



Randomized controlled trial comparing the combination of a polymeric membrane dressing plus negative pressure wound therapy against negative pressure wound therapy alone: The WICVAC study

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Manuscript received: August 6, 2015
Accepted in final form: June 12, 2016

DOI:10.1111/wrr.12457

The material and consumables used for this study were part of the routine care for patients at the Department of Vascular and Endovascular Surgery, and purchased by the Wilhelminenhospital Vienna. Neither Ferris Mfg. Corp., Fort Worth, TX nor Kinetic Concepts Inc., San Antonio, TX had any involvement in planning or design of the study.

ABSTRACT

Negative pressure wound therapy (NPWT) is the treatment of choice for chronic wounds; yet, it is associated with considerable workload. Prompted by its nonadhesive and wound-healing properties, this study investigated the effect of an additional polymeric membrane interface dressing (PMD; PolyMem WIC) in NPWT. From October 2011 to April 2013, 60 consecutive patients with chronic leg wounds or surgical site infections after revascularization of lower extremities were randomly allocated to either treatment with conventional NPWT (control arm) or NPWT with an additional PMD (intervention arm). The primary outcome was wound healing achieved within 30 days, the secondary endpoints included: number of days between dressing changes, wound-related pain, cost efficiency, and occurrence of adverse events (ClinTrials.gov Identifier: NCT02399722). Forty-seven patients completed follow-up. No difference in wound healing was observed ($p > 0.05$) between both study arms. The additional PMD allowed significantly longer wearing times (days) between dressing changes (intervention: 8.8 ± 0.5 , control: 4.8 ± 0.2 ; $p < 0.001$). Pain was slightly higher in patients randomized to NPWT alone (VAS score: 4.8 ± 2.9) compared to NPWT + PMD (VAS score: 3.0 ± 2.9 , $p = 0.063$). No wound infections were observed. Costs were reduced by 34% per patient in the intervention arm. These results suggest that the combination of NPWT and an additional interface PMD is a safe and economic method for the treatment of chronic wounds, which requires significantly fewer dressing changes for a comparable wound healing.

Almost two decades after its introduction, negative pressure wound therapy (NPWT) is widely used for the treatment of chronic wounds and surgical site infections,^{1–5} including leg ulcers due to diabetes, peripheral arterial occlusive disease (PAOD), chronic pressure, or other causes.⁶ A polyurethane foam, which is directly applied to the wound bed and which is sealed with a transparent occlusive film, is an integral part of most NPWTs. However, prolonged placement of the foam in the wound bed results in tissue ingrowth, which causes pain, bleeding, and traumatization of the healing wound during removal.⁷ Therefore, foam dressings are recommended to be changed in noninfected wounds every third to fifth day, at discretion of the attending physician,⁸ and even more frequently in infected wounds.⁸ This, however, may result in an immense workload and sometimes blockage of valuable operating room (OR) capacities in cases where NPWT changes have to be performed in the OR because of exposed vessels or likelihood of excessive pain. Therefore,

we hypothesized that an additional nonadherent polymeric interface membrane dressing (PMD) may reduce the limitations of foam-related tissue ingrowth, eventually resulting in prolonged wear time and thus, fewer required dressing changes as the time point for needed change is indicated by loss of the dressing's pink color when ingredients are exhausted.⁹ Further advantages of such employed PMDs may be reduction of pain during treatment and autolytic wound cleansing.

The aim of this study was to investigate the effect of an additional nonadherent PMD used as an interface between the wound bed and a foam during NPWT of chronic and surgical site wounds.

