Clinical experience of a new NPWT system in diabetic foot ulcers and post-amputation wounds

• **Objective:** The primary aim of this pilot observational study was to assess the reduction in wound depth and area achieved with a new negative pressure wound therapy (NPWT) system in diabetic patients with foot ulcers and post-amputation wounds. Secondary aims were to assess pain levels, extent of exudate removal, and ease of use of the system for both the patient and care giver.

• **Method:** Patients in both acute and home care settings were enrolled into this 4-week study. Dressings were changed three times per week. Wound area and depth, exudate removal and pain severity were evaluated at each dressing change. At the final visit, the investigators and patients were surveyed with respect to equipment and dressings used in the study..

• **Results:** Sixteen patients were enrolled into the study. Data relating to 14 patients with a variety of post-amputation wounds were included in the intention-to-treat (ITT) analysis. The post-amputation wounds showed a general trend for a reduction in the median wound surface area between baseline (22.9cm^2; range 0.5–55) and the final visit (15.3cm^2; range 2.4–63.5). This equates to a median change (calculated from the percentage change in wound area for each patient individually) of -41% (range -82% to +15%). There was also a general trend in reduction in the median depth between baseline (17mm; range 0–35) to final visit (5mm; range 0–35). One patient presented with a foot ulcer that demonstrated a 50% reduction in depth from baseline to the final assessment. The device effectively managed wound exudate and most patients reported low pain levels during therapy. Ease of use of the system was rated very highly by investigators and patients.

• **Conclusion:** This pilot study indicates that the use of the new NPWT system can be expected to have a positive effect on the healing of post-amputation wounds and foot ulcers in patients with diabetes. The findings demonstrate that the system is easy to use, effectively controls exudate and minimises pain and inconvenience for patients being treated with NPWT.

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wound pain; wound healing; amputation

Negative pressure wound therapy (NPWT) has gained rapid acceptance by physicians, surgeons and wound care practitioners for the management of acute, traumatic, infected and chronic wounds.[1] To date, only a small number of randomised controlled trials (RCTs) have been evaluated its efficacy in the management of diabetes-related foot wounds.[2-5] In two of these, NPWT resulted in more rapid and complete healing,[2,3] although both used saline-moistened gauze as the comparator and had very small patient populations (n=10). In a large multicentre RCT involving patients who had undergone partial diabetic foot amputations, NPWT increased rates of granulation tissue formation and decreased healing times. The investigators concluded that NPWT could lead to fewer re-amputations than are currently experienced in post-amputation diabetic patients receiving standard care.[4] This trend is supported by a more recent and larger multicentre RCT involving diabetic foot ulcers (DFUs) in which the incidence of secondary amputations was significantly lower (p=0.035) for NPWT (4.1%) than for advanced moist wound therapy (10.2%).[5] A smaller study found that NPWT accelerated granulation tissue formation.[6] These results are particularly relevant as first ray amputations are associated with re-ulceraton,[7,8,9] and subsequent re-amputation.[7]

Avance is a new NPWT system (Mölnlycke Health Care) that uses a lightweight and portable pump, and so can be used in both acute and home care settings. The docking station supplied with the pump has been designed to promote patient mobility during treatment, and users have the choice of two sizes of canister (800ml and 300ml) for collecting wound fluid. Dressing kits supplied with the system

G. Stansby, M Chir FRCS, Professor of Vascular Surgery, Freeman Hospital, Newcastle upon Tyne, UK;
V. Wealleans, RGN, Vascular Research Sister, Freeman Hospital, Newcastle upon Tyne, UK;
L. Wilson, RGN, Vascular Research Sister, Freeman Hospital, Newcastle upon Tyne, UK;
D. Morrow, MSc, FRCS, Consultant Vascular Surgeon, Norfolk and Norwich University Hospital, Norwich, UK;

Continued overleaf.

