinction of a NPWT system"*. While the authors were able to capture data on adverse events, however, due to the lack of studies comparing one NPWT system to another NPWT system, they were unable to determine the severity of adverse events for one NPWT system compared to another.

As part of their systematic review, the AHRQ identified 22 existing systematic reviews (2000-2008) that included studies on NPWT versus other wound treatments for patients with a broad range of wound types. All of the systematic reviews noted that there was a lack of high-quality evidence to support NPWT versus other treatments.

Randomized Controlled Trials on Negative Pressure Wound Therapy

From the updated search, two RCTs met our inclusion and exclusion criteria. (4;5) RCTs included in the AHRQ review were also reviewed to identify the studies that could meet our inclusion and exclusion criteria. From the nine RCTs in the AHRQ review, two met these criteria and were included in this review. (6;7)

Two of the trials included patients who had a diabetic foot ulcer and two trials included patients who were hospitalized for skin grafting. The studies of diabetic foot ulcer compared NPWT with advanced or standard moist wound therapy. The studies of skin graft compared NPWT with standard wound care without using NPWT.

Table 1 shows studies included in this report.

Table 1: List of Randomized Controlled Trials Included in the Review

Study	Patients	Type of wound	Comparison	Setting
Blume et al. 2008 (4)	342	Diabetic foot ulcer	Advanced moist wound therapy	Days of home care therapy/total therapy: NPWT: 89.5% Control: 95.3%
Armstrong et al. 2005 (6)	162	Diabetic foot amputation	Standard moist wound care	In-patient/Out-patient
Vuerstaek et al. 2006 (7)	60	Skin graft for venous/arterial, and combined venous and arterial ulcers	Standard wound care	In-patient
Llanos et al. 2006 (5)	60	Skin graft for ulcers due to injuries	Similar dressing without NPWT	In-patient

NPWT, Negative pressure wound therapy

Studies that were excluded from the review and the reason for exclusion are listed in Table 2.

Table 2: List of Randomized Controlled Trials Excluded From the Review

Study	N	Small sample size	Included all types of wounds	Home-made systems	Wounds with abdominal wall loss	Wounds due to fracture/ high energy trauma	Wounds at donor site
Perez et al. 2010	40			✓			
Stannard et al. 2009	59					✓	
Choi et al. 2009	54						✓
Bee et al. 2008	51				✓		
Wild et al. 2008	10	✓					
Mouës et al. 2007	54		✓				
Braakenburg et al. 2006	66		✓				
Stannard et al. 2006	Hematoma: 44 Fracture: 44					✓	
Etoz et al. 2004	24	✓					
Moisidis 2004	20	✓	✓				
Jesckle et al. 2004	12	✓					
Wanner 2003	22	✓					
Eginton et al. 2003	10	✓					
Ford 2002	28	✓					
Joseph 2000	24	✓					
McCallon et al. 2000	10	✓					

Trials on Diabetic Foot Ulcer

Study Characteristics

The two trials on diabetic foot ulcer (4;6) investigated the NPWT system manufactured by KCI and both received research funding from the manufacturer. Both trials were multicentre and the study period was 16 weeks in both.

The study by Blume et al. (4) investigated the effectiveness of NPWT in the treatment of diabetic foot ulcers compared with advanced moist wound therapy. The study enrolled 342 patients with a mean age of 58 years. The study by Armstrong et al. (6) investigated the effectiveness of NPWT in the treatment of amputation wounds of the foot in patients with diabetes and compared the effectiveness of the NPWT with moist wound therapy. This study enrolled 162 patients with a mean age of 59 years.
The primary outcome and its definition were similar in the two studies. Both studies reported 80% power for detection of 20% between group differences in the proportion of patients who achieve the primary outcome. In both studies data was analyzed based on intention to treat principle.

In these trials, it was not possible to mask the investigators or the patients to the treatment assignment. In the study by Blume et al. (4) randomization was accomplished by generating blocks of numbers. Numbers were assigned to a treatment group and then sealed in opaque envelopes containing black paper labelled with treatment and patient ID. Envelopes were sequentially numbered before site distribution. At patient randomization, treatment was assigned on the basis of the next sequentially labelled envelope. In the study by Armstrong et al. (6) the sponsor prepared the randomization scheme and were distributed in sealed envelopes containing the treatment assignment to be opened sequentially as patients were enrolled.