MATERIALS AND METHODS

This randomized, open-label, single-center study was designed to investigate the effect of an additional polymeric interface membrane dressing (PMD) during NPWT compared to

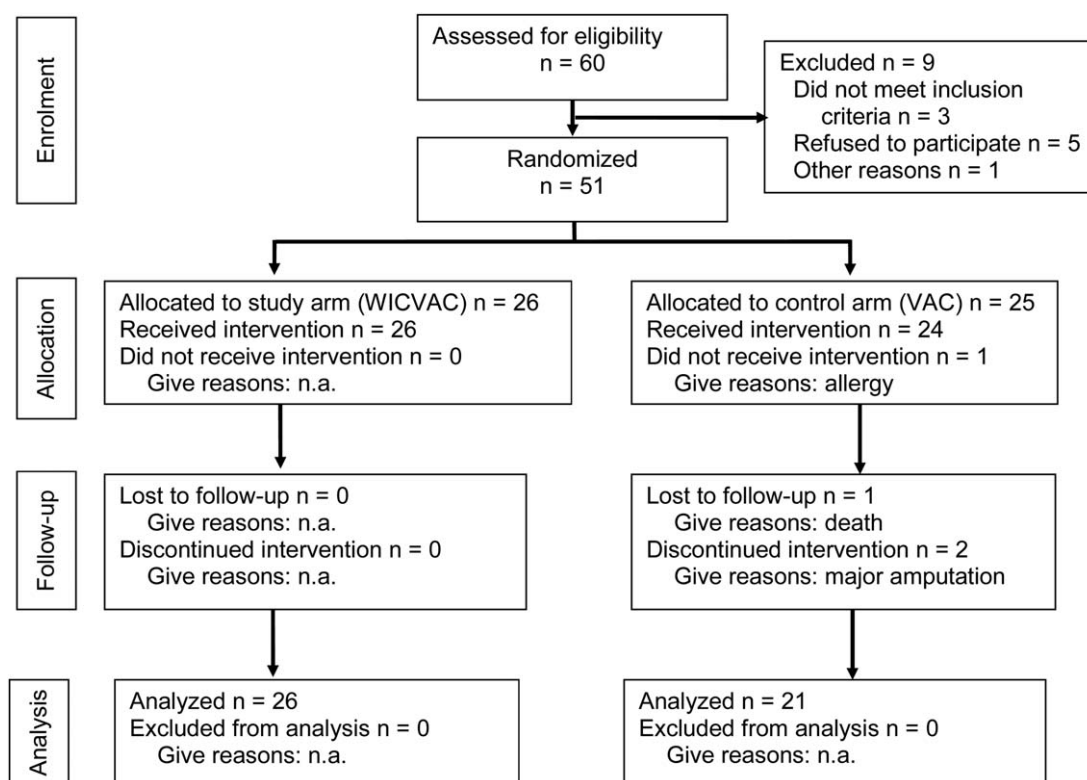


Figure 1. CONSORT diagram.

NPWT alone. The study was conducted at the Department of Vascular and Endovascular Surgery in a large tertiary care medical center in Austria from October 2011 to April 2013. The institutional ethics committee approved the study (Ethics Committee no.: EK 11-111-0711). All patients gave their written informed consent prior to randomization (ClinTrials.gov Identifier: NCT02399722).

Patient population

Patients with chronic wounds of the lower leg on basis of an underlying PAOD, diabetic ulcers, or surgical site infection after revascularization of the lower extremities were assessed for eligibility (Figure 1). Inclusion criteria comprised an age over 18 years, presence of a chronic or infected wound with adequate perfusion after successful revascularization of an underlying PAOD or diabetic macroangiopathy of lower extremities within 24–48 hours before study allocation. Surgical procedures for revascularization included thromboendarterectomy, bypass surgery, and percutaneous transluminal angioplasty of stenosed or occluded arterial vessels. Exclusion criteria were not feasible or unsuccessful revascularization, preexisting documented allergies against study-related material, or the patient's refusal to participate in the study. Postprocedural perfusion improvement was verified by angiography and ankle brachial index measurement. Sixty patients were included into the study and equally randomized to either intervention or control arm. Envelope-based computer-

generated randomization allocated each patient to either study arm.