C. Gooday, BSc (Hons), PGDip, Principal Podiatrist, Norfolk and Norwich University Hospital, Norwich, UK;
K. Dhatariya, MD, FRCP, Consultant Endocrinologist, Norfolk and Norwich University Hospital, Norwich, UK.
Email: Gerard.stansby@nuth.nhs.uk

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Diabetic foot ulcers and post-amputation wounds associated with diabetes suitable for NPWT according to the investigator's judgement
Wound size between 1cm² and 200cm²
Male or female, aged ≥18 years
Signed informed consent form
Subject understands the written patient information
Inclusion criteria
Need for frequent dressing changes (<72 hours between changes)
Dry wounds
Critical ischaemia (for wound healing), according to investigator's judgement
Malignancy in wound and/or wound margin
More than 10% wound surface area consisting of necrotic tissue with eschar present after debridement
Target ulcer/wound previously treated unsuccessfully with NPWT within last 48 hours
Poorly controlled diabetes, according to the investigator's judgement
Osteomyelitis left untreated
Infection left untreated
Unexplored fistula
High risk of bleeding complications
Exposed major blood vessels, organs or nerves
Chemotherapy or irradiation either ongoing or within last three months
Known hypersensitivity to the dressing material
Expectation that it will be impossible to seal the film in order to maintain a vacuum for treatment
Expectation of non-concordance with study protocol
Pregnancy
Subject not suitable for investigation, according to the investigator's judgement
Subject previously included in this investigation
Subject included in other ongoing clinical investigation at present or within the past 30 days

include a wound filler (either foam- or gauze-based), a transparent film dressing (Avance Transparent Film) and a flat surgical drain. In addition, an atraumatic soft silicone wound contact layer (Mepitel) can be applied between the wound bed and the wound filler to minimise pain at dressing changes and prevent in-growth of tissue into the wound filler.[10,11] A pre-clinical unpublished study has demonstrated that the foam and gauze dressings supplied with the Avance NPWT system are equivalent in function to those of other commercially available dressings for use with NPWT.[12]

This pilot study is one of the first 'in-use' clinical investigations of the Avance NPWT system. It set out to evaluate its performance in the treatment of DFUs and post-amputation wounds precipitated by DFUs that had deteriorated to the point where toe amputations were required. The rationale was to collect clinical data on healing and exudate/pain control, and to investigate any side-effects. Importantly, the practical applications in a 'real-life' clinical environment were also evaluated.

Method

This was a prospective, open, non-controlled, clinical investigation conducted at two centres in the UK. Patients presenting with DFUs or post-amputation wounds (mostly the result of one- or two-digit amputations) associated with diabetes were enrolled consecutively over a 4-month period. Both in- and outpatients were considered for inclusion. The inclusion/exclusion criteria are listed in Table 1. Two investigators, one from each centre, participated in the study. Both had considerable experience of using NPWT on DFUs and post-amputation wounds of patients with diabetes.

Research ethics committee approval was obtained before starting the study, which was performed in accordance with the Declaration of Helsinki and with applicable regulatory requirements.

The primary outcome measure was the reduction in wound depth and area, and extent of new tissue formation. Secondary objectives included:

- Pain severity
- Visual checks of exudate removal
- Ease of use for both patient and care giver.

Treatment protocol

One ulcer/post-amputation wound in each patient was treated with Avance NPWT system (continuous pressure setting of -120mmHg) for a maximum of 4 weeks. Only Avance Foam Dressing Kits were used, which consist of:

- Avance Foam — a green hydrophobic polyurethane foam dressing with a large open cell structure that can be cut to size. It is used as a wound filler to distribute pressure across the wound surface and allow the passage of exudate through to the drain tubing
- Avance Transparent Film — a flexible, transparent, breathable film dressing made of polyurethane, and coated with a polyacrylic adhesive. It is used to fixate the wound filler, form a tight seal with the

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skin, and aid the maintenance of a moist wound environment
* Flat drain — used to transfer negative pressure to the wound filler and transport exudate from the wound to the canister in Avance NPWT system.

The investigators also had the option of using Mepitel between the wound bed and the wound filler. Exudate can pass through this into a secondary dressing.

