Effect of high negative pressure wound therapy in diabetic foot ulcer healing

Authors
Laila Al-Sabbagh, Rashad A Bishara, Ihab N Hanna, Amr Abdel-Mawgoud, Mohamed Ramadan Meabed, Nehad A Fouad and Ramez O Shehata

The effective range of negative pressure wound therapy (NPWT) lies between 50 mmHg and 150 mmHg, yet no optimal pressure has been identified. This study assessed the effect of negative pressure level on the rate and duration of wound healing in patients with non-ischaemic diabetic foot ulcers (DFUs). Patients were randomised to standard (–120 mmHg; *n*=87) or high (–160 mmHg; *n*=88) NPWT, managed following a standard wound care protocol and followed until complete healing or for a maximum of 12 months. The high NPWT group had a significantly greater rate of complete wound healing (P<0.00001), significantly shorter time to healing (P=0.003), significantly lower amputation rate (P=0.003) and fewer deaths (P=0.07) than the standard NPWT group. Greater negative pressure accelerated healing and reduced major amputations and death in patients with non-ischaemic DFUs.

Negative pressure wound therapy (NPWT) was introduced in clinical practice in the early 1990s (Argenta and Morykwas, 1997). Over the past 15 years, it has revolutionised wound care. NPWT is currently used in the management of complex and non-healing wounds of different aetiologies in various anatomic locations. Studies on porcine models have demonstrated that the application of NPWT at pressures between –50 mmHg and –150 mmHg is effective and recommend a pressure of –125 mmHg (Morykwas et al, 2001). No randomised clinical studies have compared the effects of different levels of negative pressure on wound healing. The objective of this study was to assess the effect of high versus standard negative pressure on the duration and rate of wound healing in patients with non-ischaemic diabetic foot ulcers (DFUs).

Method

This prospective randomised study was performed at one institution over a 6-month period, from July 1 to December 31, 2018. Consecutive patients with DFUs for whom NPWT was prescribed were included in the study. Patients presenting with a DFU on severely ischaemic feet or whose ischaemia was not adequately corrected by vascular intervention were excluded. Eligible patients were randomised to receive standard NPWT (–120 mmHg) or high NPWT (–160 mmHg) in a one-to-one ratio.

Participants were examined and their full medical history taken by the treating physician. Wound size was measured with a plastic ruler and a digital photo taken at a distance of 30 cm from and perpendicular to the wound. Debridement was performed where necessary. Infection was treated according to the Infectious Diseases Society of America guidelines (Lipsky et al, 2012). Ischaemic feet were revascularised according to international guidelines (Bus et al, 2016; Conte et al, 2019). Patients initially presenting with severe ischaemia had their ischaemia corrected prior to randomisation. Patients whose ischaemia was not adequately corrected were excluded. Offloading was performed for plantar ulcers, according to International Working Group on Diabetic Foot recommendations (Bus et al, 2016). DFUs were classified according to the WIFI classification for Wound severity, Ischemia and Foot Infection. Wound severity was graded from W0 to W3 and foot infection graded from FI0 to FI3 (Mills et al, 2014).

The RENASYS ™ NPWT system (Smith & Nephew) was used to treat all of the patients

***Laila Al-Sabbagh** is Head-Nurse and Research Assistant, **Rashad A Bishara** is Director, **Ihab N Hanna, Amr Abdel-Mawgoud, Mohamed Ramadan Meabed** and **Nehad A Fouad** are all Consultant Vascular Surgeons, **Ramez O Shehata** is Vascular Specialist; all at Diabetic Foot Center, Cairo, Egypt*

Table 1. Participant demographics and comorbidities in the groups (*n*=175).			
Demographic/comorbidity	**Standard NWPT, n (%)**	**High NWPT, n (%)**	***P*-value**
Age, years (mean)	60	59	0.120
Male gender	54 (62.0)	59 (67.0)	0.490
Smoker	33 (37.9)	34 (38.6)	0.900
Hypertension	51 (58.6)	39 (44.3)	0.058
Renal impairment	17 (19.5)	14 (15.9)	0.520
Ischaemic heart disease	19 (21.8)	31 (35.2)	0.070
Ischaemia	40 (45.9)	36 (40.9)	0.490

