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REVIEW ARTICLE

Negative-pressure wound therapy for management of diabetic foot wounds: a review of the mechanism of action, clinical applications, and recent developments

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Negative-pressure wound therapy (NPWT) plays an important role in the treatment of complex wounds. Its effect on limb salvage in the management of the diabetic foot is well described in the literature. However, a successful outcome in this subgroup of diabetic patients requires a multidisciplinary approach with careful patient selection, appropriate surgical debridement, targeted antibiotic therapy, and optimization of healing markers. Evolving NPWT technology including instillation therapy, nanocrystalline adjuncts, and portable systems can further improve results if used with correct indications. This review article summarizes current knowledge about the role of NPWT in the management of the diabetic foot and its mode of action, clinical applications, and recent developments.

Keywords: *vacuum therapy*; *subatmospheric pressure dressing*; *topical negative-pressure therapy*; *diabetic ulcers*; *wound bed preparation*; *amputation*

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Negative-pressure wound therapy (NPWT) is an innovative technique in managing complex wounds. It was first described by Charikar (1) as an experimental technique for treating subcutaneous fistulas. However, it was the clinical work by Argenta and Morykwas a decade later that allowed NPWT to gain recognition as a useful clinical tool for managing complex and difficult wounds (2–4).

Today, NPWT is well established for treating trauma wounds, general surgical wounds, and diabetic foot wounds. Supporting evidence for NPWT in the treatment of diabetic foot wounds includes numerous prospective and multi-centered randomized controlled trials (5–9). This review article summarizes current knowledge about NPWT's role in diabetic foot management, focusing on its mode of action, clinical applications, and recent developments.

Mechanism of action

Much of the understanding of NPWT's mode of action is built upon Morykwas' work on animal models, describing NPWT's role as a facilitator in creating an 'ideal' wound-healing environment (3). The following are some of the proposed mechanisms by which NPWT 'prepares' the wound bed (Fig. 1).

Improve local blood flow

NPWT is thought to improve dermal blood flow through vasomotor mediators (10). Morykwas showed that negative pressures of up to 125 mmHg resulted in an increased blood flow in swine wound models (4). This pressure level is generally accepted in clinical practice though there are reports to suggest that higher negative-pressure levels may in the long term increase blood flow (11). On the contrary, very high pressures (>400 mmHg) have been shown to reduce the overall wound bed vascular flow (4).

Induce macrodeformation

Direct macrodeformation induced by NPWT leads to wound contraction and size reduction. This is an important mechanism that reduces large defects in diabetic wounds after radical debridement (4, 10, 12).

Induce granulation and angiogenesis

Granulation is an important clinical sign that indicates wound healing. Laboratory experiments on swine and

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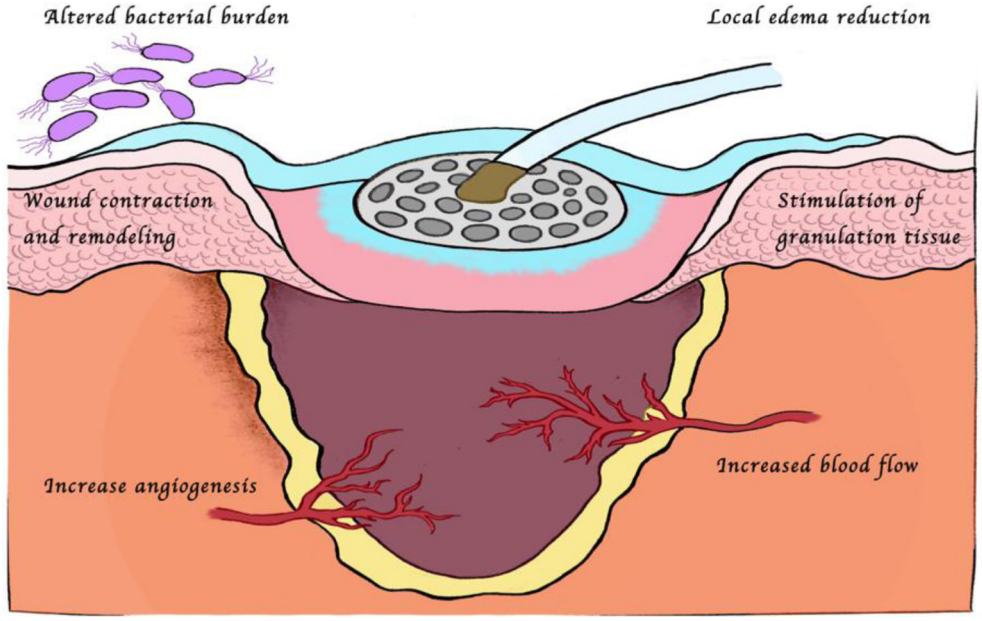