Dressing changes were undertaken three times per week. At the first visit, baseline demographics (age, gender, medical history) and the wound history were recorded for each patient.

Efficacy measurements and variables

The following primary parameters were measured at the baseline visit and at each study visit (ie, dressing change undertaken by the investigator or research nurse):
* Wound area, using a validated tracing method involving a digital planimeter (KP-90N, Sokkia)[13]
* Wound depth, measured in accordance with standard practice at the participating centres; the target area was the deepest part of the wound that could be reached vertically with a probe within the wound margin, i.e. not in fistulas and tunnels.

The following secondary parameters were measured at the baseline visit and at all subsequent visits:
* Exudate removal, assessed by visual inspection of fluid in the collection canister
* Pain severity at activation of NPWT and dressing removals at each visit (the study protocol stipulated that each patient had to rate pain severity at the scheduled time points as 'none', 'minor', 'average', 'moderate', or 'severe')

At the final study visit, clinicians were asked to assess ease of use of the dressing kit, tube, canister, pump unit, and the instructions for use, rating the various aspects of the NPWT system as 'very easy', 'easy', 'somewhat easy' or 'not easy'. Patients were asked to rate (using the same scale as above) pump handling, changing of the canister, ease of use of the written instructions, and portability of the system. Finally, patients were also asked to rate the overall noise level of the system as either 'disturbing' or 'not disturbing'.

Safety measurements and variables

Investigators were instructed to record the presence of inflammation or signs of infection in the wound as well as other adverse events, serious adverse events, adverse device effects, and serious adverse device effects. According to the study protocol, if infection developed during the study period, it had to be treated appropriately and registered on the case report form as an adverse event. The decision of whether or not to withdraw the affected patient from the study was left to the judgment of the treating clinician.

Statistical analysis

Descriptive statistics (median, minimum and maximum) were applied to the primary objectives when quantitative data were established. Patients were evaluated if they healed at or before 4 weeks, or if the investigator judged that the wound had responded adequately to NPWT before 4 weeks and wound management could be continued with an alternative therapeutic intervention.

Results

Sixteen patients were enrolled into the study. Data relating to 14 patients with post-amputation wounds were included in the intention to treat (ITT) analysis. Data from one patient with a post-amputation wound were excluded from ITT analysis as it became apparent after enrolment that the subject had learning difficulties that made the collation of reliable data impossible. Due to the differences between DFUs and post-amputation wounds, the data from one patient who presented with a DFU were also excluded from ITT analysis, and are reported separately.

The median age of the sample was 65 years (42–88), and 11 (79%) were males. The median systolic blood pressure was 138 (range 80–168) and the median diastolic blood pressure was 72.5 (range 40–93). Details of the surgical procedures (undertaken within the 6-month period before enrolment), wound type, wound duration, wound location and the presence (or otherwise) of neuropathy for each patient are presented in Table 2.

Efficacy outcomes

Results of the efficacy data for each subject are given in Table 3. In terms of the ITT population, the post-amputation wounds showed a general trend for a reduction in area between baseline (median 22.9cm^2; range 0.5–55) and the final visit (median 15.3cm^2; range 2.4–63.5). This equates to a median change (calculated from the percentage change in wound area for each patient individually) of -41% (range -82% to +15%). The wounds were also associated with a reduction in depth from baseline (median 17.0mm; range 0–35) to final visit (median 5mm; range 0–35).

The vast majority of patients reported no pain at the times of dressing application, activation of negative pressure, deactivation of negative pressure and dressing removal (Fig 1).

Exudate levels associated with the wounds treated in this study varied from low to moderate. The NPWT system effectively managed to remove the exudate, as indicated by visual checks of the canisters throughout the study period.

Results of the investigators' and patients' surveys looking at the ease of use of the system are summarised in Fig 2. It is noteworthy that 92% of patients surveyed did not find the noise level of the pump to be disturbing.