Treatment of wounds

Patients received either conventional NPWT (V.A.C., Kinetic Concepts Inc., KCI, San Antonio, TX) with polyurethane foam dressing (PFD, GranuFoam; control arm, VAC, Supporting Information Figure S1), or an additional polymeric membrane dressing (PMD; PolyMem WIC, Ferris Mfg. Corp., Fort Worth, TX; intervention arm, WICVAC, Supporting Information Figure S2) used as interface dressing between the wound bed and the PFD, Figure 2. Finally, the PMD and the PFD were sealed with an occlusive transparent film prior to induction of a negative pressure at 125 mmHg continuous suction. The pink PMD, which was partially left visible at the margin of the wound bed (Figure 2C and D) under the black PFD indicated the time of the next dressing change once its pink color started to fade⁹ (Figure 3). In the control arm, dressing changes were performed in time intervals of 3 to 5 days, according to the manufacturer's instructions for use.

Polymeric membrane dressing (PMD)

The investigated PMD is a multifunctional dressing with functional properties. According to the manufacturer, the dressing is made of a hydrophilic polyurethane matrix, which contains a superabsorbent starch co-polymer, F-68 surfactant, and glycerin.⁹ The superabsorbent polymer

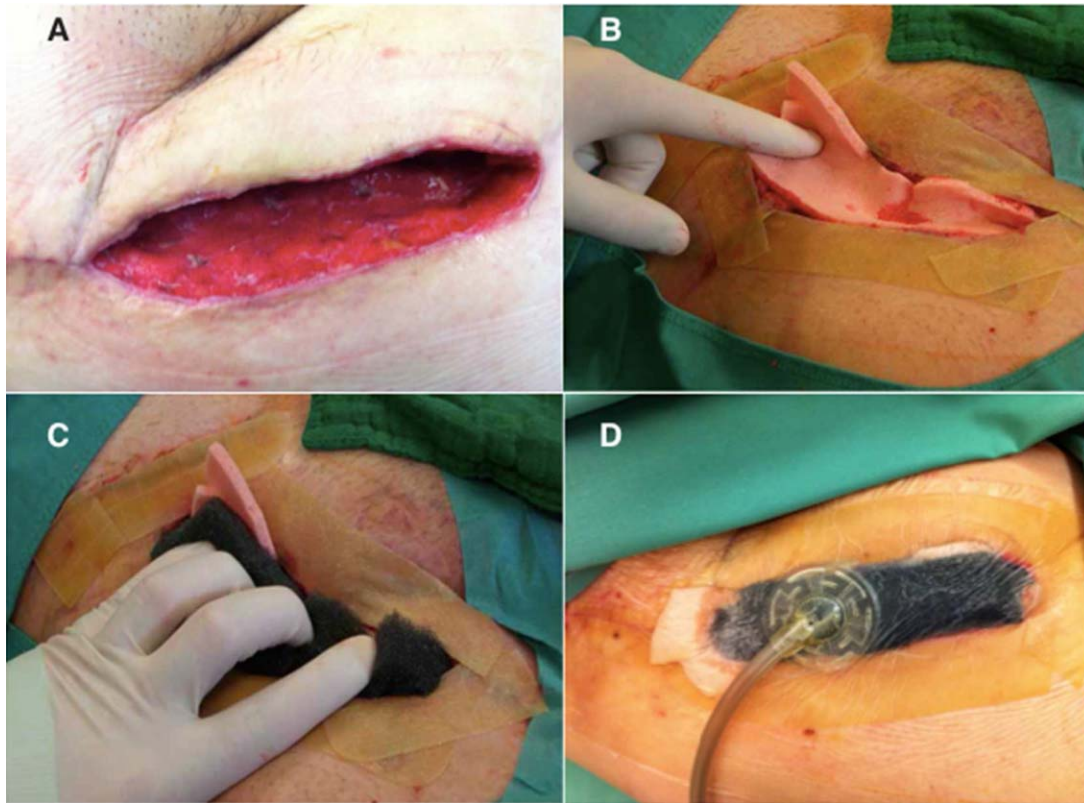


Figure 2. Application of the NPWT with an additional polymeric membrane interface dressing (PMD). (A) Preparation of the wound bed, (B) Application of the nonadherent polymeric membrane surrounded by a wound margin protection, (C) Application of the PFD, and (D) occlusion with a transparent film and initiation of negative pressure by continuous suction (125 mmHg).