Fig. 1. Schematic illustrating NPWT's mechanism of action.

rabbit wound models showed increased granulation tissue after treatment with NPWT (2, 4). Clinical trials in diabetic wounds have also demonstrated NPWT's superiority in producing granulation compared to conventional dressings (13–15).

NPWT also induces angiogenesis and vascular proliferation (16, 17). Microdeformation at the wound interface is thought to activate vasculogenic growth factors. Furthermore, NPWT mobilizes the systemic endothelial progenitor cells (EPCs) that are markers of healing and repair. Seo et al. (18) noted significant increase in systemic EPC numbers in patients treated with NPWT, reflecting underlying angiogenesis and repair.

Reduce edema

Infective wounds generally produce higher levels of exudates leading to local soakage and edema. NPWT removes excess wound fluid that not only reduces edema (19) but also enhances local blood and nutrient flow. Continuous outflow also reduces the build-up of anti-inflammatory mediators such as metalloproteinase, which degrade adhesion proteins necessary for wound repair (20, 21).

Reduce bacterial colonization

Studies involving swine wounds demonstrated that wounds treated with NPWT showed a more rapid reduction in bacterial colonization (4). While the mode of bacterial clearance is unclear, NPWT is thought to provide a safety barrier that shields the wound from environmental contaminants. In diabetic wounds, there are clinical reports to suggest that NPWT aids bacteria clearance (9, 22), though a recent systematic review on bacterial load and vacuum therapy shows equivocal results with recommendation for further research (23).

Clinical applications

NPWT gives optimal results when used by a multidisciplinary team in the management of diabetic foot wounds. Indications of usage include post-debridement wounds following surgery for necrotizing fasciitis, foot abscesses, infective heel ulcers and exposed bone, capsule and tendon. Factors contributing to a successful outcome include the following.

Careful selection criteria and application of NPWT

Patients selected for NPWT must be meticulously examined for conditions that may lead to suboptimal treatment outcomes:

- *Is there wound ischemia?* – NPWT should be used carefully in diabetic wounds with chronic ischemia. These wounds must be closely monitored and higher negative pressures should be avoided as it may worsen ischemia (9). Wounds selected must have at least one palpable foot pulse and a good capillary filling time (<2 s). Severely ischemic wounds are not suited for NPWT (9).
- *Is there sensory neuropathy?* – Neuropathy is a key contributor to foot complications in diabetic patients and must be assessed appropriately prior to NPWT initiation, that is, Semmes–Weinstein Monofilament Testing and neurothesiometer testing. Though not a contraindication to NPWT application, neuropathy is an important predictor for ulcer recurrence (24).

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- *Is there deep infection?* – Deep infections such as osteomyelitis and septic arthritis are contraindications for NPWT, as application of the device over underlying infection can essentially enclose the infection creating an abscess. These sources must be surgically removed prior to any form of NPWT. Patients require a thorough assessment with a combination of clinical examination, inflammatory markers (i.e. white blood cell [WBC] count, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]), and medical imaging. In cases with occult deep infection, modalities such as magnetic resonance imaging (MRI), bone scintigraphy, may even be necessary.

Radical debridement before application

NPWT can only be successful when adequate and proper debridement has been performed to remove all devitalized, necrotic, and infected tissue.