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Safety outcomes

During the study period, adverse events were reported for five patients. The post-amputation wound of one patient required further surgical revision; the same patient developed ulceration on the plantar aspect. Another patient experienced nausea/diarrhoea and their wound was confirmed as positive for meticillin-resistant *Staphylococcus aureus* (MRSA). Two other two patients experienced wound deterioration and MRSA infection respectively. One patient experienced peri-wound skin deterioration, making it impossible to maintain an airtight seal. None of the adverse events were deemed to be serious and all were thought to be unlikely to be related to the NPWT system.

Discussion

In general, wounds treated with Avance NPWT system exhibited clinically relevant reductions in wound area (median 41%).[14,15] In addition, the wounds demonstrated a decrease in wound depth (median values of 17.0mm and 5mm at baseline and final visits, respectively). Wound depth appears to be significantly affected by NPWT and may be a more sensitive indicator of the healing process.[16]

Although three wounds increased in area, this is not surprising bearing in mind the heterogenous nature of the wound types involved and the therapy used.

Of the 14 patients evaluated, it was possible to measure wound depth in all but one. Eleven of the wounds exhibited reductions in depth (ranging from 20% to 100%): the other three wounds did not demonstrate any change in wound depth, possibly because they were very shallow to begin with. The patient with the DFU also demonstrated a positive response in terms of wound healing profession (i.e. a 50% reduction in wound depth).

The healing response observed in this study is in accordance with the findings of clinical evaluations of other NPWT systems in the management of diabetic foot wounds.[4,5] Smaller RCTs studies have come to similar conclusions.[2,3,6,17]

In general, an increase in the proportion of viable tissue in the wound bed was observed following treatment with the NPWT system, i.e. the mean ratio of non-viable to viable tissue was 40:60 at baseline and 30:70 at the final study visit. However, close examination of the data showed significant intra-patient variance between study visits, possibly indicating limitations of using a subjective measurement tool for this parameter. However, with respect to the patients who completed the study per protocol, it was judged that the wounds had adequately responded to treatment with the NPWT system and that the treatment objective had been fulfilled.

Generally, NPWT is associated with relatively high levels of pain.[18] Wound-related pain not only affects patient quality of life but it can delay wound healing.[19] Although one patient experienced severe pain at dressing change throughout the period of treatment, the proportion of visits at which patients reported either no or mild pain at the time of dressing application, activation of NPWT, deactivation of NPWT and dressing removal was 78.7%, 89.7%, 96.3% and 82.8%, respectively (Fig 1). While it should be noted that the majority of patients in the sample had neuropathy, preliminary evidence indicates that these patients can still experience pain in the lower leg.[20] Pain severity in between dressing changes was not formally evaluated in this study, but anec-

Fig 1. Pain severity ratings during dressing application, activation of negative pressure, deactivation of negative pressure, and dressing removal

