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Health Technology Assessment of the Negative Pressure Wound Therapy for the treatment of acute and chronic wounds: efficacy, safety, cost effectiveness, organizational and ethical impact

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ABSTRACT

BACKGROUND: the aim of the study was to assess the safety, efficacy and cost-effectiveness of Negative Pressure wound therapy (NPT) for people with chronic and acute wounds.

METHODS: the scope and the final draft of the report have been submitted to the stakeholders (producers, payers and patients). Safety issues were addressed through a systematic review of the meta-literature. Efficacy was addressed through a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing NPT and other standard therapies in patients with chronic or acute lesions. Cost-consequence was analyzed through a systematic review of the existing studies.

RESULTS: we retrieved 19 studies, 13 of which were included in the meta-analysis. Many studies had biases that may have resulted in a better performance for NPT. NPT showed: a slightly shorter healing time (-10.4 days, p=0.001), with no heterogeneity, apart from one small study with very positive results, and 40% more patients healed (p=0.002, no heterogeneity).

We identified 15 original research papers on NPT costs and cost per outcome. The costs-per-patient-treated varied from +29% to -60%, with several studies reporting savings for NPT.

CONCLUSIONS: despite serious methodological flaws, the body of evidence available was sufficient to prove some clinical benefit of NPT in severe chronic and acute wound treatment. There is a need for independent and contextualized cost analyses.

Key words: Chronic Wound, Acute wound, Systematic review, Negative pressure therapy, Health technology assessment

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This scientific article reports the results in detail of the HTA assessment produced by the Agency of Public Health available at www.asplazio.it

INTRODUCTION

The pathology

Skin lesions often have multiple and intricate pathogeneses. This assessment distinguishes acute skin lesions, which complete the natural cycle of healing / scarring within 8 weeks, and chronic lesions of longer duration, which have lost their ability to rebuild anatomical and functional integrity (1).

Many factors can impede wound healing and can lead to the development of a chronic lesion. These factors may be systemic (poor nutrition, metabolic disorders, medications) or local (tissue hypoxia, infection, dry wound) (1).

Acute and chronic skin lesions affect at least 1% of the population (2). Chronic wounds are a major cause of morbidity, leading to considerable disability, and are often associated with increased mortality (1, 3).

Conventional Treatment

Optimal management of skin lesions begins with an early and accurate etiopathogenetic diagnosis (4).

The conventional treatment for all types of wounds includes: removing any necrotic tissue, keeping the wound moist and controlling infection (1). These treatments are combined with other intervention modalities specific to wound and patient type. Unfortunately there are no widely accepted standard protocols that identify the optimal mode and intensity of treatment (1).

For lesions that do not heal with conservative therapy, surgical therapy may be considered. The restoration of blood flow through arterial revascularization surgery is the main goal when treating vascular insufficiency (1). A skin graft can be performed on chronic wounds that do not heal and cannot be subjected to surgical revascularization (1). Even the indications for skin graft are not standardized. Skin grafts can be subject to rejection and the graft may not take. In addition there is substantial morbidity associated with grafts, such as pain or infection (5). Finally, the last resort treatment is amputation if the benefit of eliminating the lesion exceeds the harm intrinsic to the treatment (1).

The treatment setting varies from home care to highly specialized hospital care. The setting can also influence treatment modalities.

In everyday clinical practice, there is great variability in the treatment of skin lesions and there is evidence of substantial deviation from the already non-uniform indications in the guidelines (6). Therefore, patients who have a second round of treatment may find it very different from what they may have already received.

Topic Negative Pressure or Negative pressure wound therapy (NPT)

The goal of negative pressure wound therapy is to improve the healing of cutaneous and chronic lesions and to treat acute wounds.

The rationale on which it is based is that the negative pressure removes the extra-cellular fluid and the exudates which reduces swelling and improves blood flow, thus providing oxygen and nourishment to the tissues at the wound site and speeding up healing; it also reduces the bacterial load (7, 8).

The negative pressure is applied within a range between 50-200 mm Hg and can be done intermittently or continuously. A foam padding or gauze is applied to the area around the lesion, a small tube is inserted into the wound, and the whole wound area is sealed with an adhesive film. The breathable film allows for the exchange of gases while protecting the wound. The tube applies negative pressure creating a suction effect around the application of the foam or gauze. Changing the foam is recommended every 48 hours for adults and daily for adolescents and children, whilst a change of gauze is recommended every 72 hours (9).

The therapy is mainly used to manage patients with acute and chronic skin lesions, including pressure ulcers, diabetic ulcers, trauma, burns, and surgical incisions that have reopened.

NPT is generally proposed as a second line treatment (10), that is, for lesions that have not reduced in size by 50% one month after the start of standard treatment. As it is considered a non-invasive therapy, it is a good candidate for patients who cannot undergo surgery (8, 11). Based on the manufacturer's indications, treatment is contraindicated for patients with lesions involving a malignancy, for those with untreated osteomyelitis, in the presence of fistulas that have reached organs or body cavities, when there is a presence of a tumor at the edges of the wound, where veins or arteries are exposed, and when necrotic tissue is present. It must also be

used with caution in the presence of bleeding and if the patient is taking anticoagulants.

At the time of this assessment, devices from two firms, KCI and Smith & Nephew, were sold in Italy, while a third company, Covathech, was interested in launching its own device (Table 1).

Objective

The purpose of this report is to evaluate the impact resulting from the introduction of NPT in the treatment of acute and chronic cutaneous lesions based on the evidence available and with particular focus on the following aspects:

- safety
- efficacy
- costs
- impact on the organization of health care services
- ethical impact

METHODS

HTA (Health Technology Assessment) process

An HTA was performed in four phases:

1st phase creation of the working group (authors of the report) and of the consulting committee (external experts and stakeholders, see appendix 1).

2nd phase definition of the scope, a detailed articulation of the objective into specific questions to which the evaluation intends to respond to, subject to approval by the consulting committee which assessed the scope's relevance, comprehensiveness and clarity. The working group reviewed and reformulated the scope based on comments received.

3rd phase evaluation of the technology by the Working Group.

4th phase elaboration of the final document submitted to the consulting committee for comments and suggestions and modification in its final version by the Working Group

Systematic Review

The systematic review was divided into two steps:

1. review of the meta-literature, identification of fields and periods covered by revisions already published;
2. update and integration of existing revisions.

The research criteria were:

- population - patients with acute or chronic skin lesions
- intervention - application of negative pressure on the wound
- control - standard treatment or other treatment not based on negative pressure
- outcome - efficacy: percentage recovery or effect on preparation for surgery, reduction in

TABLE 1

DEVICES ON THE MARKET			
COMMERCIAL NAME	FILLER (FOAM BANDAGE)	OPERATING PRESSURE RANGE	PRODUCER /DISTRIBUTOR
VAC*	GranuFoam® polyurethane foam (PU) / WhiteFoam® polyvinyl alcohol foam (PVA)/ GranuFoam Silver® composition not given	-125 mmHg	KCI, Kinetic Concepts Inc, San Antonio, Texas
VISTA* / RENASYS*	Polyurethane foam (PU) / Antimicrobial gauze with poliesametilene biguanide (PHMB)	-60 / -120 mmHg	Smith & Nephew, Hull UK
-	-	-	Convatec

* Marketed in Italy since 1/5/2009

wound surface, reduction in healing time and reduction in pain. Safety: adverse events. Costs: cost per patient treated, cost per patient cured, cost per day of treatment.
- Type of study - first step: guidelines, systematic revisions, HTA report. Second step: efficacy (RCT or quasi-experimental). Safety: RCT, Register of adverse events. Costs: RCT with cost evaluation; studies of costs; analysis of cost-effectiveness studies based on RCT or on models.

Sources and research modalities

The first step of the research, which was the review of the meta-literature, was carried out using PubMed and other major databank sites of meta-literature.

The second step, the review of the primary literature, was carried out entirely using MedLine and cross-checked with the bibliographical references of the works identified. We decided to update the 2008 Cochrane (12) review with works published from 2007 to 2009 and to widen it to include acute lesions. Appendix 2 lists the keywords.

Extraction and synthesis of data

The data were extracted independently by two authors and then checked by a third. We proceeded first to extract the outcomes identified in the research scope, which we then integrated with all others cited in the studies included.