In the study by Blume et al. (4) patients were examined weekly for the first 4 weeks and then every 2 weeks until the end of the study (16 weeks) or ulcer closure. At each visit, several outcomes including the area, ulcer closure, and granulation tissue formation were assessed. In the study by Armstrong et al. (6) assessments were based on both wound observation and photographs taken by the treating clinician. Wound photographs were taken on days 0, 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 12 weeks, and 16 weeks. Additionally, a bi-layered wound tracing was made for planimetric measurements and granulation tissue formation was estimated and recorded. Comparison of the wound observation method and digital photographs for complete wound closure was made and the complete agreement was recorded.

The primary outcome was the proportion of patients who achieved complete wound closure within 16 weeks after the initiation of the treatment. Complete wound closure was defined as skin closure (100% reepithelialisation) without drainage (4;6), and dressing (4). The median time to achieve complete wound closure was the secondary outcome in both trials. Blume et al. (4), also assessed the decrease in wound area at 4 weeks after initiation of treatment as another secondary outcome. Both studies measured 76% to 100% granulation tissue formation on patients with 0% to 10% granulation at the baseline as well as the median time to achieve this outcome. Partial wound closure was also assessed in the trial by Blume et al. (4) Kaplan-Meier survival analysis was used to estimate the median time to closure.

Rates of secondary amputations and adverse events were recorded in both studies. Table 3 shows study characteristics for the trials of diabetic foot ulcer.

Table 3: Study Characteristics of Included Studies: Diabetic Wounds

Trial	Patients randomized/ Received treatment	Study duration/ & follow-up	Wound characteristics	Mean age Years/ Percent of males	Treatment centres/& Setting	Control group	Assessment of the wound after treatment	Frequency of dressing changes	Power/ Analysis	Primary outcome	Secondary outcomes
Blume et al. 2008 (4)	•341 diabetes patients >=18 years old Received treatment: NPWT 169 Control 166	<u>Duration</u> 16 weeks or until complete wound closure <u>Follow-up</u> 3 & 9 months for patients whose wounds achieved complete closure	•Wounds stage 2 or 3 as defined by Wagner's scale •Wounds >=2 cm2 in area after debridement •Calcaneal, dorsal, or plantar	58/ 78.5	Multicentre: 37 centres including one Canadian Treatment in both acute and home care settings	Advanced moist wound therapy; predominantly hydrogels and alginates	Weekly for the first 4 weeks, then every other week until day 112 or complete wound closure	NPWT: Every 48-72 hours (no less than 3 times/week) Control: On the basis of manufacturer's guideline and institutional treatment protocols	80% ITT 335 patients analyzed Performed by KCI	Proportion of complete wound closure	•Time to achieve wound closure by either surgery or secondary intention •Reduction in wound area over time •Complications including secondary amputations
Armstrong et al. 2005 (6)	162 patients with partial foot amputation due to diabetic wounds >=18 years old Up to the transmetatarsal level and evidence of adequate perfusion Received treatment NPWT: 77 Control: 85	16 weeks or until complete wound closure <u>Follow-up</u> No	University of Texas grade 2 or 3 in depth	59/ 81	Multicentre: 18	Standard care with moist wound therapy with alginates,hydrocolloids, foams, or hydrogels	Wound photographs on days 0, 7, 14, 28, 42, 56, 84, and 112	NPWT: every 48 hours Control: every day unless otherwise recommended	80% ITT Was not performed by KCI	Proportion of complete wound closure	•Time to achieve wound closure by either surgery or secondary intention •Complications including secondary amputations

NPWT, Negative pressure wound therapy; ITT, Intention to treat

Results of the Trials of Diabetic Foot Ulcer

In the study by Blume et al. (4) patients received mostly home-based treatment. The proportion of home care therapy days to total therapy days was 89.5% in the NPWT group and 95.3% for control group. In both studies, debridement was performed within 2 days of randomization to remove non-viable tissue. In these trials, patients in either group received off-loading therapy as deemed necessary. Dressing change was performed for NPWT every 48 hours in the study by Armstrong et al. (6) and no less than three times per week in the study by Blume et al. (4).

Primary Outcome:

Intention to treat analysis showed that the proportion of patients who achieved complete ulcer closure was higher in NPWT than the control in both studies. In the study by Blume et al. (4) 73 of 169 (43.2%) patients in the NPWT group and 48 of 166 (28.9%) patients in the control group achieved this outcome (P = .007). In the study by Armstrong et al. (6) 43 of 77 (56%) in the NPWT group and 33 of 85 (39%) in the control group achieved this outcome (P = .04).

In the study by Bloom et al. (4) analysis for patients who completed the study showed that a greater percentage of NPWT treated ulcers achieved ulcer closure than the control group (NPWT 73/120 [60.8%], control 48/120 [40%]; P = .001). In this study, sixteen of 169 (9.5%) of the wounds in NPWT treated wounds and 14 of 166 (8.4%) of the wounds in the control group were surgically closed by split thickness skin grafts, flaps, sutures, or amputations. In the study by Armstrong et al. (6), 12 (16%) patients in the NPWT group and 8 (9%) in the control group had healed wounds via surgical closure (P = .244).