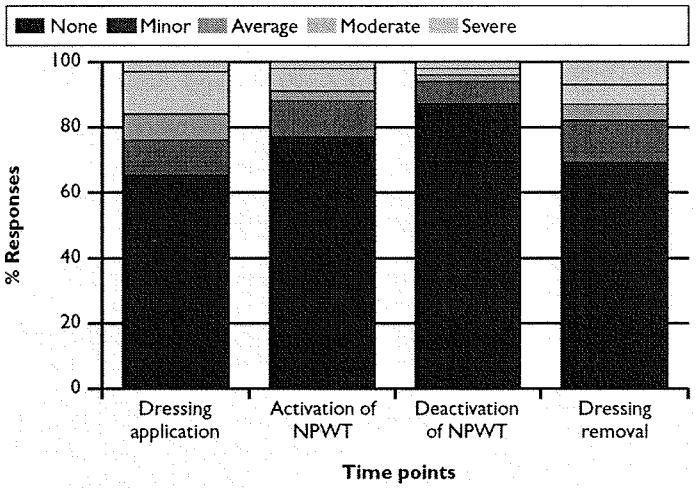

Fig 2. Ease of use of NPWT system

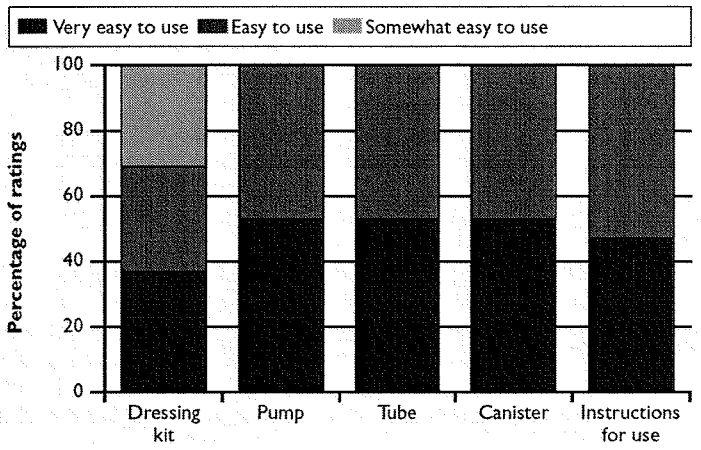

Table 2. Medical and wound history

	Diabetes type (duration)	Surgery within last 6 months	Wound type/ duration	Wound location	Neuropathy present (Y/N)
0101	Type 2 (1 year 1 month)	Left hallux and head of first metatarsal amputation	Post-amputation (2 days)	Left hallux	N
0102	Type 1 (35 years 3 months)	Amputation of right second and third toes	Post-amputation (2 months)	Right digitalis II-V	Y
0103	Type 2 (duration n/k)	None stated	Post-amputation (3 weeks)	Left hallux and digitalis II-V	N
0104	Type 2 insulin-dependent (duration n/k)	None stated	Post-amputation (11 weeks)	Left 4th and 5th toe amputation bed	N
0105	Type 2 (4 years 3 months)	None stated	Post-amputation (9 weeks)	Right digitalis II-V plantar	N
0106	Type 2 (5 years 7 months)	None stated	Post-amputation (3 months)	Left digitalis II-V plantar	Y
0201	Not stated (19 years 3 months)	Right leg bypass; trans metatarsal amputation	Post-amputation (4 days)	Right trans metatarsal amputation	Y
0202	Type 2 (9 years 3 months)	First ray amputation	Post-amputation (2 days)	Right amputation 1st ray	Y
0203	Type 2 (25 years 5 months)	Left foot surgical debridement	Post-amputation (24 months)	Right plantar lateral arch	Y
0204	Not stated (duration n/k)	Bilateral iliac stents; amputation right 4th and 5th toes; amputation right 2nd toe further debridement; right femoral popliteal bypass	Post-amputation (4 days)	3, 4, 5 right foot amputation	Y
0205	Type 1 (duration n/k)	Amputation left 1st toe and ray	Post-amputation (2 days)	Left amputation 1st ray	Y
0206	Not stated (3 years 8 months)	Amputation 3rd (22/03/2010) and 4th toe	Post-amputation (4 days)	Amputation 3rd and 4th toe	Y
0208	Type 2 (duration n/k)	Left popliteal angioplasty	Post-amputation (4 months)	Dorsal	Y
0209	Type 2 (25 years 3 months)	Angioplasty RI SFA superficial femoral artery; further surgical debridement R 5th	Diabetic foot ulcer (4 days)	Right 5th lateral border	Y
0210	Type 2 (duration n/k)	Soft tissue debridement 1+2nd; amputation 1+2 ray amputation	Post-amputation (1 month)	Left dorsal area	Y

dotal feedback from patients suggests that they experienced a high degree of comfort during the treatment period.

Avance NPWT system has been developed as an easy-to-use, lightweight and portable system that promotes patient mobility and is minimally obtrusive. This is supported by the data presented in Fig 2 which considers the practical aspects of the therapy and rates all the variables as easy/very easy to use. In addition, over 90% of patients rated the noise level of the pump as 'not disturbing'.