Estimated risk of bias in included studies

The selected papers were evaluated using the CONSORT check list (13). Selection bias: we determined whether randomization was performed and how it was conducted. Detection bias: blindness to the intervention was not possible for the patient or physician. Blindness can only be hypothesized for the final assessment, with a wash-out period to eliminate the marks around the lesion left by the device. However, this is feasible for patients who end follow-up and decide to discontinue therapy, a condition difficult to achieve, as well as being unethical. A blinding of the assessment is only possible by quantifying the wound area or volume in the computerization phase or biopsies. Bias of follow-up: for each study, the number of patients lost to follow-up was reported, and broken down by intervention (when given). Funding: any financial support received was reported.

Unit of analysis

The unit of analysis used was always the one proposed by the authors. When this coincided with that of the patient there were no problems, but often the unit of randomization was a single lesion, and since a patient could have more than one, there was a risk of underestimating the variance.

Estimated heterogeneity

A test of heterogeneity was reported for each outcome and each comparison.

Data synthesis

We present six types of comparisons between NPT and other therapies (standard therapy not further specified; wet gauze, hydrocolloids, gels, hydrocolloids and alginates; polyglactin mesh (MESH)). A summary was also reported of the comparison between NPT and any other therapy. For each comparison, estimates of the synthesis of the treatment effect with respective 95% confidence intervals were calculated. A Fixed effects model was fitted if the heterogeneity was not significant, whilst a random effect model was used in the presence of significant ($p<0.05$) heterogeneity. The data were analyzed using Review Manager 5 (the Cochrane Collaboration).

Numerous analysis were carried out for chronic, acute and mixed wounds, and among chronic wounds, an analysis was carried out on a subgroup of pressure ulcers.

RESULTS

The revision of the meta-literature helped identify 8 systematic revisions (2, 12, 14-19) and 5 HTA reports (1, 9, 20, 21, 22). The secondary scientific literature review agrees with the view of a weak/lack of evidence supporting NPT (Table 2).

TABLE 2

GUIDELINE SUMMARY	
SYSTEMATIC REVIEWS	
Hammond C, Clift M. *Vacuum Assisted Closure therapy*. NHS, Centre for Evidence-based Purchasing. June 2008 (12)	Due to the methodological limitations of the studies reviewed it is not possible to draw firm conclusions. However, the evidence suggests that NPT is at least as effective as the treatments it was compared with. The majority of evidence does indicate a benefit in comparison with 'standard wound care' e.g. saline moist gauze, however the benefit is less clear when compared with 'advanced wound care' e.g. hydrocolloids, alginates, in the treatment of chronic and acute wound.
Higgins S. *The effectiveness of vacuum assisted closure in wound healing*. Clayton, Victoria: Centre for Clinical Effectiveness (CCE) 2003 (13)	The three articles identified and included in this report represented four primary studies (2 in the systematic review), with 78 patients randomized to receive vacuum assisted closure (VAC) or another wound dressing. The systematic review and one randomized controlled trial suggest that VAC may have advantages compared to other forms of wound dressing studied in terms of chronic wound healing and wound closure, with one trial finding no difference in the time for wounds to reduce in volume by 50 per cent. However, methodological limitations of the two trials included in the systematic review, and of the two further studies appraised in this report, limit the validity of any conclusions that can be drawn from them. No studies were identified which reported outcomes such as patient mobility levels or quality of life associated with VAC. Presently, there have been too few reports published of randomized patients to suggest which patient groups may benefit most from VAC, or what regimen is most efficacious.
Mendonca DA, Papini R, Price PE. *Negative-pressure wound therapy: a snapshot of the evidence*. Int Wound J 2006; 3:261–271 (14)	Based on the evidence to date, the clinical effectiveness of negative-pressure therapy is still unclear. Although case reports and retrospective studies have demonstrated enhanced wound healing in acute/traumatic wounds, chronic wounds, infected wounds, wounds secondary to diabetes mellitus, sternal wounds and wounds located on the lower limb; there are very few randomized controlled trials with mixed results. The evidence for using NPT to enhance wound healing in patients with decubitus ulcers, concomitant diabetes and peripheral vascular disease and to improve skin graft take is lacking. In order to justify its increasing use, further long-term randomized controlled trials are needed.
Pham CT, Middleton PF, Maddern GJ. *The safety and efficacy of topical negative pressure in non-healing wounds: a systematic review*. J Wound Care. 2006 Jun;15(6):240-250 (15) (updating: Pham C, Middleton P, Maddern G. *Vacuum-Assisted Closure for the Management of Wounds: An Accelerated Systematic Review*. ASERNIP-S REPORT NO. 37. December 2003)	There is a paucity of high quality RCTs on NPT for wound management with sufficient sample size and adequate power to detect differences, if there are any, between NPT and standard dressings. More rigorous studies with larger sample sizes and adequate randomization methods assessing the use of TNP on different wound types are required. However, based on the data from the included studies, the TNP technique does appear to result in better healing, with few serious complications, and thus looks to be a promising alternative for the management of various wounds. Application of the therapy is simple, but it requires training in order to ensure it is used appropriately and competently.
NHS; National Institute for Health and Clinical Excellence. *Negative pressure wound therapy for the open abdomen*. Issue date: December 2009 (16)	Current evidence on the safety and efficacy of negative pressure wound therapy (NPWT) on open abdomen is inadequate in quality and quantity. There have been concerns about the occurrence of intestinal fistulae associated with this procedure but there is currently no evidence about whether NPWT is the cause.
Wasiak J, Cleland H. *Topical negative pressure (TNP) for partial thickness burns*. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD006215. DOI: 10.1002/14651858. CD006215.pub2 (17)	There is a paucity of high quality RCTs on TNP for partial thickness burn injury with insufficient sample size and adequate power to detect differences, if there are any, between NPT and conventional burn wound therapy dressings.
Gregor S, Maegele M, Sauerland S, Krahn JF, Peinemann F, Lange S. *Negative pressure wound therapy: a vacuum of evidence?* Arch Surg. 2008 Feb;143(2):189-96 (2)	Although there is some indication that negative pressure wound therapy (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.
Ubbink DT, Westerbos SJ, EvansD, Land L, Vermeulen H. *Topical negative pressure for treating chronic wounds*. Cochrane Database of Systematic Reviews 2008, Issue 3 (18)	Trials comparing NPT with alternative treatments for chronic wounds have methodological flaws and data do demonstrate a beneficial effect of NPT on wound healing; however more, better quality research is needed.

TABLE 2 (CONTINUED)

GUIDELINE SUMMARY	
HTA REPORTS	
Costa V, Brophy J, McGregor M. *Vacuum-assisted wound closure therapy (V.A.C.)*. Montreal, McGill University Health Centre, July 2005 (modified: March 2007) (20)	The published comparative studies did not show a consistent statistical or clinical difference in meaningful health outcomes between patients with complex wounds treated with Vacuum Assisted Closure (VAC) and other therapies. The quality of the evidence is poor, with small studies and inconsistent study methodology. Therefore, we are led to concur with the 5 other recent technology assessments, and one systematic review, that the available evidence does not support the routine use of VAC. While VAC may, under certain circumstances, require less nursing time due to less frequent dressing changes, any saving in nursing time may be offset by the increased material costs associated with VAC treatments.
Fisher A, Brady B. *Vacuum Assisted Wound Closure Therapy*. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA). Issue 44; March 2003 (10)	Four controlled trials and one interim analysis provide poor quality data and weak evidence that VAC therapy may be superior to conventional methods used in healing wounds. Complications with VAC therapy are uncommon. More research is needed to support the available evidence. The best evidence to determine benefits of this technology will be obtained from multi-site, randomized, controlled trials that include larger sample sizes, long-term follow-up, measurements of quality of life, measurements of pain using validated tools and cost analysis.
IQWiG. Negative Pressure Wound Therapy. Institute for Quality and Efficiency in Health Care. Year: 2006 No. 041 (21)	There are at present no results of adequate reliability which provide proof of the superiority of negative pressure wound therapy (NPWT) in comparison with conventional therapy and which would justify broad use of this method outside clinical trial settings. It would be advisable to re-examine this question in 2 to 3 years.
Medical Advisory Secretariat. *Negative pressure wound therapy: an evidence-based analysis*. Ontario Health Technology Assessment Series 2006;6(14). [21]	Based on the review and analysis of this study, OHTAC found that: • due to methodological limitations, existing data from controlled trials do not convincingly support a benefit of negative pressure wound therapy (NPWT) over standard care for the rate of complete wound closure; • it is not possible to reliably comment on the time needed to complete wound closure; and • there may be an increased rate of wound infection associated with NPWT compared to standard care.
Samson DJ, Lefevre F, Aronson N. *Healing Technologies: Low-Level Laser and Vacuum-Assisted Closure*. AHRQ Publication No. 05-E005-2. December 2004 (1)	Evidence was limited by poor trial quality. Concerns centered on: randomization adequacy; group comparability at baseline and follow-up; use of complete healing as the primary endpoint; adjustment for confounders; and intention-to-treat analysis. Sample sizes were generally small, making it difficult to find statistically significant differences between groups. The best available trial did not show a higher probability of complete healing at 6 weeks with the addition of low-level laser compared to sham laser treatment added to standard care. Study weaknesses were unlikely to have concealed existing effects. Future studies may determine whether different dosing parameters or other laser types may lead to different results. Vacuum-assisted closure trials did not find a significant advantage for the intervention on the primary endpoint, or complete healing, and did not consistently find significant differences on secondary endpoints and may have been insufficiently powered to detect differences. Ongoing RCT protocols may provide better evidence on outcomes of interest. Given the sparse evidence for these two interventions, at the present time, it is not possible to find variables in these trials that may be associated with better results.