Secondary Outcomes:

In both trials time to complete wound closure was measured by the Kaplan-Meier method. Both trials showed that the median time to complete wound closure was significantly shorter in the NPWT group than the control group. In the study by Blume e t al. (4) the median time to complete ulcer closure was 96 days for the NPWT group but could not be estimated for the control group (P = .001). In this study, the duration of therapy was shorter in the NPWT group than the control group (63.6±36.57 days vs. 78.1±39.29 days). In the study by Armstrong et al. (6) the median time to complete wound closure was 56 days in the NPWT group [IQR 26-92] and 77 days in the control group [IQR 40-112] (P = .005).

Blume et al. (4) reported a significant difference between the two groups in assessing ulcer area and partial wound closure. The decrease in the wound area from baseline was 4.32 cm^2 in the NPWT group and 2.53 cm^2 in the control group (P = .021). In the NPWT group 105/169 (62.1%) of the ulcers and in the control group 85/166 (51.2%) of the ulcers achieved 75% wound closure (P = .044).

Wound bed preparation and granulation tissue formation was reported by both studies. Blume et al. (4) reported that among patients who had 0-10% granulation tissue at the baseline, 70.8% in NPWT group and 36.4% in the control group achieved 76-100% granulation tissue formation (P .019). Median time to this event, measured by Kaplan-Meier method, were 56 days (95% CI 42-84 days) for NPWT and 114 days (95% CI 44-ND) for the control group (P =.022). In the study by Armstrong et al. (6) 19 patients in the NPWT group and 15 patients in the control group had 0-10% granulation tissue at the baseline. The median time to achieve 76-100% granulation tissue formation in these patients was significantly shorter in the NPWT group than the control group (NPWT 42 days [IQR 40-56 days], control 84 days [IQR 57-112 days]; P = .002).

Table 4 summarizes the outcomes of the two trials on diabetic foot ulcer.

Table 4: Results of Studies on Diabetic Wounds

	Complete (100%) wound closure within 16 weeks N (%)	**Median time to complete wound closure* Day (95% CI)**	**75% wound closure within 112 days of active treatment without need for drainage or dressing N (%)**	**Median time to 75% wound closure* Day (95% CI)**	**Decrease in wound area from the baseline on day 28 cm^2**	**76%-100% granulation tissue formation on patients with 0% to 10% granulation at the baseline N (%)**	**Median time to 76%-100% granulation tissue formation* Day (95% CI)**
Blume et al. (4)	NPWT: 73/169 (43.2) Control: 48/166 (28.9) P = .007 <u>Surgically closed</u> NPWT: 16/169 (9.5%) Control: 14/166 (8.4%)	NPWT: 96 (75-114) Control: Not estimable P = .001	NPWT: 105/169 (62.1) Control: 85/166 (51.2) P = .044	NPWT: 58 (53-78) Control: 84 (58-89) P = .014	NPWT: -4.32 Control: -2.53 P = 0.021	NPWT: 17/24 (70.8) Control: 8/22 (36.4) P = .019	NPWT: 56 (42-84) Control: 114 (44 –ND) P = .022
Armstrong et al. 2005 (6)	NPWT: 43/77 (56) Control: 33/85 (39) P = .04 <u>Surgically closed</u> NPWT: 12 (16%) AMWT: 8 (9%) P = .244 Healed without surgical closure: NPWT: 31 (40%) AMWT: 25 (30%)	NPWT: 56 (26-92) Control: 77 (40-112) P = .005	NR	NR	NR	NR	NPWT: 42 (40-56) Control: 84 (57-112) P = .002 Note: Similar results for those who had 0-25% granulation at baseline (P = .01)

NPWT, Negative pressure wound therapy; ND, Not determined

Trials of Ulcers Requiring Skin Grafting

Study Characteristics

Two randomized controlled trials investigated the effectiveness of NPWT in the treatment of ulcers requiring skin grafting. (5;7) The study by Vuerstaek et al. (7) used the device manufactured by KCI and the study by Llanos et al. (5) used a negative pressure device that was modified from the original. However, in the study by Vuerstaek et al. (7) KCI had no influence or vote regarding study design, data collection, analysis, interpretation, report writing, or decision to submit the manuscript for publication.

Vuerstaek et al. (7) investigated the efficacy of NPWT in 60 hospitalized patients with chronic leg ulcers and Llanos et al. (5) investigated the efficacy of NPWT in 60 patients in a burn centre who had wounds with skin loss. The mean age of the patients in the study by Vuerstaek et al. (7) was 74 years in the NPWT group and 72 years in the control group. The mean age of the patients in the study by Llanos et al. was 34 years.