tweaks wound exudate into the dressing and supports to balance moisture levels and to reduce the risk of maceration. The wound cleanser surfactant F-68, which is continually released into the wound, reduces tension between the fringes of healthy and necrotic tissue, and debris, allowing the penetration of active ingredients into the wound bed, which supports an autolytic debridement.¹⁰ The moisturizer glycerin is simultaneously released in order to create a moist wound environment and to prevent the dressing from sticking to the wound bed.⁹

Evidence suggests that the PMD may reduce the inflammatory response at the wound site and in the surrounding tissues¹¹ with an associated decrease in bruising and swelling. The PMD may also modify pain-signaling pathways by inhibiting the function of nociceptors,¹² and absorbing sodium ions from the skin and subcutaneous tissues below the dressing.¹³

Wound documentation

Patient characteristics, wound size (cubic centimeters, ccm) at each dressing change, pain during treatment, administration of analgesics, and the number of dressing changes required until wound closure were documented. Measurement of wound size was performed by surgeons during dressing changes with a measuring tape in written form and

photographically. Pain evaluation was standardized using a visual analog scale (VAS 0–10).¹⁴ Patients were asked for the degree of pain ranging from 0 to 10 during daily ward rounds and during dressing changes by their attending surgeons. Occurrence of any non-preexisting infection under treatment was recorded following criteria established by Cutting.¹⁵ Wound closure was performed by secondary suture, spontaneous epithelialization, split skin grafting, or local flap plasty techniques.

Study trial outcomes

The study's primary endpoint was wound-healing (wound closure or reduction of wound size in ccm) within 30 days of treatment. Secondary endpoints were the number of dressing changes, the number of days between dressing changes, therapy-related pain, and the occurrence of adverse events (wound infection) during therapy. Finally, costs for both study arms were documented. Costs were based on numbers provided by the hospital and consisted of expenses for the NPWT device, the additional consumables used for NPWT, the PMD, and the OR including materials and staff. At the study facility, expenses for a single change of the NPWT were EUR 96.2 and EUR 103.2 for NPWT together with PMD. The NPWT system was a rented device that cost EUR 35 per day.



Figure 3. Color indicator: a visible piece of Polymem, which signals the need for dressing change by loss of the pink color.

Standardized dressing change in the OR cost additional EUR 964.14.

Statistical analysis

Sample size estimation was based on detecting a 20% difference in the number of dressing changes in favor of the intervention arm (NPWT + PMD), with a type I error of 0.05 and type II error of 0.2. Based on the power calculation, at least 23 patients were required for each study arm. Data were analyzed for statistical distribution. Due to skewed data distribution Mann–Whitney–*U*-tests were applied for assessment of differences in primary and secondary endpoints. To estimate the effect of acknowledged risk factors on wound closure rate, proportional hazard models (Cox regression) were calculated. Risk factors included sex, hypertension, diabetes, cardiac disease, renal and venous insufficiency, nicotine abuse, anticoagulation, and grade of PAOD. A two-sided *p*-value (*p*) of less than 0.05 was considered to indicate statistical significance. Cox proportional hazard models are presented as hazard ratio with 95% confidence intervals. All analyses were performed with the use of SPSS 20 (IBM Inc., Somers, NY).