Safety

From the analysis of the technical data supplied by the manufacturers there were no critical safety issues for either the electric aspects or for possible malfunction.

A NICE report was found, entirely dedicated to the safety of the technique in the treatment of an open abdomen (16), which concluded that current evidence on the safety and effectiveness of NPT on an open abdomen is inadequate both in quantity and quality. There is careful attention paid to the onset of intestinal fistulae associated with this technique, but at this time there is no evidence that NPT is the cause.

The NICE report also identifies two trials (23, 24) and three sets of cases. The first trial studied 51 patients randomized for NPT, control,

and MESH experimental treatment, and reported the development of entero-cutaneous fistulas, respectively in 21% and 5% of cases (p = 0.14). A second trial, on 72 patients who were randomized for NPT or for primary abdominal closure, reported that a highly productive entero-cutaneous fistula developed in 1 out of 37 (3%) patients treated with NPT. A series of cases reported a 5% (13/258) development of entero-cutaneous fistulae, whilst 12 fistulas occurred after surgery that included bowel resection and anastomosis. One series reported intestinal fistulas in 21% of patients (6/29) on follow up at 20 days. Finally, a study of 42 patients, of whom 34 had received an anastomosis, sutured enteretomy, or abdominal surgery, reported that 2 (5%) had developed a fistula during NPT at 5 and 9 days of follow up.

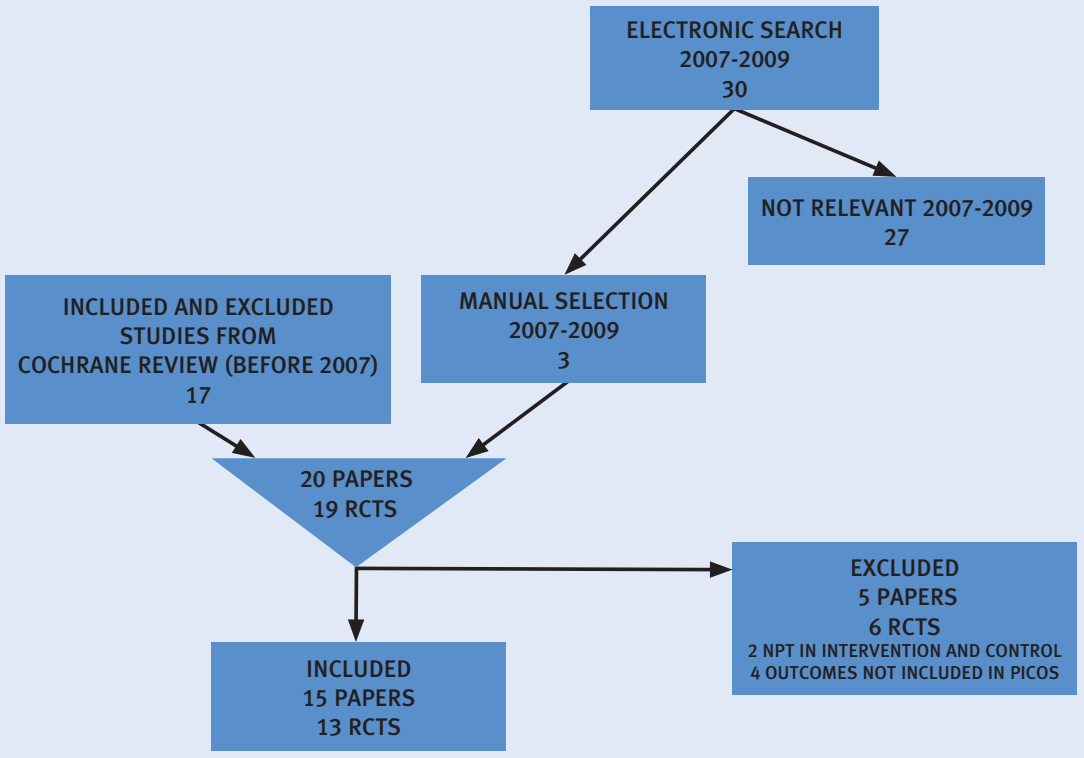
The Food and Drug Administration (FDA) in November 2009 published a note (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm190658.htm) which reported six deaths and 77 injuries associated with the use of NPT in the past two years. Most of the deaths occurred at home or in long-term care facilities. The presence of hemorrhage was the most serious complication, which occurred in all deaths and in 17 of the injury cases. Extensive hemorrhage occurred in patients with vascular grafts (femoral or popliteal grafts as-femoral), in patients with chest or groin injuries, in those who had received anticoagulant therapy and during the removal of bandages attached to tissues. Patients with hemorrhage required emergency room visits and/or hospitalization, and were treated surgically or with blood transfusions. 27 cases showed a worsening of the lesion resulting from infection of the original open wound or from pieces of gauze left inside, and 32 noted some lesions caused by foam padding attached to or embedded in the wound tissue. Most patients required surgery for the removal of pieces of foam retained in the tissue, for wound debridement, and for treatment of dry dehiscent wounds, as well as additional hospitalization and antibiotic treatment.

Efficacy

The search strategy identified 30 papers. After a review of abstracts, 3 papers were considered

FIG. 1

FLOWCHART FOR STUDY SELECTION AND EXCLUSION



relevant. Another 17 papers were identified by the previous Cochrane review (18). Finally, 20 articles about 19 controlled studies were retrieved (Figure 1): one study reported the results of two independent randomized trials, while three papers reported the various outcomes of the same randomized study. Thirteen studies were useful to assess the outcomes considered for a total of 893 patients. Of these, 12 evaluated the KCI device and one evaluated a new device manufactured by the hospital (homemade) (25); no studies were retrieved regarding the Smith & Nephew or Covatech products.

Table 3 shows the 6 excluded studies (26-30) and table 4 shows those included.

Assessment of study quality

Randomization was described in a satisfactory manner in the studies of Eginton (31), Ford (32), Moues (33), Vuerstaek (34), Braakenburg (35), Bee (22) and Etoz (36).

Other studies described the method in ambiguous ways: Joseph (37), MacCallon (38). The method was not reported at all in the studies of Armstrong (39), Wanner (40), Mody (25) or Blume (41).

Only some studies (31-33, 35, 37) were blind to the quantification of the wound area or the volume at the computerization phase or for biopsies. This remains one of the major potential sources of bias, because many of the outcomes used had a certain amount of subjectivity in measurement.

Studies with longer follow-up periods lost a high number of subjects. Blume (41) and Mody (25) had different losses in the control and the treatment groups. For Armstrong (39), the losses were similar in the two groups. Some studies did not report the expected outcomes in the study design, but they could be determined when the methods reported the principal outcomes expected. The extreme fragmentation of the outcomes presented, however, indicate certain arbitrariness in the way the results were reported.

As described in the preceding paragraph, for individual studies there was a risk that only positive outcomes were reported. The site www.clinicaltrials.gov reported some terminated or abandoned trials, even if the number of these is much lower than those concluded or in progress. All the completed studies were traced to the publications that we found.

Another possible source of bias was the duration of follow-up, and many studies, in fact, observed patients for very brief periods.