Regular monitoring of wound

During each change of dressing, the wound must be carefully inspected and managed. Small sloughing must be subjected to bedside debridement and wounds may be scraped to remove biofilm before the application of a new NPWT device. If there is persistent slough, a definitive surgical debridement needs to be repeated.

Optimizing glycemic control and healing markers

- Glycemic control is essential for successful treatment outcome. Hemoglobin A1C (HgA1C) level is a reliable marker of glycemic control and suboptimal levels suggest likelihood of delayed wound healing.
- Reduced hemoglobin (Hb) levels reflects poor tissue oxygenation. Healing will be poor if hemoglobin is low ($<$10 g/dL) and unable to provide sufficient oxygen for the healing wound bed.
- Albumin and prealbumin are markers of nutritional status and reflect the body's healing potential. Prealbumin is the earliest laboratory indicator for nutritional status and correlates well with patient outcomes in a wide variety of clinical conditions (25). Both these serum protein levels must be monitored and maintained for patients on NPWT.
- Lymphocyte count is another healing marker that can aid in gauging treatment outcomes during NPWT therapy. Counts $<$1,500 cell/μL denotes malnutrition and a weakened immune response (26).
- Creatinine level reflects renal function. Renal impairment as suggested by a raised creatinine level can negatively affect all aspects of healing and affect overall treatment outcome.

Appropriate antibiotics

The antibiotics sensitive to the organism cultured must be administered to help clear the infection and achieve a reduction in bacterial load.

Device application

- NPWT device is applied on the wound in a standard manner (Fig. 2).
- Once the dressing is applied, a standard negative pressure of 125 mmHg is applied to the wound, often in continuous mode.
- Dressing is usually changed once every 3 days though this duration may vary depending on wound and dressing type. At each change, the wound is assessed carefully to determine if it is progressing (clean, red, and granular). If infection or slough appears in the wound, additional bedside or surgical debridement should be performed before a new dressing is applied.
- Once the wound bed is filled with granulation tissue and wound bed preparation has been achieved, NPWT may be stopped.
- The prepared wound is allowed to close either with secondary intention or covered via a split thickness skin graft (STSG) once the culture and sensitivity of the wound bed are negative for microorganisms. If STSG is performed, NPWT can be used as a bolster dressing to aid graft uptake.

Technical considerations for NPWT device application

Wound filler type: black foam, white foam, or gauze?

Wound filler characteristics determine most of the effects of NPWT on the wound bed. Commonly used fillers in diabetic wounds are polyurethane (PU), polyvinyl alcohol foam, and saline-moistened gauze. The conventional 'black' PU foam is hydrophobic or water repelling and enables the dressing to conform to the wound bed providing the foam–tissue interface. This foam results in thick and rapid granulation (27) and is ideal for wounds with large defects after radical debridement. Foam-induced scarring further aids in wound contracture and size reduction. The polyvinyl 'white' foam is hydrophilic or moisture retaining. Its higher tensile strength and less adherent properties are typically indicated for use in tunnels and shallow undermining. It is also beneficial for use on exposed tendons and bones. Antimicrobial (i.e. silver) impregnated foam is also available to provide antibacterial cover during NPWT (28, 29).