RESULTS

Sixty patients were included in the study, and 47 patients (control arm: *n* = 21, intervention arm: *n* = 26) completed the follow-up of 30 days. Thirteen patients were excluded from the study because of major amputation due to

massive tissue loss, failed revascularization due to re-occlusion of bypass or stent, allergic reaction to dressings, refusal of further participation, or death (CONSORT diagram, Figure 1). Patients' baseline characteristics are summarized in Table 1.

Primary outcome

After 30 days of follow-up, no significant difference in the wound closure rate (Figure 4), or wound size reduction (Table 2) between the two study arms was observed (*p* > 0.05). The investigated risk factors (Table 1) did not show a significant association with the wound closure rate (*p* > 0.05) and therefore, did not bias the findings of the statistical analysis.

Secondary outcomes

Patients with an additional interface dressing (intervention arm) had significantly longer intervals (days) between their dressing changes (intervention arm: 8.8 ± 0.5 ; control arm: 4.8 ± 0.2 , *p* < 0.001; Table 2 and Figure 5). Although the consumption of analgesics did not differ significantly between the two study arms (*p* = 0.063), the mean VAS scores during treatment and dressing changes were higher in patients randomized to the control arm (mean VAS score: 4.8 ± 2.9) than in the intervention arm (mean VAS score: 3.0 ± 2.9). In both study arms, no new wound infections were observed (Table 2). Less than half (44.7%) of all dressing changes were performed in the OR in the control arm, and 47.8% in the intervention arm. Full costs of NPWT added up to EUR 104,400 for the control arm (*n* = 21) and EUR 84,941 for the intervention arm (*n* = 26), correlating to a reduction of 34.3% of costs per patient if PMDs were used together with conventional NPWT.

DISCUSSION

This study demonstrates that an additional nonadhering interface PMD significantly reduces the number of required dressing changes in vascular surgery patients treated with NPWT. With adequate vascularization, excellent results have been achieved by using NPWT in vascular surgical patients with PAOD, or diabetes-related leg ulcers.^{16,17} Because this study only included patients with wounds after optimal revascularization, a potential bias of different perfusion in the two study groups could be eliminated.

Wound healing

Orgill et al. described four primary NPWT mechanisms of action: macrodeformation, microdeformation, fluid removal, and environmental control of the wound. Secondary effects, as result of an interaction of the primary mechanisms, are granulation tissue formation, cell proliferation, and modulation of inflammation.¹⁸ Especially, microdeformations produced by the combination of polyurethane foam (PFD) and suction play an important role in wound healing. Several studies showed that these effects are associated with increased fibroblast proliferation and up-regulation of gene expressions in fibroblasts.^{19,20} In addition, the dressing material has a significant effect on cell response during NPWT.²¹

Table 1. Demographic and clinical variables of study patients ($n = 47$) finalizing follow-up

| Scale | All patients | | VAC | | WICVAC | | <i>p</i> -Value |
|------------------------------|--------------------|---------|--------------------|---------|--------------------|---------|-----------------|
| | Mean | std± | Mean | std± | Mean | std± | |
| Age (years) | 66.4 | 9.5 | 67 | 9.8 | 65.9 | 9.4 | 0.704 |
| BMI (kg/sqm) | 26.7 | 5.1 | 28.5 | 4.3 | 25.1 | 5.1 | 0.040 |
| Dichotomous | Count (<i>n</i>) | Percent | Count (<i>n</i>) | Percent | Count (<i>n</i>) | Percent | |
| Sex, male | 31 | 66.0 | 17 | 55 | 14 | 45 | 0.053 |
| Hypertension | 34 | 79.1 | 16 | 47 | 18 | 53 | 0.659 |
| Diabetes | | | | | | | |
| NIDDM | 15 | 34.9 | 8 | 53 | 7 | 47 | 0.979 |
| IDDM | 11 | 25.6 | 5 | 46 | 6 | 55 | n.a. |
| Cardiac disease | 14 | 35.0 | 7 | 50 | 7 | 50 | 0.822 |
| Renal insufficiency | 7 | 16.3 | 4 | 57 | 3 | 43 | 0.641 |
| Chronic venous insufficiency | 5 | 13.9 | 3 | 60 | 2 | 40 | 0.641 |
| Nicotine abuse | 22 | 52.4 | 10 | 46 | 12 | 55 | 0.703 |
| Antiplatelet therapy present | 26 | 55.3 | 14 | 54 | 12 | 67 | 0.167 |
| Antiplatelet therapy | | | | | | | |
| Aspirin | 15 | 36.6 | 10 | 67 | 5 | 33 | |
| Clopidogrel | 3 | 7.3 | 2 | 67 | 1 | 33 | |
| Marcoumar | 6 | 14.6 | 2 | 33 | 4 | 67 | |
| Combined | 2 | 4.9 | 0 | 0 | 2 | 100 | |
| PAOD present | 38 | 80.9 | 19 | 50.0 | 19 | 50 | 0.138 |
| PAOD grade | | | | | | | |
| IIb | 5 | 13.2 | 3 | 60 | 2 | 40 | |
| III | 6 | 15.8 | 4 | 67 | 2 | 33 | |
| IV | 27 | 71.1 | 12 | 44 | 15 | 56 | |