TABLE 3

STUDIES EXCLUDED FROM THE EFFICACY ANALYSES

AUTHOR	YEAR	REASONS FOR EXCLUSION
Genecov (26)	1998	The outcomes were not included in the PICOS of the review in the analyses. Furthermore the study is not randomized and has very high dropout considering a 7 day follow up period only.
Llanos (27)	2006	Comparison of NPT with an identical device but without the application of the vacuum, with the objective of distinguishing the effect of pressure from that of the foam and adhesive bandage, the objective is to clarify the therapeutic mechanism.
Moisidis (28)	2004	The principal and secondary outcomes do not correspond with any of the outcomes identified as relevant in the methods; it was randomized half by NPT and half by Mepitel, Acriflavina, and cellulose foam.
Stannard (29)	2006	2 studies: the principal and secondary outcomes do not correspond to the outcomes identified as relevant in the methods. The outcomes were drainage time, infections, serum albumin and thrombo-prophylaxis.
Timmers (30)	2005	Compared two different applications of NPT 100-500 mmHg vs 25 mmHg.

TABLE 4

STUDIES INCLUDED IN THE EFFICACY ANALYSES

AUTHOR	YEAR	COUNTRY	METHODS	STUDY SIZE	WOUND TYPE	INTERVENTION	CONTROL
Armstrong (39)	2005	USA	RCT; no method of randomization; UoR=pz; UoA=patients	Patients=162; NPT=77; Control=85	acute	NPT	Alginates, hydrocolloids, foams, hydrogel
Bee (23)	2008	USA	RCT; closed envelope; UoR=patients; UoA=wounds	Patients=51; NPT=31; MESH=20	acute	NPT -150mmHg	Polyglactin MESH: polyglactin mesh copolymer 910(re-absorbable)
Blume (41)	2008	USA	RCT, multicenter, block randomization; UoR=patients; UoA=wounds	Patients=335; NPT=169; control=166;	chronic; acute	NPT	Alginates, hydrogel, saline solution, collagen, hydrocolloids, other
Braakenburg (35)	2006	Holland	RCT; block randomization with closed envelopes; UoA=patients; UoA=wounds	Patients=65; NPT=32; control=33	mixed	NPT with pressure -125 mmHg	Hydrocolloids, alginates, acetic acid, sodium hypoclorite
Eginton (31)	2003	USA	RCT crossover random number generator; UoR=pz; UoA=wound	NPT: 11 wounds; Control: 11 wounds; Patients=10	chronic	NPT with continuous pressure at -125mmhg, with foam	Hydrocolloidal gel gauze bandage
Etoz (36)	2004	Turkey	RCT; randomization using last number of hospital admission protocol (even number =TNP) and odd (control); UoR=patients; UoA=wounds	Patients=24; NPT=12; Control=12	chronic	NPT standard medical aspirator with foam, -125mmHg, manufactured by (Bicakcilar Inc (Istanbul).	Gauze with saline solution
Ford (32)	2002	USA	RCT; table of random numbers; UoR=pz; UoA=wounds	Paz=28; wounds=41; NPT=20 HP=15	chronic	NPT	Healthpoint System=gel products - Accuzyme, Iodosorb, panafil
Joseph (37) (from Ubbink 2008 (18))	2000	USA	RCT; labeled files, UoR=patients; UoA=wounds	Patients=24; NPT=18; Control=18	chronic	NPT	Gauze with 0.9% saline solution
McCallon (38) (from Ubbink 2008 (18))	2000	USA	RCT; coin toss, UoR=patients; UoA=wounds	Patients=10; NPT=5; Control=5	chronic	NPT -125mmHg continuous and after first bandage change intermittent pressure	Gauze with 0,9% saline solution

TABLE 4 (CONTINUED)

STUDIES INCLUDED IN THE EFFICACY ANALYSES							
AUTHOR	YEAR	COUNTRY	METHODS	STUDY SIZE	WOUND TYPE	INTERVENTION	CONTROL
Mody (25)	2008	India	RCT, block randomization; UoR=patients; UoA=wounds	Patients=48 (7 lost after randomization); NPT=15, control=33	mixed	NPT at -125mmHg	Gauze soaked with saline solution or dry bandage
Mouës (33)	2004	Holland	RCT; choice of closed envelope with therapy description; UoR=pz; UoA=wound	Patients=54; NPT: early=12, late=17 Control: early=8; late=17	mixed	NPT continuous pressure -125 mmHg with foam	Moist gauze with saline solution 0,9%, nitrofuralam 0,2%, acetic acid solution 0,2% sodium hypochlorite ,2%
Vuerstaek (34)	2006	Holland	RCT; randomization stratified into three groups of patients; block randomization of 8 UoR=Pz; UoA=wound	Patients=60 wounds=72 NPT=venous=13; combined=4; ateriosclerotic=13 Control=venous=13 combined=4; ateriosclerotic=13	chronic	NPT pressure at -125mmHg	Bandages, including hydrogel and alginates
Wanner (40)	2003	Switzerland	RCT; no randomization method; UoR=pz; UoA=wound	Patients=22 NPT=11; Control=11	chronic	NPT continuous pressure at -125mmHg with foam	Gauze with ringer's solution

RCT= Randomized controlled trial
UoR= unit of randomization
UoA= unit of analysis

In addition, there was a lack of consistency in the formulation of the endpoints.

NPT versus standard therapy

Three studies compared NPT with the generic standard therapy: one study of 162 patients who underwent foot amputation due to diabetes (39), a study of diabetic ulcers (41) with 335 patients, and a final study about chronic and acute wounds (35) with 65 patients.

The reduction of the wound area was significantly greater in the group treated with NPT in Blume's study (41) (Squared Mean Difference (SMD) = -1.27cm, 95% CI [-1.51, -1.04]), while the study by Braakenburg (35) did not show any benefit (SMD = -0.07, 95% CI [-0.55, 0.42]). The overall effect was not statistically significant: SMD = -0.69, 95% CI [-1.87, 0.49].

The proportion of patients with closed wounds was greater in the NPT group in both studies where it had been evaluated (39, 41), with a statistically significant overall effect: RR = 1.47, 95% CI [1.18, 1.84].

The reduction in average wound closure time was 21 days (95% CI [-36.74, -5.26]) in Armstrong's study (39), while Braakenburg's study (35) reported only a 4 day reduction (95% CI [-12.06, 4.06]). The overall effect was not statistically significant (Mean Difference (MD) = -11.10 days, 95% CI [-27.53, 5.33]).

Also in Blume's study (41), the average amount of time it took for the wound to close was 96 days for patients undergoing NPT, but it was

undetermined for the controls. The authors also calculated the time to 75% recovery, and in the NPT group this was significantly lower than in the non-NPT group: 58 days vs. 84 days (p = 0.014).

The study by Armstrong (39) observed no differences in complications between the two groups, whereas Braakenburg's study (35) reported no complications such as hemorrhage, fistulas, osteomyelitis or sepsis.

Studies of diabetic limbs have also evaluated the percentage of amputations (41) or re-amputation (39), and have shown a statistically significant reduction of these: Relative Risk (RR) = 0.35, 95% CI [0.17, 0.74].

One study evaluated the bacterial load and found a greater increase in patients treated with NPT (35), although the difference (RR = 1.45, 95% CI [0.95, 2.21]) was not statistically significant.

Only one study evaluated pain intensity (35) and it did not find any significant differences, but, instead, reported two cases where treatment was discontinuous due to the pain provoked when the gauze was changed.

NPT versus moist gauze

Six studies compared NPT with the moist gauze technique, four of these on chronic wounds (Etoz (36) with 24 patients; McCallon (38) with 10 patients; Joseph (37) with 24 patients; Wanner (40) with 22 patients) and two on mixed wounds (Moues (33) with 54 patients; Mody (25) with 48 patients).

A reduction in wound size was reported in four studies (33, 36-38), all of which found a an overall statistically significant effect in favor of the NPT approach: SMD = -1.69, 95% CI [-2.91, - 0.47].

One study (40) reported an average reduction of 50% in the initial volume though did not find statistical differences (MD = -1.0, 95% CI [-8.21, 6.21]).

Average preparation time for surgical treatment was evaluated by Moues (33), who found a three day decrease in the NPT group, though this was not statistically significant (95% CI [-6.11, 0.11]).