Table 2. Diabetic foot ulcer classification according to WIFI class*.			
Demographic/ comorbidity	**Standard NWPT, *n* (%)**	**High NWPT, *n* (%)**	***P*-value**
W2 + W3	65 (74.7%)	71 (80.6%)	0.34
I2 + I3	40 (45.9%)	36 (40.9%)	0.49
FI2 + FI3	49 (56.3%)	58 (65.9%)	0.19

*W = wound; I = ischaemia; FI = foot infection.

Table 3. WIFI stage of diabetic foot ulcers in the two groups.			
WIFI stage	**Standard NWPT, *n* (%)**	**High NWPT, *n* (%)**	***P*-value**
1	0	0	N/A
2	15 (17.2%)	10 (11.3%)	0.20
3	22 (25.2%)	24 (27.2%)	0.76
4	41 (47.1%)	49 (55.6%)	0.70

Table 4. Outcomes in the two negative pressure wound therapy groups.			
Outcome	**Standard NWPT, *n* (%)**	**High NWPT, *n* (%)**	***P*-value**
Ulcers completely healed	51 (59)	76 (90)	0.00001*
Days to complete healing	216	163	0.003*
Major amputations	16	4	0.003*
Mortality	12	5	0.070

*Significant difference.

in this study. It was applied according to the manufacturer's instructions under aseptic conditions at the centre. Continuous pressure mode was used and patients were provided with instructions on how to operate the system. To ensure reproducibility, all dressing changes were performed at the centre by the research nurse. Foam dressings were changed twice a week and 1,000 mL normal saline was applied during dressing changes. New photos and measurements of the wound were taken at each dressing change.

The total duration of NPWT was determined by the treating physician. After removing the NPWT, patients received wound care according to standard protocols. Patients visited the centre every 14 days for follow-up until complete healing was achieved or one of the other endpoints (major amputation and death) was reached.

The study protocol was approved by the Ethical Committee of the centre. Informed consent was obtained from all participants.

Statistical analysis

Continuous variables were compared using students' t-test and categorical variables compared using chi-squared test. Analysis of variance was used to study the interaction between the method of treatment (standard versus high NPWT), presence of ischaemia at initial presentation (I), wound severity (W) and degree of infection (FI). Multinomial logistic regression was performed to model the relationship between these variables and the outcomes (complete healing, major amputation and mortality). A *P*-value <0.05 was considered statistically significant.

Results

A total of 175 patients were randomised into two groups: standard (*n*=87) and high (*n*=88) NPWT. Patient demographics and comorbidities are presented in *Table 1*. Patients' DFUs were classified according to WIFI class *[Table 2]* and stage *[Table 3]* (Morykwas et al, 2001; Lipsky et al, 2012) on initial presentation. There were no significant differences between the two groups in terms of demographics, comorbidities or WIFI classification on enrolment.

Participants in the standard NPWT group were followed-up for a mean 207 days; the high NPWT group for 203 days. Six patients in the standard NPWT group were lost to follow-up; none from the high NPWT group.

There were significant differences between-group in time to healing and rates of complete healing and major amputation *[Table 4]*. The percentage of wounds that completely healed was significantly greater in the high NPWT group (*P*=0.00001) and the mean time to complete healing was significantly longer in the standard NPWT group (*P*=0.003). Regarding adverse events, major amputation was significantly more frequent (*P*=0.003) and mortality more frequent in the standard NPWT group *versus* the high NPWT group.