p-Value by ANOVA.

NIDDM, non-insulin-dependent diabetes mellitus; VAC, control arm; WICVAC, study arm (see Methods).

However, this study only documented the clinical outcomes, whereas no biopsies of the wound bed were taken. Pertaining to macroscopic findings no differences in granulation tissue formation between the two therapeutic modalities were observed. Likewise, wound closure rates also showed no significant difference. The advantage of the interface PMD was that the newly formed granulation tissue did not grow into the PMD, and therefore, prevented traumatization of the granulation tissue during dressing change and facilitated dressing changes on the ward. However, our study could not detect fewer dressing changes performed in the OR. One possible explanation could be the method of randomization, which could not control other factors indicating dressing change in the OR, such as inguinal wounds after groin incisions or the presence of exposed vascular prostheses.

Economic aspects

The results of this study may have important clinical implications as the investigated approach with an additional interface PMD may help to alleviate the daily shortage of resources in healthcare. It was demonstrated that each

time a PMD was used, the wearing time could be doubled, thus one NPWT dressing change could be saved. Thereby, the workload associated with dressing changes was nearly halved (Figure 6), resulting in a reduction of 34.3% of costs per patient.

Patient comfort

The currently suggested intervals of dressing changes every third to fifth day⁸ during conventional NPWT, dressing changes result in patient discomfort. Furthermore, delayed changes often cause in-growth of granulation tissue into the PFD foam, leading to painful removal.⁷ Also, granulation tissue and reepithelialization may be damaged and consequently, wound healing may be prolonged.^{22,23} Therefore, the option of a dressing with prolonged wearing time and all the benefits of standard NPWT without negative effects are clinically desired advantages.

The duration of chronic wound therapy may range from a few weeks up to months, depending on the nature of the wound. Moreover, as wound beds also change in quality during the healing process, rather than following a fixed