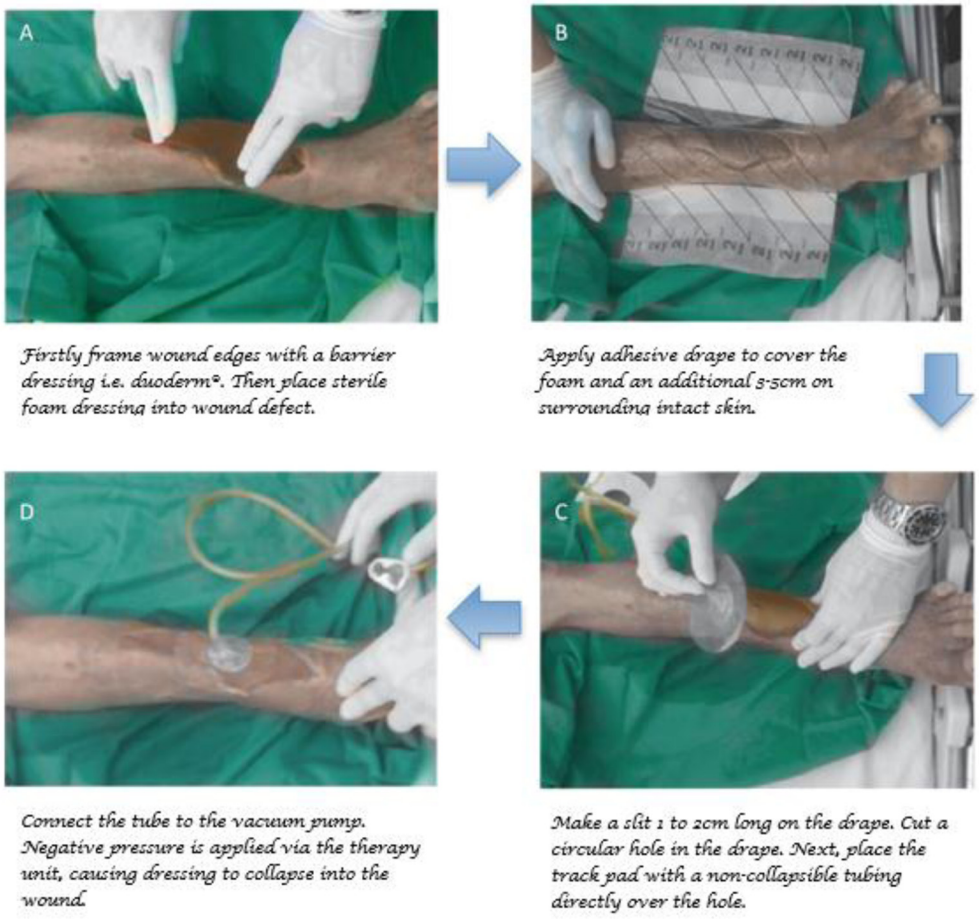

Fig. 2. Application of NPWT dressing.

Gauze is alternate filler and is useful for irregular wounds because of its conformability and ease of application (27). Similar to white foam, gauze is also useful in wounds where post-debridement soft tissue structures such as tendons and bone are exposed. Although underlying wound deformation by foam and gauze are different, studies show no differences in the time to complete healing between the two filler types (30).

Pressure setting: what pressure level and whether continuous, intermittent, or variable?

The NPWT pump delivers the desired negative pressure to the entire system. *In vitro* studies showed that at subatmospheric pressures of 125 mmHg, there is a fourfold increase in blood flow (4). In clinical practice, 125 mmHg is the normal setting though levels can vary between 50 and 150 mmHg depending on the wound type (31). Higher pressures can be used when there is high exudate and wound fluids (32) or in instances such as application of a bridge NPWT dressing. Bridge modification enables the suction pad to be placed outside weight-bearing area of the foot allowing patients to wear protective shoes and offloading gear while on NPWT. However, it is recommended to avoid using higher NPWT pressures in wounds with compromised vascularity or risk of ischemia (9). Pressures can also be lowered if the patient experiences pain or excessive amount of blood is seen in the canister despite hemostasis.

Pressure modes can be changed between continuous, intermittent, and variable delivery. Though preclinical studies show higher granulation under intermittent and variable pressures, continuous delivery is the established normal setting in clinical practice (33). In clinical application, intermittent mode has shown an increased potential for pain due to repeated wound filler contraction and expansion (33). It can also result in granulation ingrowth into the foam causing additional pain during foam removal. Variable mode is a recent introduction and involves cycling between two negative pressure levels (10–80 mmHg). Currently, this mode is mainly limited to research with limited evidence of its use in clinical practice.