The study by Vuerstaek et al. (7) had a power of 95% to detect a minimal time difference of 7 days between the two groups in achieving wound closure. The study by Llanos et al. (5) had a power of 90% to detect a between group difference of 15 to 5 cm^2 in the area of graft loss.

In both studies, the treatment assignment was through computer generated random numbers in permuted blocks of 8 (7) or 6 (5). In the study by Vuerstaek et al. (7) masking the intervention was not possible. Patients were examined clinically by the same independent research physician and consultant dermatologist twice a week until wound closure. Patients were then monitored by the same physician at 3, 6, and 12 months after discharge. The study by Llanos et al. (5) was a double-blinded trial. In this study, digital photographs were taken at the moment the graft was uncovered to evaluate area of graft loss. The person in charge of measuring the area in the photographic register was masked to the intervention. In addition, the data analyst was masked to the groups of intervention when analyzing the data. To ensure that the surgeon who performs the skin grafting does not modify the technique according to the treatment assignment, he was masked to the treatment assignment until the skin graft was performed.

One patient in the study by Vuerstaek et al. (7) crossed over from control arm to NPWT arm after 8 weeks due to unsatisfactory therapeutic outcome but there was no cross over in the Llanos study (5).

The two studies had different primary outcomes as the nature of the wounds was different in the two studies. While the median time to complete healing was the primary outcome in the study by Vuerstaek et al. (7) Llanos et al. (5) had area loss of skin graft at the fourth post-operative day as the primary outcome in their study. Duration of wound bed preparation, rate of ulcer recurrence, and graft survival were the secondary outcomes in the study by Vuerstaek et al. (7), and need for re-grafting and length hospital stay were the secondary outcomes in the study by Llanos et al. (5).

Table 5 shows study characteristics of the trials of skin grafting.

Table 5: Study Characteristics of Included Studies: Skin Grafts

Trial	Patients randomized	Study duration (Outcome assessment) and follow-up	Wound characteristics	Mean age Years/ Percent of males	Treatment centres/ Setting	Initial Debridement	Power/ Analysis	Primary outcome	Secondary outcomes
Vuerstaek et al. 2006 (7)	60 hospitalized for full thickness punch skin grafting Received treatment: NPWT: 28 Control: 26	Until wound closure Follow-up 3, 6, 12 months after discharge	Chronic venous/combined venous and arterial, and microangiopathic leg ulcer of > 6 months duration	NPWT: 72/23 Control: 74/23	2 hospitals	Performed in both groups	95%/ ITT	Time to complete healing	Duration of the wound bed preparation Percentage of wound recurrence <-1 year after discharge Skin graft survival
Llanos et al. 2006 (5)	60 patients with skin loss (2/3 from burns) in a burn unit for split thickness skin grafting	4th post-operative day Follow-up: Until discharge from hospital	Acute traumatic injuries and skin loss	NPWT: 34/86.7) Control: 34.5/80	1 hospital for work related injuries	Performed in both groups	90%/ITT	Area loss of the skin graft in cm^2 measured at 4th day	Need for regrafting Ratio between graft size and loss area Hospital stay

NPWT, Negative pressure wound therapy; ITT, Intention to treat

Results of Trials of Ulcers Requiring Skin Grafting

Primary outcomes in both studies showed significantly better results in NPWT group than the control group. In the study by Vuerstaek et al. (7) Kaplan-Meier survival analysis showed that the median time to complete healing was 29 days (95 % CI 25.5-32.5) in the NPWT group vs. 45 days (95% CI 36.2-53.8) in the control group (P = .0001). Only one ulcer in each group failed to heal. Since all patients were discharged after complete healing, the length of hospital stay equaled the total healing time. In the Llanos study (5), the median graft loss in the NPWT group was 0 cm^2 (range, 0-11.8 cm^2) and in the control group it was 4.5 cm^2 (range 0-52.9 cm^2) (P = .001), and the median percentage of graft loss was 0% (0%-62%) in NPWT group and 12.8% (0%-75.9%) in the control group (P < .001). Further analysis showed that the results were independent of the age, gender, and wound etiology.

For secondary outcomes, Vuerstaek et al. (7) showed that the median time to wound bed preparation was 7 days (5.7-8.3 days) days in the NPWT group and 17 days (10-24 days) days in the control group (P = .005). Within 2 weeks, 90% of the ulcers in the NPWT could be cleaned vs. 37% in the control group. A Cox multivariate regression analysis showed significantly shorter time to complete healing in the NPWT group than the control group (HR = 3.2, 95% CI 1.7-6.2) and preparation time (HR = 2.4, 95% CI 1.2-4.7). Vuerstaek et al. (7) also performed a survival analysis which showed skin graft survival of 83% (SD 14%) for the NPWT group and 70% (SD 31%) for the control group (P = .011).