Three studies (25, 33, 38) evaluated complete recovery time and did not find any significant differences: -7 days 95% CI [-30.55, 16.45].

A study by Mody (25) reported the proportion of wounds that had reached satisfactory closure and did not find any differences (RR = 0,96; 95% CI [0.50, 1.83]).

Moues (33) found a worse performance in patients with NPT regimens, although the difference was not significant, even though there had been a reduction of total bacterial load (CFU/tissue in grams: 0,06 NPT versus -0.05 controls (p=0.22).

Three studies compared the risk of complications and found no differences (25, 33, 37): RR = 1.03; 95% CI [0.29, 3.71].

NPT versus hydrocolloids

Only one study (31) with 10 patients made this comparison, and it referred to chronic wounds. The study showed no significant differences in the percentage reduction of the wound surface size (MD = -22.30, 95% CI [-58.48, 13.88]), while the reduction in volume was significant (MD = -58.90, 95 % [-93.44, -24.36]).

NPT versus gels

One study (32) with 28 patients, made this comparison and it, too, focused on chronic wounds.

The study found a slight advantage for NPT, which was not significant in reducing volume (-51.8% vs. -42.1% NPT gel (p = 0.46)). There were no differences in the proportion of wounds that had completely healed: 2 (n = 20) vs VAC 2 (n = 15) HP.

NPT versus hydrocolloids and alginates

Only one study (34) with 146 patients carried out this comparison on chronic wounds. The study found significantly different healing times (MD = -16.00, 95% CI [-25.47, -6.53]), surgical preparation times (MD = -10.00, 95% CI [-17.12, -2.88]) and differences in the percentage of patients surviving skin grafts (MD = 13.00%, 95% CI [0.00, 26.00]).

The study showed no significant differences between treatments in terms of pain intensity (MD = -0.20, 95% CI [-0.53, 0.13]), or quality of life measured with two instruments (EuroQol 5D = MD 1.00, 95% CI [-6.88, 8.88], Short form McGill Pain Questionnaire MD = 0.00, 95% CI [-0.51, 0.51]).

The study reported a higher rate of complications in the NPT group (40%) compared to the control group (23%), but the difference was not statistically significant (p = 0.17).

NPT versus MESH

One study with 48 patients compared these two therapies in trauma/emergency patients

who had undergone an exploratory laparotomy, were thus waiting for temporary closure of the abdomen (23), and in which both experimental treatments were applied. There were no significant differences in any of the outcomes analyzed (fascial closure time, fistula, abdominal abscess, intra-hospital mortality). Although NPT appeared to have produced a slightly faster closing rate (RR = 0.60, 95% CI [0.31, 1.15]), the MESH treatment resulted in fewer fistulae (RR = 1.97, 95% CI [0, 44,8,74]).

NPT versus all other treatments

Figures 2-6 show a Forest graph for the outcomes common to most studies. A reduction of the wound surface (Figure 2) was observed both in acute and chronic injuries (SMD = -1.10 effect, 95% CI [-1.78, -0.42]).

For surgery preparation time (Figure 3), the difference was statistically significant: MD = -4.12 (95% CI [-6.97, -1.27]), while total healing time (Figure 4) decreased by 10.42 days also (95% CI [-15.98, -4.86]), as did the proportion of healed wounds (Figure 5), with a relative risk of RR = 1.40, 95% CI [1.14, 1.72].

Finally there were no statistically significant differences observed in the occurrence of complications (Figure 6), RR = 1.07, 95% CI [0.61, 1.85].

Analysis for pressure ulcers

The only studies of NPT applied to pressure ulcers were those of Ford (32) and Wanner (40). In studies that included various wound types, including pressure ulcers, the number of pressure ulcers was very low (25, 37).

Costs

Results of a systematic search of research papers dealing with treatment costs and costs of NPT

33 articles were found in PubMed. An analysis of the abstracts identified 13 articles that reported at least a partial cost analysis (25, 34, 35, 42-51).

From an analysis of the bibliographic references, four other publications were identified (Table 5) (52-55).