Analysis of variance identified a statistically significant interaction between treatment group and foot infection ($F(2,15)= 5.569$, $P=0.003$). The high NPWT group took less time to heal than the standard NPWT group on average, but this effect was greater for patients with FI-1, compared to

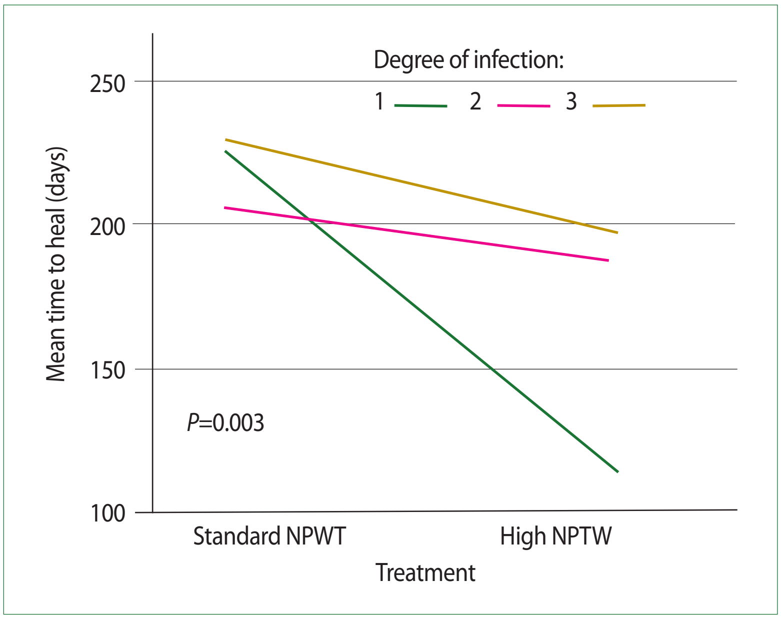

Figure 1. Effect of degree of foot infection on time to complete healing

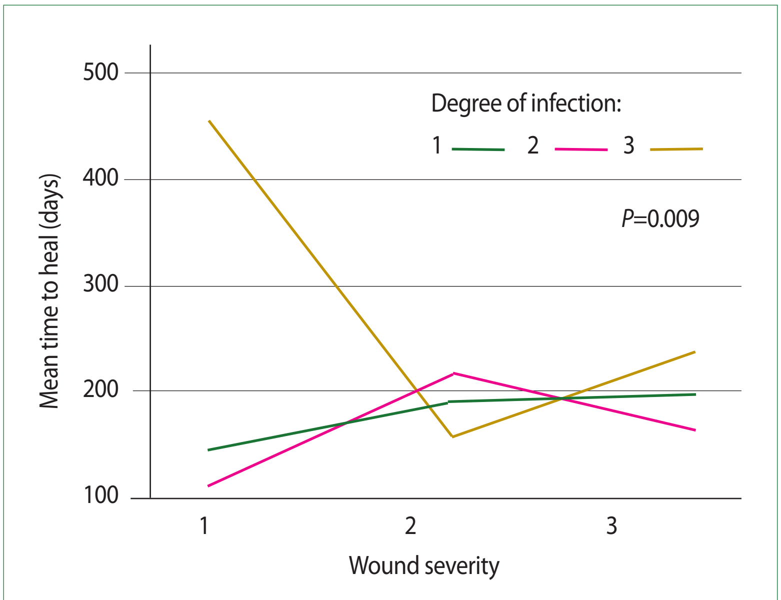

Figure 2. Effect of degree of foot infection and wound severity on time to complete healing

FI-2 and FI-3 *[Figure 1]*. There was also a statistically significant relationship between foot infection and wound severity (F(4,15)=3.557, *P*=0.009) *[Figure 2]*.