Case study

A 62-year-old female with a 10-year history of diabetes mellitus presented with a dorsal forefoot abscess involving the second toe with pus tracking towards the sole. Upon examination, both dorsalis pedis and posterior tibial pulses

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were palpable. Infection markers on initial presentation were as follows: WBC count of 16×10^9/L, ESR of 80 mm/h, and CRP of 102 mg/L. Markers of wound healing included 12.5% for HbA1c, 12 g/dL for Hb, and 30 g/L for albumin. Patient underwent a second ray (metatarsal and toe) amputation and radical surgical debridement (Fig. 3a). Wound cultures grew *Pseudomonas aeruginosa* and *Enterococcus faecalis*, which were both sensitive to ceftazidime. Intravenous ceftazidime was thus started after infectious disease consultation.

Post-debridement NPWT dressing was applied to the wound. Webspace location of the wound (between first and third toes) made dressing application slightly challenging as sealing this area can occasionally pose difficulty. During each NPWT dressing application, the following steps were performed:

- Wound edges were first cleaned using alcohol wipes to remove loose debris. Edges were then covered using strips of duoderm™ hydrocolloid dressing acting as a barrier to prevent maceration.
- Black PU foam was then cut elliptically and curled around the center to fit both dorsal and plantar aspect of the wound.
- To adequately seal the wound, a barrier drape was cut into a rectangular strip sized according to the webspace wound. The strip was then placed longitudinally over the foam. Smaller drape strips were then used to reinforce the edges and protect the seal.
- Track pad was then placed on the foam over an opening made in the seal.
- Once connected to the pump, a continuous NPWT at 125 mmHg was applied to the system.

The patient was continued on NPWT for 4 weeks (Fig. 3b). During this period, the patient also underwent aggressive systemic optimization (i.e. glycemic control, nutritional support, and antibiotic therapy). At the last follow-up of 6 weeks after surgery, the wound was noted to have completely healed and the patient was ambulatory with minimal assistance (Fig. 3c).

Clinical evidence

Since the experimental work by Morykwas and Argenta (3), numerous studies have demonstrated the NPWT's effectiveness and safety in general wound management. Specifically for diabetic foot treatment, the NPWT's efficacy has been demonstrated in several clinical trials (Table 1). The early randomized controlled trials (5, 8) were primarily single center work with limited sample sizes. In 2005, Armstrong et al. conducted the landmark