Median recurrence rate for NPWT group and control group was at month 4 and month 2 respectively (P = .47). After 12 months, 12 (52%) ulcers treated with NPWT relapsed compared with 10 (42%) in the control group (P = .47). Llanos et al. (5) reported higher rate of re-grafting in the control group than NPWT group (NPWT 16.7%, control 40%; P = .045) this was directly related to the area of graft loss.

The median time from intervention to discharge was 8 days (range, 7-13 days) in the NPWT and 12 days (range, 7-23 days) in the control group (P = .001). The length of hospital stay was shorter in the NPWT group than the control group (NPWT 13.5 days [range, 11-22 days], control 17 days [range, 10-31 days]; P = .01).

In the study by Vuerstaek et al. (7) quality of life scores during the first week were significantly lower in the NPWT group than the control group (P = .031). However, this difference disappeared in the second week and during follow-up. During the first week of treatment, there was no difference in pain scores between the two groups. From week 5 onward, pain scores were significantly lower in the NPWT group.

Tables 6-7 show the results of the trials of skin grafting.

Table 6: Skin Grafting: Outcomes Reported by Vuerstaek et al. (7)

Time to complete healing Day (95% CI)	Healed within 43 days	Wound bed preparation Day (95% CI)	Recurrence after 1 year follow-up N (%)	Median percentage skin graft survival (SD)	Quality of Life	Pain scores
NPWT: 29 (25.5-32.5) Control: 45 (36.2-53.8) P = .0001 HR = 3.2 (95% CI 1.7-6.2)	NPWT: 90% Control: 48%	NPWT: 7 (5.7-8.3) Control: 17 (10-24) P = .005 HR = 2.4 (95% CI 1.2-4.7)	NPWT: 12 (52) Control: 10 (42) P = .47	NPWT: 83 (14) Control: 70 (31) P = .011	Significant increase at the end of therapy in both groups 1st week: Lower in NPWT (P = .031) 2nd week No difference Follow-up No difference	Significant decrease at the end of therapy in both groups 1st week: No difference 1st week: Lower in NPWT

NPWT, Negative pressure wound therapy; HR, Hazard Ratio

Table 7: Skin Grafting: Outcomes reported by Llanos et al. (5)

Loss of split thickness skin graft Median (95% CI) cm^2	Percentage of graft loss (Range) cm^2	Re-grafting	Time from intervention to discharge Median, range (Day)	Total length of stay Day (Range)
NPWT: 0 (0-11.8) Control: 4.5 (0-52.9) P = .001	NPWT: 0 (0-62) Control: 12.8 (0-75.9) P = .001	NPWT: 5 Control: 12 P = .045	NPWT: 8 (7-13) Control: 12 (7-23)	NPWT: 13.5 (11-22) Control: 17 (10-31) P = .01

NPWT, Negative pressure wound therapy

Secondary Amputation and Adverse Events in Randomized Controlled Trials of Negative Pressure Wound Therapy

In the study by Blume et al. (4) there were no significant differences between the two groups in regards to the safety outcomes except that the rate of secondary amputation was significantly lower in NPWT group than the control group. However, the majority of amputations in the control group were minor amputations.

In the study by Armstrong et al. (6) the rate of second amputation was lower in the NPWT group than the control group but the difference did not reach significance level. Overall, 3 percent of patients in the NPWT group and 11 percent in the patients in the control group required second amputation. No patient in the NPWT group required high level (above foot) amputation while 5 patients in the control group required below or above knee amputations (P = .06). The proportion of patients with one or more adverse events was not significantly different between the two groups (NPWT 52%, control 54%; P = .875). Treatment related adverse events occurred in 9 (12%) of patients in NPWT group and in 11 (13%) of patients in control group. One of the treatment related adverse events in NPWT group and 5 in the control group were classified as serious.

In the study by Vuerstaek et al. (7), the overall rate of adverse events was higher in the NPWT group than the control group (40% vs. 23%; P = .17). This included pain, erysipelas, wound infection, cutaneous damage, bleeding at donor site, and non-healing ulcers.

Table 8 shows the details of adverse events in these trials.