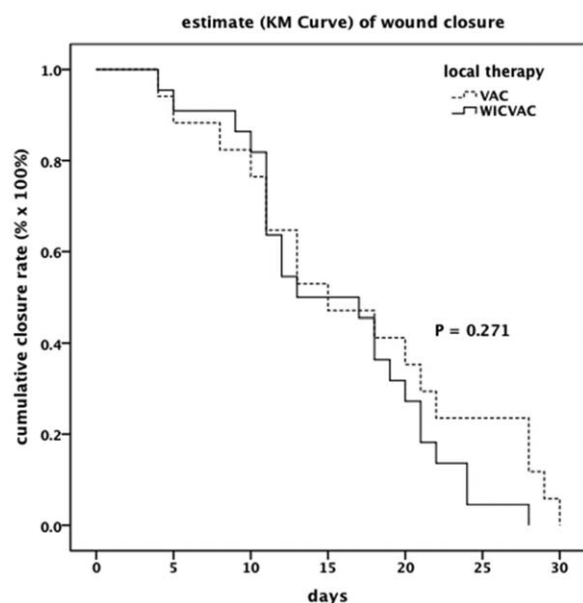


Figure 4. Cumulative wound closure rate (Kaplan–Meier Curve) for each wound dressing of 47 patients within 30 days. *p*-Value by log-rank test. VAC, conventional NPWT as control arm (dotted line); WICVAC, NPWT plus a polymeric interface dressing as intervention arm (solid line).

time schedule for dressing changes, it would be more beneficial to employ dressings which indicate the present condition of the wound, and hence, signal the optimum time point for dressing change in each patient individually. Indeed, an important feature of the investigated PMD was its ability to be used as “color indicator,” by leaving the polymeric membrane partially visible at the dressing’s margin (Figure 2C and D). As the pink color of the dressing disappears with time, reflecting consumption of its ingredients, the need for a dressing change can be determined by visual inspection alone. This demand-guided dressing

change allowed individualized wearing-times and was one of the chief reasons why the use of PMD was studied in this trial. However, it is important to note that the color change was different between patients and also during different phases of wound healing in the same patient.

The PMD demonstrated anti-nociceptive properties in an animal model,¹¹ eventually caused by a direct pain reduction through inhibition of the pain-sensing nerve endings.⁷ Nevertheless, patients in our study reported only a nonsignificant pain reduction during treatment and pain medication did not differ in both study arms. Also, dressing changes in the intervention arm could not be performed more often on the ward in our study sample. This was due to the fact that more wounds in the intervention arm requiring an OR for dressing changes due to surgical reasons. This aspect should be addressed in larger studies.

Various efforts have been made to decrease wound tissue damage and pain during dressing change, including the use of different primary wound fillers, administration of topical analgesics, or placement of various interface dressings.^{24–26} As shown in several studies before,^{10–13} PMD is a nonadherent dressing, which combines anti-inflammatory and pain-relieving properties. Reduction of pain and inflammation is an important aspect of wound management and essential for an improvement of patient quality of life. Furthermore, PMDs are supposed to enhance autolytic debridement, thus promoting a wound cleansing while handling exudates without further trauma.¹⁰ For this purpose, PMDs can also be used for drainage and wound care of abscesses and deep narrow wounds with good results, even in patients suffering from diabetic foot abscesses and osteomyelitis.²⁷

These product properties of the PMD appeared promising, furthermore, the therapeutic approach of combining it with standard NPWT did not interfere with wound healing, had no adverse effect on pain and safety, and was cost-effective.²⁸

CONCLUSIONS

In conclusion, the combination of NPWT and a PMD used as an additional interface between the wound bed and a PFD demonstrated to be a safe method for the treatment of vascular surgical patients with chronic and infected

Table 2. Primary and secondary study outcomes of patients ($n=47$) during and after treatment with either local treatment (VAC—control, WICVAC—study arm)

| | Total | | VAC | | WICVAC | | <i>p</i> -Value |
|-------------------------------|--------|-------|--------|-------|--------|-------|-----------------|
| | Median | SE± | Median | SE± | Median | SE± | |
| Wound size change (ccm) | 3.90 | 32.95 | 7.50 | 61.04 | 3.60 | 34.45 | 0.549 |
| Treatment duration (days) | 18.00 | 1.91 | 20.00 | 2.65 | 18.00 | 2.75 | 0.645 |
| Dressing change intervals (d) | 6.0 | 0.40 | 4.80 | 0.20 | 8.80 | 0.54 | <0.001 |
| VAS score (0–10) | 3.00 | 0.47 | 5.00 | 0.71 | 2.50 | 0.59 | 0.073 |
| Wound infection | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | n.a. |

p-Value by Mann–Whitney-*U*-Test.

ccm, cubic centimeter; d, days; nr, number; VAC, control arm; VAS, visual analog scale; WICVAC, study arm.