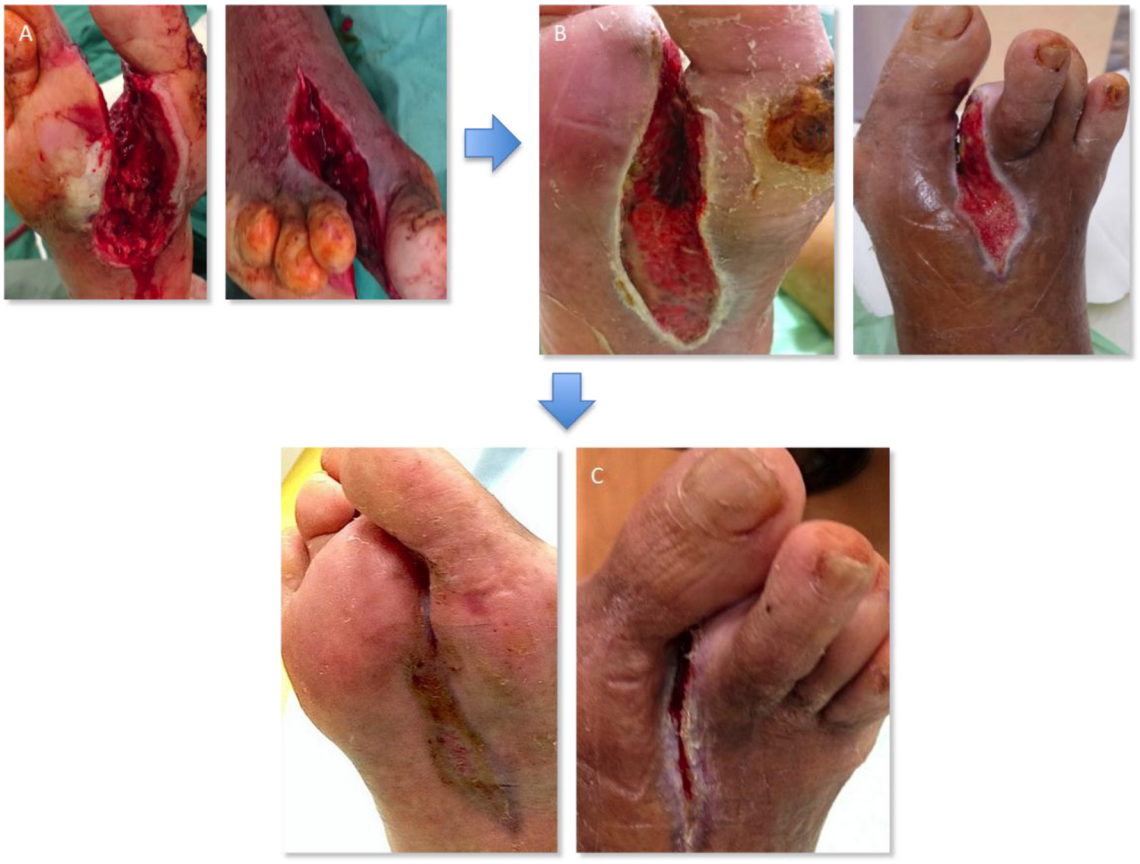

Fig. 3. (a) Wound after surgical debridement. (b) Wound after 2 weeks of NPWT. (c) Healed wound at 6 weeks post-surgery.

Table 1. Clinical evidence on negative pressure wound therapy and diabetic foot

Publication	Design	Sample	Methods	Results and conclusion
Dumville et al. (15)	Meta-analysis	605	Systematic review of 5 RCTs examining NPWT effectiveness	NPWT is more effective in healing diabetic postoperative foot wounds and ulcers compared with moist wound dressings
Paola et al. (34)	RCT (Study 1)	70 (NPWT = 35, moist dressing = 35)	Skin-graft wounds assigned to NPWT or moist dressings	Greater proportion of complete skin-graft uptake in NPWT group (80%) compared to moist dressings (68%), $p = 0.05$
Paola et al. (34)	RCT (Study II)	130 (NPWT = 35, moist dressing = 35)	After debridement, patients assigned to NPWT or moist dressings	NPWT group had faster granulation (65 days vs. 98 days) $p = 0.005$ and more rapid infection clearance (10 days vs. 19 days) $p = 0.05$
Noble-Bell et al. (14)	Meta-analysis		Systematic review of 4 randomized controlled trial examining NPWT effectiveness	NPWT therapy more effective than conventional dressings with increased granulation and healing rates
Blume et al. (35)	RCT	335 (NPWT = 169, moist dressing = 166)	Assigned to either NPWT or moist dressings (predominately hydrogels and alginates)	NPWT group achieved higher wound closure rates (43.2% vs. 28.9%) with fewer secondary amputations, $p = 0.035$
Armstrong et al. (36)	RCT	162 (NPWT = 77, moist dressings = 85)	Partial foot amputation wounds assigned to NPWT or moist dressings	NPWT group had increased healing (56% vs. 39%, $p = 0.040$. The rate of healing was also faster in the NPWT group, $p = 0.005$. Adverse effects were similar in both groups
Eginton et al. (8)	RCT crossover after 2 weeks	6	Assigned to receive moist gauze dressings or NPWT treatments for 2 weeks, after which subjects crossed over	NPWT resulted in a greater wound size reduction compared to moist dressings
McCallon et al. (5)	RCT	10 (NPWT = 5, moist dressings = 5)		Wound healing faster in NPWT group (22.8 ± 17.4 days vs. 42.8 ± 32.5 days for the control group)
Nather el al. (37)	Prospective	11	Diabetic foot ulcers treated with NPWT were prospectively studied	100% granulation and bacterial clearance at the end of therapy. Healing was achieved in all wounds (9 closed by SSG, 2 by secondary closure)

multi-center controlled study comparing NPWT with standard dressings. They demonstrated a statistically significant reduction in healing time, higher percentage of healed wounds, and reduction in the number of re-amputations in the NPWT treated group (36).