Table 8: Rate of Secondary Amputation and Frequency of Adverse Events

	Amputation **N (%)**	**Adverse Events** **N (%)**
Blume et al. 2008 (4)	**Secondary amputation** NPWT: 7 (4.1) Control: 17 (10.2) P = 0.035 Note: 2 in NPWT and 13 in control were minor amputations	**At 6 months** Wound infection NPWT: 4 (2.4) CL: 1 (0.6) P = .37 Osteomyelitis NPWT: 1 (0.6) CL: 0 (0) Staphylococus infection NPWT: 1 (0.6) CL: 0 (0) Infected skin ulcer NPWT: 1 (0.6) CL: 2 (1.2) P = .6 Edema NPWT: 5 (3) Control: 7 (4.2) P = .57 Cellulitis NPWT: 4 (2.4) Control: 1 (0.6) P = .37
Armstrong et al. 2005 (6)	**Second amputation** NPWT: 2 (3) Control: 9 (11) P = .06 RR, 0.225 (95% CI 0.05-1.1) High level (below or above knee) amputation: NPWT: 0 Control: 5 (2 above knee) P = .06	**Treatment-related adverse events** NPWT: 9 (12); 1 was serious CL: 11 (13); 5 were serious Mean duration of treatment-related adverse events NPWT: 18 days (SD 22.3) Control: 24.3 days (SD 34.5) Wound infection NPWT: 13 (17); Not related to NPWT CL: 5 (6); 2 related to treatment

	Amputation N (%)	Adverse Events N (%)
Vuerstaek et al. 2006 (7)	None	Wound infection NPWT: 0 CL: 1 Not significant Cutaneous damage secondary to therapy NPWT: 7 CL:2 P < .05 Pain NPWT: 3 CL: 1 Not significant Other Erysipelas: 1 in NPWT Bleeding at donor site: 2 in CL
Llanos et al. 2006 (5)	None	NR

NPWT, Negative pressure wound therapy; NR, Not reported

Cost of the Treatment

Two studies reported the cost of the treatment. Resource utilization and average cost of the treatment reported by these studies are shown in Table 9.

Table 9: Reported Cost of Treatment

	Resources used	Average cost of treatment
Armstrong et al. 2005 (6) **Apelqvist et al. 2008 (8)**	**For patients treated for a minimum of 8 weeks** **NPWT: 63** **Control: 72** Number of surgical procedures (Debridement, grafts, amputations, other) NPWT: 63 Control: 72 Mean (Range) of outpatient dressing changes per patient NPWT: 42 (6-140) Control: 118 (12-226) P < .001 Mean (Range) of outpatient clinic visit NPWT: 4 (0-47) Control: 11 (0-106) P = .044 Antibiotic usage Number of courses: NPWT: 86 Control: 71 Not significant	**For patients treated for a minimum of 8 weeks** **NPWT: 63** **Control: 72** Average weekly total cost for patients treated for 8 weeks or longer NPWT: $3,338 (480-36,673) Control: $4,853 (238-130,791) Average total direct cost per patient treated for 8 weeks or longer, independent of clinical outcome NPWT: $27,270 Control: $36,096 Incremental cost difference: $8,826 Average total cost to achieve complete healing NPWT: $25,954 (n=43) Control: $38, 806 (n=33) Incremental cost difference: $12,852 **For all patients based on ITT** **NPWT: 77** **Control: 85**

	Duration of use/patient (mean days, range): NPWT: 22 (1-114) Control: 24 (1-114)	 NPWT: $26,972 Control: $36,887 Incremental cost difference: $9,915
Vuerstaek et al. 2006 (7)	**Time consumption:** <u>Nursing time</u> NPWT: 232±267 Control: 330±178 P = .001 <u>Physician time</u> NPWT: 177±76 Control: 181±91 P = .937	<u>Average cost of treatment</u> NPWT Products: $847 Bandages & dressing: $2,391 Personnel costs: $583 Nurse costs: $124 **Total cost: $3,881** <u>Control</u> Bandages & dressing: $4,770 Personnel costs: $508 Nurse costs: $175 **Total cost: $5,452** NPWT vs. control, P = .001

Quality of Studies

The PEDro scale was used to measure the quality of the RCTs. The scale has an additional criterion that measures the external validity (generalizability). According to this scale, all studies had good external validity.