FIG. 2

FOREST PLOT – WOUND SURFACE REDUCTION

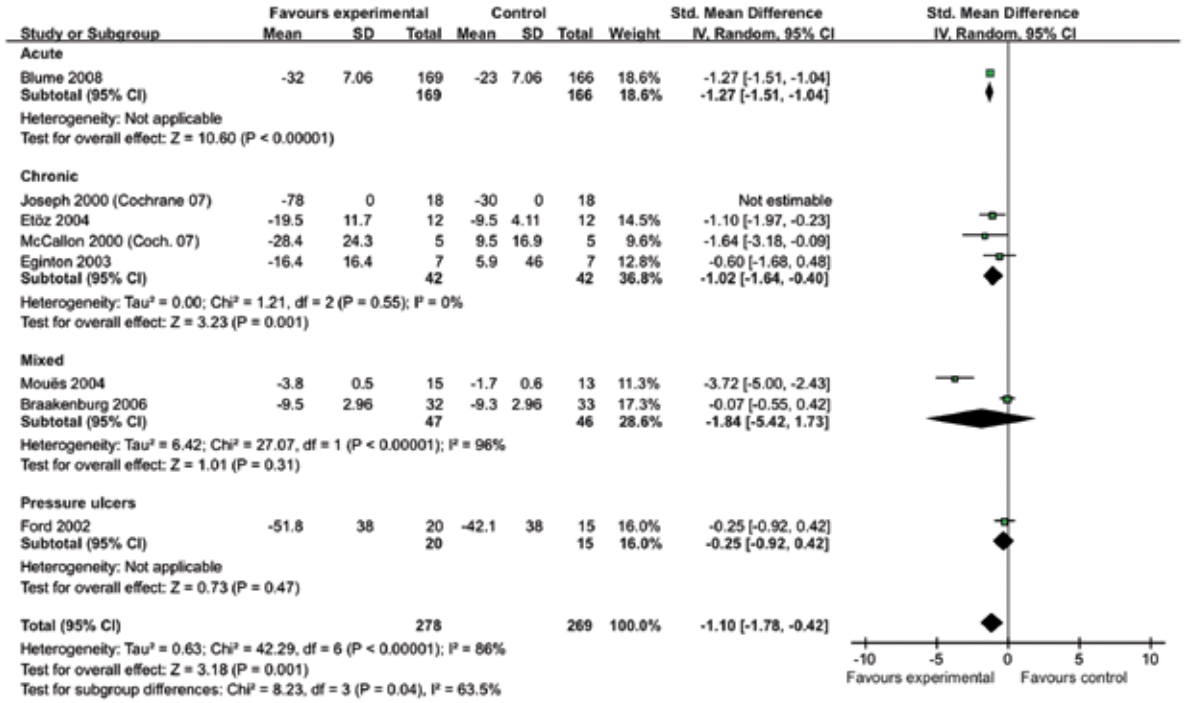


FIG. 3

FOREST PLOT – SURGICAL PREPARATION TIME

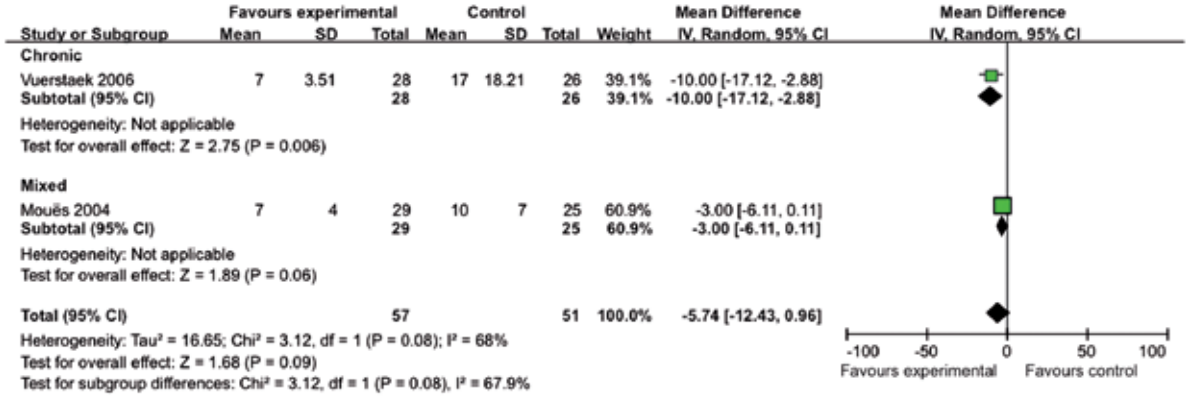
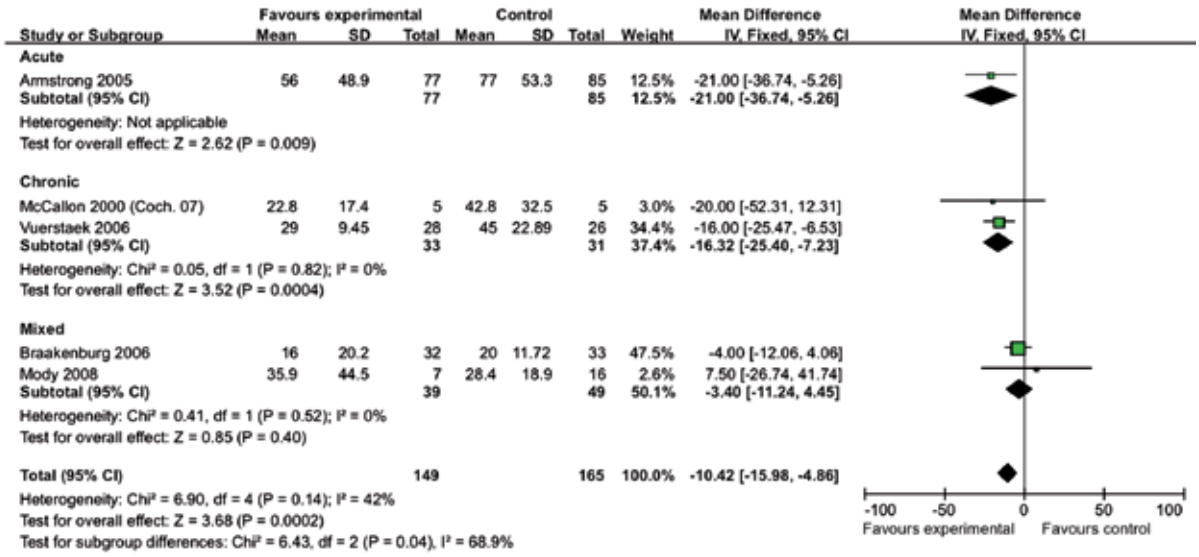


FIG. 4

FOREST PLOT – COMPLETE HEALING TIME



Summary of results of studies

Of the 8 studies for which it was possible to analyze the original publication, 6 were financed or conducted by manufacturers (5 by KCI, and one by the home-made device produced by the authors of the paper), one had only public funding and another did not report the funding source or if there were conflicts of interest.

The case studies considered all regarded chronic ulcers (3 diabetic feet, 1 leg ulcer, 1 pressure ulcer and 2 various) with the exception of two studies on post-surgical case studies (postCABG and one various) and two on both chronic and acute cases. HTA reports were not recovered as they were no longer available on the web, and the publishing Agencies and authors did not send the paper version. Two studies, one from 1999 (i.e. before any trial results had been published) and one from 2001 (when the first results of randomized trials were published) were found but neither study dealt with cost analysis.

Four studies carried out a cost-effectiveness analysis, three based on models (44, 45, 49) and one based on results of a trial (35).

The oldest of the models (49) derived the parameters of treatment efficacy by comparing the times and the outcomes from a group

FIG. 5

FOREST PLOT – PERCENTAGE OF WOUNDS HEALED

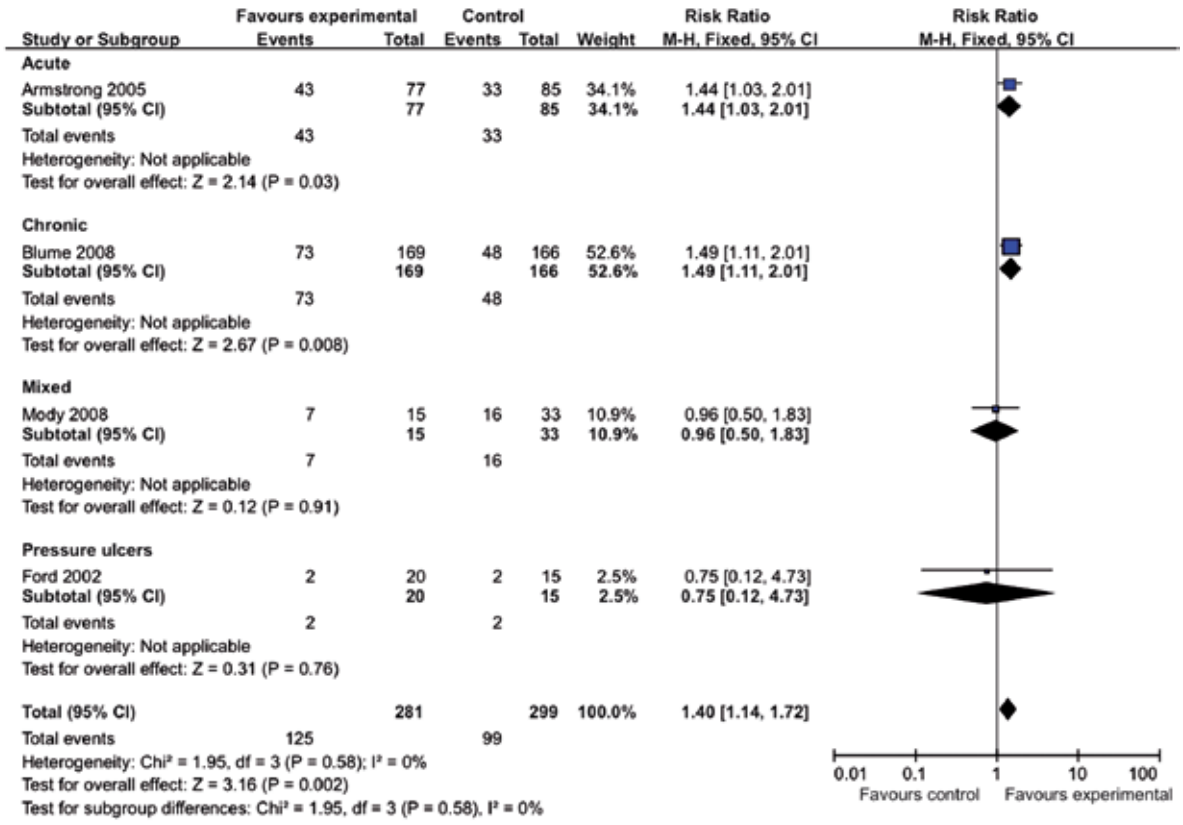
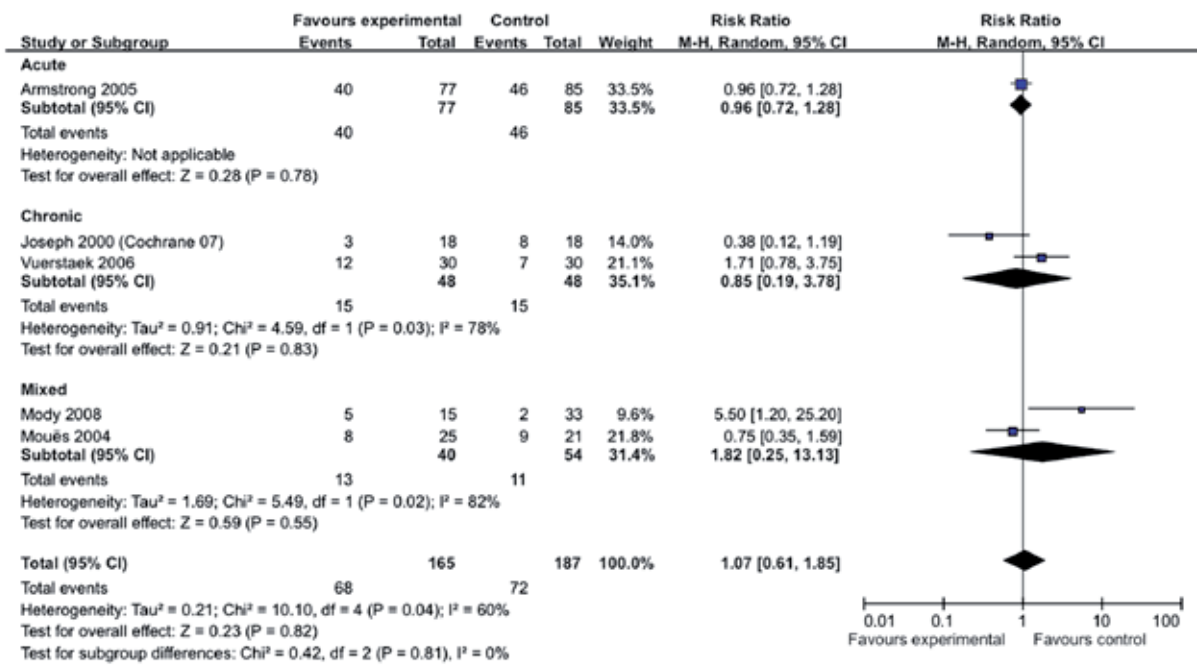


FIG. 6

FOREST PLOT – COMPLICATIONS



of Medicare patients treated with NPT, with the results of standard therapy observed in a published trial, in which treatments other than NPT were compared. In order to make the two groups comparable, the authors adjusted for wound size. There were many debatable assumptions required to justify these choices. The results showed that NPT dominated, with overall better outcomes and lower costs. The cost per healed wound was estimated to be -40% for NPT cases.