Blume et al. (35) conducted a larger trial. They noted that a greater proportion of diabetic foot ulcers achieved complete closure with NPWT than with standard wound therapy (43.2 vs. 28.9%). A trial by Paola et al. (34) further showed that NPWT reduced the need for subsequent amputations in a 6-month follow-up period. In a parallel trial, this group also showed a higher uptake of skin graft in wounds assigned to NPWT when compared to standard dressings (80 vs. 68%) (34). In two published systematic analysis of randomized trials, NPWT was concluded to be more effective in treating diabetic foot wounds and ulcers than standard dressings. Wounds treated with NPWT showed increased granulation, faster healing, and reduced amputation rate (14, 15).

New developments and adjuncts

The Food and Drug Administration (FDA) cleared the first device for NPWT in 1997. Since then, the system has evolved considerably with various new devices and upgrades. The original V.A.C.™ system (KCI, Inc., San Antonio, TX, USA), however, is still the most widely used with majority of clinical evidence on the use of NPWT in wound management (including diabetic wounds) pertaining to this system (6). Some of the other alternate options include Renasys-GO™ (Smith & Nephew GmbH, Hull, UK) and Vivano™ (Paul Hartmann AG, Heidenheim, Germany). Renasys-GO™ (Smith & Nephew GmbH) has been effectively used in treating diabetic foot wounds (9). A recent randomized controlled trial comparing V.A.C.™ and Renasys-GO™ showed no difference in clinical efficacy between the two systems when treating both acute and chronic wounds (38). V.A.C.™ and Vivano™ have also been compared with results showing similar outcomes in complex wound management (39).

In diabetic wound management, NPWT is still an evolving technology. As most of these wounds present with infection, the success of NPWT in this cohort is still highly dependent upon the adequacy of surgical debridement and antimicrobial coverage. However, the following mentioned new device upgrades and adjuncts have been introduced to make the therapy more efficient in the management of diabetic wounds.

NPWT and silver antimicrobials

Silver dressings have long been recognized as a powerful antimicrobial for infective wounds (40). It binds to DNA of bacteria and spores and reduces their ability to replicate. It also binds to cell membranes, causing irreversible damage to microbial architecture (41). Silver-resistant organisms are extremely rare (42). Nanocrystalline silver has further enhanced silver's antimicrobial effect. It utilizes nanotechnology to release clusters of extremely small and highly reactive silver cation particles (43). When incorporated into wound dressings, nanosilver can provide a continuous flow of charged silver cations to the wound bed. This creates a sustained and effective antimicrobial environment. Existing clinical data suggest that nanosilver dressings are cost-effective, lessen wound exudate, reduce microbial level, and promote healing in chronic wounds (44–46). Various commercial silver products compatible with NPWT are available for clinic use. They are either combined with the polyurethane foam or used as a wound contact dressing under the NPWT foam.

- *Silver foam products:* The silver impregnated foam structure has a dual role in stimulating granulation tissue formation and providing antimicrobial cover. When in contact with fluids, the silver of the foam dressing oxidizes to ionic silver. V.A.C. GranuFoam™ (KCI, San Antonio, TX, USA) is a reticulated, silver-coated, polyurethane foam, compatible with the V.A.C. NPWT system. *In vitro* efficacy of this foam dressing has been demonstrated against microbes including *Staphylococcus aureus* and *Staphylococcus epidermidis* (29). CuraVAC™ Ag (Daewoong Pharm Co, Ltd, Seoul, Korea) is another product that delivers NPWT through a foam dressing that contains silver nanoparticles. The latter has also been employed for treating diabetic foot wounds (18).
- *Silver dressing products:* Unlike silver foam products, NPWT compatible silver dressings are applied as wound contact layer under the foam. New generation nanocrystalline silver dressings can be placed under the NPWT foam as the dressing's porous architecture maintains flow, allowing passage of exudate. The dressing can be used in infective wounds including diabetic foot wounds, though available data on clinical efficacy and cost effectiveness are limited.