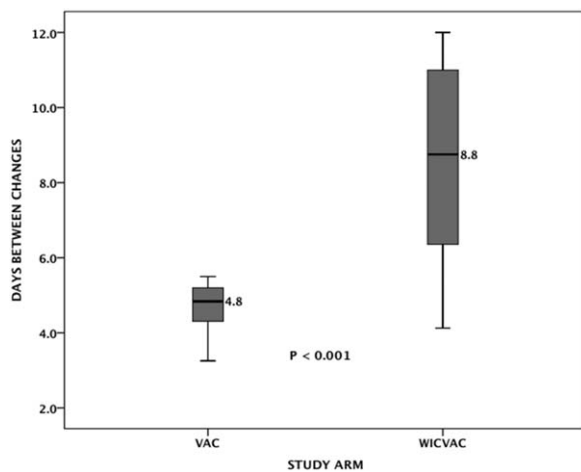


Figure 5. Box plot showing days between dressing changes by study arm within 30 days of follow up of 47 patients with chronic wounds. *p*-Value by Mann–Whitney-*U*-test. VAC, conventional NPWT as control arm; WICVAC, NPWT plus a polymeric interface dressing as intervention arm.

wounds. The frequency of dressing change could be reduced by half, with similar outcome as compared to standard NPWT, and resulted in lower overall costs.

AUTHOR CONTRIBUTIONS

GSB, ES, and AA formulated the study hypothesis. AA, OA, and ES advised on selection of the surgical field to be investigated. AA, ES, ND, SK, KH, and JB supervised patient and participant information and quality of surgical procedures, and obtained informed consent. ND, AA, and OA designed and performed the statistical analysis and interpreted statistics. ES, OA, ND, AA were involved in literature search, drafted the manuscript, and were involved in drafting and processing the study results as well as data interpretation. All authors approved the final draft.

Source of Funding: Dr. Skrinjar received a travel grant from Ferris Mfg. Corporation for presenting preliminary findings of this evaluation at the EWMA Conference 2010.

Conflict of Interest: The authors do not have potential conflicts of interest relevant to this article to report. Prof. Ojan Assadian is member of the Hutchinson santé, Beckon Dickenson, and Mölnlycke Health Care medical advisory board and declares having received consulting and lecture fees, travel compensation, and speakers honoraria from Altrazael Europe Ltd., B. Braun Melsungen AG, Ethicon Ltd., Kinetic Concepts Inc., Lohmann & Rauscher, Quantum Management & Service GmbH, and Schülke & Mayr GmbH in the past.

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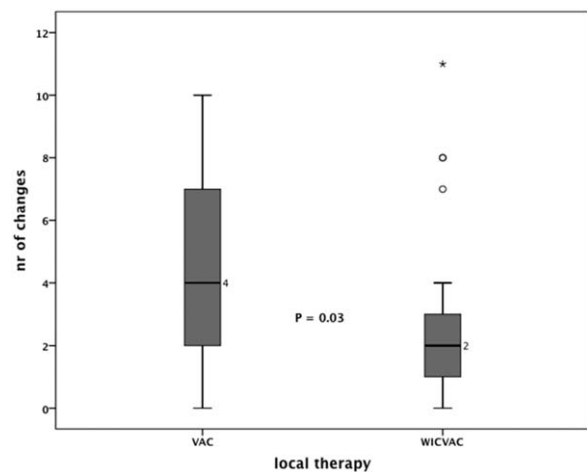


Figure 6. Box plot showing number of changes by study arm within 30 days of follow up of 47 patients with chronic wounds. *p*-Value by Mann–Whitney-*U*-test. nr, number; VAC, conventional NPWT as control arm; WICVAC, NPWT plus a polymeric interface dressing as intervention arm.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. VAC therapy.

Figure S2. WICVAC therapy.