There were similar conclusions made for the other two cost-effectiveness models, with an NPT dominance emerging over the standard treatment, and over most other therapies.

Flack (45) used a Markov model to estimate the cost of each amputation avoided and QALY (Quality Adjusted Life Years) gained. Over a one-year period, 1000 patients were simulated using transition probabilities taken from the literature. The model results indicate that NPT is less costly and more effective than both traditional therapy and advanced therapy, and the projections are robust with respect to changes in key parameters, including transition probabilities, cost of the NPT and the weight of utilities applied to the health status considered (infected ulcer, non-infected ulcer, post-amputation ulcer, healed, healed post-amputation, amputation, death).

Dougherty (44) compared the potential economic benefit of platelet rich plasma gels compared to alternative therapies (non-contact kilohertz ultrasound therapy; human fibroblast-derived dermal substitute; allogenic bi-layered skin substitute cultures; bi-layered cellular matrix, negative pressure wound therapy, and recombinant human platelet-derived growth factor BB) in the treatment of unhealed diabetic foot ulcers. An economic model simulated clinical outcomes in terms of associated costs and QALYs for a hypothetical group of 20 000 patients with unhealed diabetic foot ulcers for a period of 5 years or until death. The platelet rich plasma resulted superior to NPT, though the latter group, compared with other treatments, showed to improve the quality of life and had a lower cost over a period of 5 years.

The latest study (35) that proposed a cost-effectiveness analysis analyzed data from a Dutch trial and found a cost reduction of 25-30% for each hospitalized wound and more QALYs gained.

The remaining studies, that had conducted cost analysis, all showed similar results of lower costs for treated or healed lesions (-13%, -45%, -50%) and better per cm^2 of reached wound closure (-60%) with the exception of a study analyzing data from another Dutch trial which found a cost per treated lesion 29% higher for NPT with respect to alginate hydrocolloid use.

In all studies, the observed or expected savings were derived from:

- lower staff costs for changing wound dressings;
- less time for recovery and surgery preparation;
- fewer complications.

In contrast, the material costs were always higher for NPT.

The savings in personnel intervention are always based on the assumption of a rigid application wound-dressing change times (every 48 hours for adults and 24 children, with the KCI system used in most of the studies analyzed).

In addition, in cost-effectiveness studies, the duration of treatment evaluated was always rather short (1 to 8 weeks) and rarely included "chronic" use of NPT.

Detection and analysis of costs

Taking into account reports in the analyzed literature, NPT can lead to savings exclusively in ordinary hospital settings but not in day-hospital scenarios. In fact, the assumed or observed savings in the studies originated from a lower utilization of human resources related to the less frequent change of wound dressings. The rate of bandage change in conventional therapy is once every 24-hours only in case of hospitalization whilst, in day-hospital settings, patients' bandages are taken off 2 or 3 times a week. In contrast, the frequency of wound dressing changes in NPT is every 48 hours for hospitalized patients and for those in day-hospital.

The cost of materials for conventional bandages reported at S. Camillo in Rome is extremely variable. The proportion of standard bandages, which range from 4.2 to 18.9 €, and innovative bandages, which range from 4.2 to 53.1 €, varies depending on the wound and the patients' condition. In particular, wounds that have not healed with traditional treatments (second line treatments), and serious wounds in patients with specific risk factors for chronicity, are treated with a higher proportion of high-cost medications. It follows that the more restrictive the way in which NPT indications are applied, the more likely it is that it is going to replace high-cost bandages, and therefore the use of NPT results less expensive in any case.

TABLE 5

CHARACTERISTICS OF THE STUDIES INCLUDED IN THE COST ANALYSES

AUTHOR	YEAR	STUDY	TYPE	DATABASE	SETTING	PROSPECTIVE	CONDITIONS	COMPARISON
Apelqvist (42)	2008	Cost analysis cost-consequence	research article	RCT	hospital	Societal (includes family/patients dressings)	Diabetes related wounds	Wet gauze
Braakenburg (35)	2006	Cost effectiveness applied to RCT results	research article	RCT	hospital	HS	Mixed	Hidrocolloids alginates
Flack (45)	2008	CEA	research article	model		HS	Wounds secondary to diabetes	Standard and other advanced care
Mody (25)	2008	Cost analysis	research article	RCT	hospital	HS	Mixed	Moist gauze
Mokhtari (46)	2008	Cost analysis	research article	Hospital cohort	hospital	HS	DSWI after CABG	None
Mouës (47)	2005	Cost analysis	research article	RCT	hospital	HS	Chronic	Moist gauze
Vuerstaek (34)	2006	Cost analysis	research article	RCT	hospital	HS	Chronic leg ulcers	Hydrocolloid alginates
Only abstract								
de Leon (43)	2009	Cost consequence	research article	Doctor records	hospital	HS	Post surgical	Standard
Dougherty (44)	2008	CEA	research article	Model	n.a.	HS	Wounds secondary to diabetes	Platelet rich plasma, saline gel, standard, ultrasound, fibroblast
Only cited								
Weinberg group (50)	1999	Cost analysis cost-consequence	HTA report	medicare	home	HS	Chronic	?
Williams (51)	2001	Case study with cost analysis	HTA report	medicare+ other insurance data	hospital, home, longterm care	HS	?	?
Philbeck (49)	1999	CEA	research article	medicare-Trial by Ferrell et al 93	home	HS	Pressure ulcers	?
Excluded								
Baharestani (52)	2004		conference abstract					
Langley-Hawthorne (53)	2004		conference abstract					
Niezgoda (54)	2005		conference abstract					
Neubauer (48)	2003	Review	review	n.a.	n.a.	n.a.	?	?
Trueman (55)	2008	Review	review	n.a.	n.a.	n.a.	?	?

TNP: Topic Negative Pressure; CEA: Cost effectiveness analysis; QALY: Quality Adjusted Life Years; ICER: incremental cost effectiveness ratio; RCT: randomized controlled trial; HS: Health System; MWT: Moist; n.a.: not applicable

TABLE 5 (CONTINUED)