The practicality of the system is just as important to the clinician and was also evaluated in this study. The investigators rated the dressing kit as either 'very easy to use' (38.5%), 'easy to use' (30.7%) or 'somewhat easy to use' (30.7%). The

pump, tube, canisters, and instructions for use were also generally considered to be 'easy to use'/'very easy to use' by the investigators. These factors are important because, if not properly addressed, they can impact on time and resource within health-care settings: nursing time has a significant cost implication when treating complicated wounds.[21]

The reliability of a NPWT system is critically important, both to the clinician and the patient: a highly reliable device will avoid any disruption to therapy, promote concordance with treatment, and prevent any unnecessary inconvenience to both patients and their carers. Throughout the study period (equivalent to 6744 hours of operation), the Avance Pump performed well, without any reports of it failing to deliver the required level of negative pressure. The lack of device-related adverse events reported in this study is also highly relevant when considering the promotion of therapeutic compliance.

Dressing adhesion and in-growth of tissue into the matrix of the dressing are problematic for NPWT, causing pain and re-traumatisation to the wound.[10,11] The results of this study show that adhesion at dressing removal was generally rated as average (46%) or minor (46%). The degree of tissue in-growth into the wound filler was generally rated as none (31%) or minor (54%). The green colour of the Avance Foam was found to be advantageous; it was highly visible and facilitated easy monitoring of exudate and any bleeding.

Table 3. Change in wound area, wound depth and proportion of viable tissue at baseline and final visit

	Wound area (cm^2)			Wound depth (mm)		
Patient reference	Baseline visit	Final visit	Change (%)	Baseline visit	Final visit	Change (%)
101	14.5	9.2	-37	15	0	-100
102	11.5	4.73	-59	20	3	-85
103	40.81	22.57	-45	25	5	-80
104	20.53	22.60	+10	30	20	-33
106	10.97	3.03	-72	26	20	-23
201	49.83	44.7	-10	0	0	0
202*	55.0	63.5	+15	7	7	0
203†	0.5	0.23	-54	19	10	-47
204*	38.4	25.63	-16	3	3	0
205	33.33	17.3	-48	6	0	-100
206	25.3	13.2	-48	25	20	-20
207	16.23	17.37	+7	19	12	-37
208	13.43	2.43	-82	11	5	-63
209	6.97	7.67	+10	10	5	-50
210	44.63	43.83	-2	10	1	-90

* Subject dropped out at visit 5
† Subject dropped out at visit 4

Study limitations

It is important to stress that this observational (pilot) study lacks the rigour of a well-conducted RCT and the results are non-comparative. In order to address issues of efficacy, a comparator (either versus baseline or another treatment) is helpful. The relatively small patient population also impacts on the data and, in order to gain a better perspective of this treatment, a much larger population is needed. Nevertheless, the data presented in this study do provide an insight into the efficacy and safety of a new NPWT system in the management of patients with complex wounds that typically present clinicians with a number of difficult challenges (e.g. protracted healing, high exudation, patient quality of life issues).

Overall, it is generally accepted that more evidence is needed for NPWT. Existing evidence is at best moderate in strength, and so multicentre RCTs are needed. Bearing in mind the initial positive results from this pilot study, it is envisaged that a more formal and statistically valid clinical investigation will be undertaken to address the issues of this new system and its effect on the indications evaluated (post-amputation diabetic wounds). Specifically, that would mean an RCT in this indication using a standardised treatment as the comparator.

Conclusion

The results presented above indicate that use of Avance NPWT system can be expected to have a positive effect on the healing of foot ulcers and post-amputation wounds in patients with diabetes. The findings also demonstrate that the system is easy to use, effectively controls exudate and minimises pain and inconvenience for patients undergoing NPWT.

The results of this study should be used to help design larger clinical evaluations that could compare this new NPWT system with other negative pressure therapies and other advanced wound care interventions. A focus on the potential of this system to improve patients' quality of life and deliver cost-effective care to patients with DFUs and other diabetes-related wounds in both acute and home care settings would seem appropriate. ■

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