The scores for the two studies on diabetic foot ulcer were rated as 7/10 and the quality of these trials was considered as "moderate'. Studies on skin grafting achieved higher scores and their quality was considered as "High". (Table 10)

Table 10: Quality of the Studies Included in the Review According to PEDro Scale

	Blume et al. 2008 (4)	**Armstrong et al. 2005 (6)**	**Vuerstaek 2006** (7)	**Llanos et al. 2006** (5)
Eligibility criteria were specified*	Yes	Yes	Yes	Yes
Subjects were randomly allocated to interventions (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Yes	Yes	Yes	Yes
Allocations were concealed	Yes	Yes	Yes	Yes
The intervention groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	Yes	Yes
There was blinding of all subjects	No	No	No	No
There was blinding of all therapists who administered therapy	No	No	No	Yes
There was blinding of all assessors who measured at least one key outcome	No	No	No	Yes
Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	No	No	Yes	Yes
All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat"	Yes	Yes	Yes	Yes
The results of between-intervention group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes
The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes
Total sores	**7/10**	**7/10**	**8/10**	**9/10**

*This criterion has been included in the PEDro scale so that all items of the Delphi scale are represented. This item is not used to calculate the internal validity of the study; rather, it calculates the external validity (Generalizability) of the studies

Quality of Body of Evidence

Appendix 2 summarizes the GRADE Tables for the quality of body of evidence.

Summary and Conclusion

Results of the RCT on diabetic foot ulcer:

- Intention to treat analysis showed that the proportion of patients who achieved complete wound closure (primary outcome) was higher in NPWT group than the control group (NPWT 73/169 [43.2%], control 48/166 [28.9%]; P = .007).
- Analysis for patients who completed the study showed that a greater percentage of NPWT treated ulcers achieved ulcer closure than the control group (NPWT 73/120 [60.8%], control 48/120 [40%]; P = .001).
- In the NPWT group 9.5%, and in the control group 8.4%, of the wounds were surgically closed by skin grafts, flaps, sutures, or amputations.
- The median time to complete ulcer closure, estimated by Kaplan-Meier method, was significantly shorter in the NPWT group than the control group (NPWT 96 days [95 CI 75-114 days], control could not be estimated; (P = .001).
- The duration of therapy was shorter in NPWT group than the control group (NPWT 63.6±36.57 days, control 78.1±39.29 days).
- The decrease in the wound area from baseline was greater in NPWT group than the control group (NPWT 4.32 cm^2, control 2.53 cm^2; P .021).
- Significantly more patients in the NPWT group achieved 75% wound closure than the control group (NPWT 105/169 [62.1%], control 85/166 [51.2%]; P = .044).
- Among patients who had 0-10% granulation tissue at the baseline, 70.8% in NPWT group and 36.4% in the control group achieved 76-100% granulation tissue formation (P = .019).
- Median time to achieve 76-100% granulation tissue formation, measured by Kaplan-Meier method, were 56 days for NPWT and 114 days for the control group (P = .022).

Results of the RCT on diabetic foot amputation:

- Significantly more patients In the NPWT group than the control group achieved complete wound closure (primary outcome) within the study period (NPWT 43/77 [56%], control 33/85 [39%]; P = .04).
- In the NPWT group 16%, and in the control group 9% of the patients' wounds were closed surgically (P = .244).
- The median time to complete wound closure was significantly shorter in the NPWT group than the control group (NPWT 56 days [IQR 26-92 days], control 77 days [IQR 40-112 days]; P = .005).
- Among patients who had 0-10% granulation tissue at the baseline the median time to achieve 76-100% granulation tissue formation was significantly shorter in the NPWT group than the control group (NPWT 42 days [IQR 40-56], control 84 days [57-112]; P = .002).

Results of the RCT on venous and arterial leg ulcer:

- The median time to complete healing (primary outcome) was significantly shorter in the NPWT group than the control group (NPWT 29 days [95 % CI 25.5-32.5 days], control 45 days [95% CI 36.2-53.8]; P = .0001).
- The median time to wound bed preparation was significantly shorter in NPWT group than the control group (NPWT 7 days [5.7-8.3 days], control 17 days [10-24 days; P = .005).
- Treatment by NPWT resulted in a faster time to complete healing (HR = 3.2, 95% CI 1.7-6.2) and

preparation time (HR = 2.4, 95% CI 1.2-4.7).

- Skin graft survival was 83% (SD 14%) for NPWT and 70% (SD 31%) for the control group (P = .011).
- After 12 months, 12 (52%) ulcers treated with NPWT relapsed compared with 10 (42%) in the control group (P = .47).
- Quality of life scores during the first week was significantly lower in NPWT group than the control group (P = .031). However, this difference disappeared in the second week and during follow-up.
- During the first week of treatment, there was no difference in pain scores between the two groups. From week 5 onward, pain scores were significantly lower in the NPWT group.