NPWT and instillation

In NPWT and instillation (NPWTi) topical solutions are cyclically fed to the wound through the foam dressing and are held for a selected period before removal by vacuum pump. Cyclic irrigation of the wound optimizes healing by removing devitalized tissue, debris, infectious agents, and preparing the wound bed for closure. V.A.C. Ulta™ Therapy System (KCI) is one of the commercial NPWTi devices that combines conventional V.A.C.™ Therapy (KCI) with controlled delivery of topical instillation solutions to the wound bed using V.A.C. VeraFlo™ Therapy (KCI).

In vitro evidence favoring NPWTi shows increased granulation in wound models treated with instillation

therapy (47). In clinical practice, the solutions used can vary from topical cleansers to antibiotics and antiseptics. Gabriel et al. demonstrated that instilling silver nitrate helped to reduce bioburden, decreased time to wound closure, and allowed early hospital discharge (48). Instillation of polyhexanide (polyhexamethylene biguanide) solution as an adjunct with debridement and antibiotics resulted in positive outcomes in patients with necrotizing fasciitis and osteomyelitis (49, 50). In a diabetic wound cohort, Bernstein et al. (51) used NPWTi with bacitracin–polymyxin B solution and showed successful results with complete healing and reduced amputations.

Portable devices

A major disadvantage of conventional NPWT systems is the bulky nature of the device. Recently, introduced portable systems allow more mobility and less hindrance to routine activities. PICO® (Smith & Nephew) is a single-use canister-free NPWT device that can be placed in a pocket or attached to a belt-loop. Published data on mixed etiology wounds (including diabetic foot ulcers) show efficacy comparable to that of conventional NPWT (52). PICO® has also been designed for use over closed incisions at risk for surgical site infections. This dressing technique has been effectively used in trauma setting reducing wound dehiscence and infection (53). There is a potential for a similar role in closed amputation wounds in diabetic patients at high risk for wound complications.

Smart Negative Pressure (SNaP) Wound Care System® (Spiracur, Inc., Sunnyvale, CA, USA) is another portable device that uses specialized springs to deliver NPWT. The system consists of a cartridge, a hydrocolloid dressing layer with integrated nozzle and tubing, and a foam interface. The cartridge doubles as a storage canister and can deliver negative pressures of up to 125 mmHg (54). SNaP does not require an electrically powered pump. Its ease of application and ultraportability make it ideal for use in ambulatory settings. Efficacy comparable to that of conventional electrical NPWT (V.A.C™) has been demonstrated in a recent multi-centered trial (55). Portable NPWT devices including SNaP, however, are all limited in their usage as they are only suited with low-to-moderate exudate levels restricting their use in large diabetic foot wounds (56, 57).

Home-care protocols

There has been a recent effort to expand NPWT's usage beyond hospital settings. Aided by more compact systems and improved home healthcare support, it is now possible for rehabilitation facilities to have provisions for NPWT. The long-term cost effectiveness of these protocols is still unclear but in the short term, they do facilitate early hospital discharge and reduce hospital stay.

Conclusion

NPWT has been a major breakthrough in wound care over the last decade. In diabetic foot management, NPWT has had a significant impact on limb salvage, which is evident from existing literature. The science of NPWT is still evolving and new additions such as instillation and nanocrystalline antimicrobials may further improve outcomes in infected wounds. Portable devices and home-care protocols are also expanding NPWT's usage beyond the hospital setting. However, it is important to emphasize that diabetic foot management is a multidisciplinary effort, and NPWT is only one of the essential tools in the overall management. Successful outcome is heavily dependent on all treatment modalities including adequate wound debridement, appropriate antibiotic therapy, optimization of healing markers, and meticulous wound monitoring.

Disclaimer

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