AUTHOR	YEAR	RESULTS ICER QALY	CEA AND COST CONSEQUENCE RESULTS	OTHER RESULTS	FINANCIAL SUPPORT	NOTES
Apelqvist (42)	2008	No	Cost per healed wound: 25954$ NPT vs 38806$ MWT	Cost per 8 o + sett. Treat: 27270$ TNP vs 36096$ MWT; no reduction in hosp time; reduction of medications	KCI	horizon: 16 weeks
Braakenburg (35)	2006	No	TNP dominates Hydrocolloids alginates: cost reduction of 25-30% for each hospitalized wound and more QALYs gained	Cost per treatment day: 24€ TNP vs 14E conv; total cost per pt achieving endpoint: 353€ TNP vs 273€ conv	KCI	
Flack (45)	2008	Yes	Results of the model show an improvement in the healing rates (61% versus 59%), more QALYs (0.54 versus 0.53) and a lower general cost of treatment ($52,830 versus $61,757 per person) for patients treated with VAC compared with advanced treatments.	-	Not reported	
Mody (25)	2008	No	Cost of material per healed wound: 11.35$ NPT vs 22$ MWT	Material costs single change: TNP 2.27$ vs MWT 0.4$	Device produced by the authors	
Mokhtari (46)	2008	No	-	Cost of CABG+DSWI vs CABG: 2.5 times	Public	
Mouës (47)	2005	No		Cost / patient: 2235€ TNP vs 2565€ MWT	Not reported	
Vuerstaek (34)	2006	Superior	Cost per hospitalized ulcer 25% to 30 in less for TNP	-	KCI	
de Leon (43)	2009	No	Cost per cubic centimeter reduction was $11.90/cm(3) in the NPWT/ROCF group versus $30.92/cm in the standard group	-	?	Abstract only
Dougherty (44)	2008	Yes	Average cost of 5 years of direct wound treatment by modality and QALYs was: PRP gel, $15,159 (2.87); saline gel, $33,214 (2.70); standard of care, $40,073 (2.65); noncontact kilohertz ultrasound therapy, $32,659 (2.73); human fibroblast-derived dermal substitute, $40,569 (2.65); allogenic bilayered culture skin substitute, $24,374 (2.79); bilayered cellular matrix, $37,340 (2.71); negative pressure wound therapy, $20,964 (2.81); and recombinant human platelet-derived growth factor BB, $47,252 (2.69)	-	?	Abstract only
Weinberg group (50)	1999	?	?	Cost per 8 o + weeks Treat: 23837$ TNP vs 25762$ MWT	KCI	As reported by Neubauer 2003
Williams (51)	2001	?	?	Savings per patient per year: 1623$	KCI	As reported by Neubauer 2003
Philbeck (49)	1999	?	Cost / healed wound: 14546$ TNP vs 23465$ MWT	?	Not reported	As reported by Neubauer 2003
Baharestani (52)	2004				?	Abstract only
Langley-Hawthorne (53)	2004				?	Abstract only
Niezgoda (54)	2005				?	Abstract only
Neubauer (48)	2003	No	n.a.	n.a.	Not reported	
Trueman (55)	2008	No	n.a.	n.a.	?	Abstract only

Ethical Impact

During the literature review, two ethical aspects emerged as relevant:

1. The impact of relapses on the workload of non-professional caregivers, family members and relatives of the patient, resulting from a shift from hospital to home treatment of difficult wounds. In particular, several studies have shown that shifting from hospital to home care can bring more discomfort in the most deprived families, to patients who are alone, to the poorest families, and to those with the possibility of job loss who must care for the sick family member, especially for women with weak job positions (56). The results analyzed, however, showed that the device does not imply a relevant change in the care setting and does not reduce hospital care significantly, although many publications report this as a possible objective of negative pressure therapy. We believe, currently, that it is unlikely that the use of this therapy introduces greater pressure on patients' families, particularly on the most disadvantaged families from a social and economic point of view.

2. Possible differences in access to treatment for patients from a lower socio-cultural level. For the moment, the experience of St. Camillo Roma D does not seem to reflect disparities in access, which is, in any case, limited for all patients but certainly not according to socio-cultural status. In addition, the modest, if any, improvement in outcomes greatly reduces the amount of any ethical disparities in access.

CONCLUSIONS AND POLICY IMPLICATIONS

In the literature, safety concerns have been raised in scenarios of treatment of an open abdomen: the causal link between NPT and intestinal fistulas has not been established, but the current evidence on the safety and effectiveness of NPT on an open abdomen is inadequate in quantity and quality (16).

The FDA has issued a report citing 83 serious complications (6 fatal). The most serious cases are related to hemorrhage, a side-effect that limits the use of NPT. The home setting is one that has evidenced more problems. Other types of problems reported are the infection of the original open wound, pieces of gauze left in the wound, and injuries caused by foam padding attaching to or embedding in tissue. Both the NICE, and the FDA are recommending accurate information be supplied to patients and caregivers about these risks, and trained personnel be used for its application.

The literature search for safety did not include case reports, case series and case control studies, but relevant safety issues may be revealed in evidence studies, even if low level.

The 13 trials included in efficacy analysis showed several methodological limitations, both within and across different studies. In particular, there emerged issues related to the heterogeneity of the therapeutic procedures used in treatment and control groups, short follow-up periods, the lack of homogeneity in the definition of outcomes, and the heterogeneity in the inclusion of patients. Furthermore, the multiplicity of outcomes reported in the study, together with the difficulty in masking the intervention arm even in the assessment of outcome phase, raises doubts concerning selective outcome reporting. There are no trials about commercial products other than KCI VAC. From our meta-analysis of relevant data, there is sufficient evidence of the efficacy of negative pressure therapy in terms of reducing healing times (MD = -10.42 days, 95% CI [-15.98, -4.86]) and increasing the proportion of wounds healed (RR = 1.40, 95% CI [1.14, 1.72]).

In particular, there is evidence of the efficacy of negative pressure therapy:

1. for acute post-surgical wounds that are difficult to treat or which are compounded by specific risk factors for chronicity (e.g. diabetic foot amputation);
2. as a second-line treatment for difficult chronic skin lesions with the exception of pressure ulcers.

The evidence available for the treatment of pressure ulcers, although based on studies with low-power, suggests similar effectiveness compared to standard therapies.

As for the cost of treatment with NPT compared to standard treatments, the 8 studies included in the analysis reported a variability ranging from a +29% to -60% difference, with a higher frequency of studies reporting observed savings.

Any observed or expected cost savings were derived from:

- lower staff costs for wound-dressing changes,
- reduced healing time and surgery preparation time,
- reduction of complications.

In contrast, material costs are always much higher with NPT. Any savings in personnel costs

can only be achieved with a rigid application of bandage change times (every 48 hours in almost all studies). In a day-hospital setting, where standard bandage changes are less frequent (every 72 hours), the NPT does not save on personnel costs.

Furthermore, for the other two points, only the reduction in time yields sufficient evidence, but for the reduction of complications there is no conclusive evidence.

Negative pressure therapy represents a viable alternative to standard therapies, if the costs do not increase.

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APPENDIX 1
CONSULTING COMMITTEE MEMBERS

Manufacturers:

- *KCI*
- *Smith & Nephew*
- *Convatec (not yet on the market)*

Experts:

- *Roberto Grilli (ARS Regione Emila-Romagna)*
- *Paolo Alesse (Ospedale GB Grassi, Ostia, Roma)*
- *Lorena Mancini (Policlinico Universitario A. Gemelli, Roma)*
- *Giorgio Guarnera (IRCCS IDI, Roma)*
- *Mara Sbaffi (AO S. Camillo, Roma)*
- *Lorenzo Leogrande (Policlinico Universitario A. Gemelli, Roma)*
- *Eva Pagano (CPO Piemonte, Torino)*
- *Damiano Abeni (Laziosanità, Roma; IRCCS IDI, Roma)*

APPENDIX 2
BIBLIOGRAPHIC RESEARCH: MEDLINE

List of meta-literature data sources

- *Med-line*
- *NICE web site*
- *SIGN web site*
- *National Guideline Clearinghouse*
- *Piano Nazionale Linee Guida*
- *Cochrane database*
- *INAHTA database*
- *CADHTA*
- *CDC web site*
- *AHRQ web site*
- *Centre for Reviews and Diffusion, University of York, web site*

#5	Search (#2 OR #3) AND #4 Limits: Entrez Date from 2007/12/13 to 2009/04/28, Humans, Clinical Trial, Randomized Controlled Trial	04:39:44	30
#4	Search wound OR wounds OR ulcer OR ulcers Limits: Entrez Date from 2007/12/13 to 2009/04/28, Humans, Clinical Trial, Randomized Controlled Trial	04:37:38	2193
#3	Search vacuum assisted therapy OR negative pressure therapy Limits: Entrez Date from 2007/12/13 to 2009/04/28, Humans, Clinical Trial, Randomized Controlled Trial	04:36:22	9
#2	Search suction [MESH] OR vacuum [MESH] OR "negative pressure" OR TNP OR subatmospheric OR seal (surface) OR seal (aspirat*) OR wound* suction OR wound* drainage OR foam suction OR suction (dressing*) OR vacuum therapy OR vacuum (dressing*) OR vacuum (seal*) OR vacuum closure OR vacuum compression OR vacuum (pack*) OR vacuum drainage OR suction* drainage Limits: Entrez Date from 2007/12/13 to 2009/04/28, Humans, Clinical Trial, Randomized Controlled Trial	04:35:20	69

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