Results of the RCT on ulcers caused by injury:

- The median area of graft loss was less in NPWT group than the control group (NPWT 0 cm^2 [range, 0-11.8 cm^2], control 4.5 cm^2 [range 0-52.9 cm^2]; P = .001).
- The median percentage of graft loss was less in the NPWT group than the control group (NPWT 0% [0%-62%], control 12.8% [0%-75.9%]; P < .001).
- Rate of re-grafting was lower in the NPWT group than the control group. (NPWT 5/30 [16.7%], control 12/30 [40%]; P = .045).
- The median time from intervention to discharge was shorter in NPWT group than the control group (NPWT 8 days [range, 7-13 days], control 12 days [range, 7-23 days]; P = .001).
- The length of hospital stay was shorter in the NPWT group than the control group (NPWT 13.5 days [range, 11-22 days], control 17 days [range, 10-31 days]; P = .01).

Appendix I

Final Search – Negative Pressure Wound Therapy – 2010 Update

Search date: February 23, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1996 to February Week 2 2010>
Search Strategy:
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1 *"wounds and injuries"/ or exp wound infection/ or exp wounds, nonpenetrating/ (38811)
2 exp Wound Healing/ (37170)
3 exp Skin Ulcer/ (14965)
4 exp Diabetic Foot/ (3744)
5 ((pressure or chronic or leg* or foot or feet or skin or bed or arterial or diabetic) adj2 (ulcer* or sore* or wound*)).ti,ab. (13734)
6 (decubitus or bedsore*).ti,ab. (1507)
7 or/1-6 (88993)
8 exp Negative-Pressure Wound Therapy/ (331)
9 (vacuum-assisted closure* or negative-pressure or npwt or vac).ti,ab. (3272)
10 exp Vacuum/ (2103)
11 exp Suction/ (4220)
12 exp Pressure/ (31175)
13 or/8-12 (37546)
14 7 and 13 (2120)
15 limit 14 to (english language and humans and yr="2006 -Current") (681)
16 limit 15 to (controlled clinical trial or meta analysis or randomized controlled trial) (54)
17 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (40277)
18 (health technology adj2 assess$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (814)
19 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (79200)
20 exp Random Allocation/ or random$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (428986)
21 exp Double-Blind Method/ (59111)
22 exp Control Groups/ (901)
23 exp Placebos/ (10441)
24 (RCT or placebo? or sham?).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (106793)
25 or/16-24 (552946)
26 15 and 25 (120)

Database: EMBASE <1980 to 2010 Week 07>

Search Strategy:

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1 *wound/ or exp chronic wound/ or exp wound complication/ or exp wound dehiscence/ or exp wound fluid/ or exp wound healing/ or exp wound infection/ or exp wound care/ or exp wound closure/ (83610)
2 exp wound healing promoting agent/ (8972)
3 exp ulcer healing/ (4269)
4 exp skin ulcer/ (21204)
5 ((pressure or chronic or leg* or foot or feet or skin or bed or arterial or diabetic) adj2 (ulcer* or sore* or wound*)).ti,ab. (16777)
6 (decubitus or bedsore*).ti,ab. (2366)
7 or/1-6 (115531)
8 exp vacuum assisted closure/ (793)
9 exp vacuum/ (2563)
10 exp suction/ (1906)
11 exp pressure/ (30263)
12 (vacuum-assisted closure* or negative-pressure or npwt or vac).ti,ab. (4703)
13 or/8-12 (36477)
14 7 and 13 (1908)
15 limit 14 to (human and english language and yr="2006 -Current") (730)
16 Randomized Controlled Trial/ (181492)
17 exp Randomization/ (27531)
18 exp RANDOM SAMPLE/ (1779)
19 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (323670)
20 (health technology adj2 assess$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (786)
21 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (75378)
22 Double Blind Procedure/ (76202)
23 exp Triple Blind Procedure/ (14)
24 exp Control Group/ (5562)
25 exp PLACEBO/ or placebo$.mp. or sham$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (233152)
26 (random$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (470744)
27 (control$ adj2 clinical trial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (305122)
28 or/16-27 (865985)
29 15 and 28 (112)

Appendix 2

GRADE Table for Randomized Controlled Trials of Diabetic Foot Ulcer

Outcome	Number of studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Grade
Primary outcome: Proportion of patients who achieved 100% wound closure within 16 weeks	2	RCT	Moderate	No uncertainty	No uncertainty	N/A	Moderate
Secondary outcome: Median time to 100% wound closure	2	RCT	Moderate	No uncertainty	No uncertainty	N/A	Moderate

GRADE Table for Randomized Controlled Trials of Skin Grafting

Outcome	Number of studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Grade
(Primary outcome) Median time to 100% wound closure	1	RCT	High	1 level down to moderate	No uncertainty	N/A	Moderate
(Primary outcome) Area loss of skin graft on 4th post-operative day	1	RCT	High	1 level down to moderate	No uncertainty	N/A	Moderate

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