Multinomial logistic regression analysis found that the treatment group, ischaemia at initial presentation and wound severity had significant independent impacts on outcomes *[Table 5]*. Patients in the standard NPWT group had 5.3 higher odds of amputation than complete healing when compared to the high NPWT group (*b*=1.68, chi-squared (1)=6.78, *P*=0.009). The odds of dying *versus* complete healing were 4.9 times higher in the standard NPWT group (*b*=1.58, chi-squred (1)=6.4, *P*=0.011). Patients with severe ischaemia were 7.6 times more likely to undergo amputation than achieve complete healing when compared to patients with no ischaemia on presentation (*b*=–2.025, chi-squared (1)=8.873, *P*=0.003). Finally, wound severity significantly predicted the odds of amputation over complete healing:

- W2 was 9 times more likely to result in major amputation than W1 (*b*=–3.173, chi-squared (1)=6.134, *P*=0.013)
- W3 was 6.6 times more likely to result in major amputation than W2 (*b*=–1.884, chi-squared (1)=7.398, *P*=0.007).

Discussion

Diabetic foot disease is one of the most serious complications of diabetes and is a huge burden for patients and the healthcare system (Schaper et al, 2020). An estimated 15% of people with diabetes will suffer from foot ulcers and 10% of patients who have DFUs will eventually undergo major lower-extremity amputation (Schaper et al, 2003). It is, therefore, important to apply effective, rapid and safe treatment that accelerates wound healing and reduces the risk of major amputation. Many studies have assessed the safety, efficacy and cost–benefit ratio of NPWT (Othman, 2012). Based on data from studies, the addition of NPWT to standard care is recommended for the management of diabetic foot wounds by the International Working Group on the Diabetic Foot (Rayman et al, 2020). Although negative pressure of between –50 mmHg and –150 mmHg is effective and safe (Borgquist et al, 2010a,b), guidelines on optimal pressure and the patient groups that will benefit from specific levels of negative pressure are lacking. This study compared the effects of high (–160 mmHg) and standard negative pressure (–120 mmHg) on wound healing rate and time in patients with DFUs.

The Society for Vascular Surgery developed the WIFI classification to overcome the obstacles and limitations of the older classifications (Mills et al, 2014). WIFI has been shown to predict amputation risk and time to wound healing (Behan et al, 2017); the risk of major amputation and wound healing time both increase with increasing WIFI stage (Zhan et al, 2015). There were no significant differences between-group in WIFI classification (wound, ischaemia and infection) or stage in the current study; moreover, nearly 50% of patients enrolled were stage 4 (47.1% of the standard NPWT group and 55.6% of the high NPWT group) and therefore at greater risk of negative outcomes. Major amputations and death were more frequent in the standard NPWT group. Since these endpoints were mainly caused by sepsis in this cohort of patients, it could be argued that more efficient NPWT could reduce these adverse outcomes by reducing septic complications and time to complete healing.

Table 5. Multinomial logistic regression of factors contributing to outcomes (n=175).

Factor	Model-fitting criteria –2 log likelihood of reduced model	Likelihood ratio tests		
		Chi-squared	Degrees of freedom	Significance
Intercept	94.179	0.000	0	–
Treatment*	120.302	26.123	5	0.000
Ischaemia at initial presentation	118.496	24.317	5	0.000
Wound	116.794[b]	22.615	10	0.012
Foot infection	113.953	19.774	15	0.181

Patients were followed until complete ulcer healing over a maximum of 12 months, during which there were statistically significant differences in the rate and mean time to complete healing in favour of the high NPWT group. As the two groups had similar demographics, comorbidities, WIFI stage and care protocol, it is assumed that the differences in outcomes were a result of the pressure used during the application of NPWT.

It must be noted that patients presenting with severe ischaemia or ischaemia not corrected by revascularisation were excluded from this study. There have been previous reports of skin necrosis caused by the application of NPWT at –125 mmHg in ischaemic limbs, resulting in the suggestion of the application of low-pressure (–50 mmHg) NPWT to ischaemic limbs (Kasai et al, 2012).

The limitation of this study is that it examined two levels of negative pressure on a specific clinical presentation: non-ischaemic DFUs. It is hoped the findings will result in further research to investigate the effect of different levels of negative pressure on wound healing in various clinical scenarios with the aim of identifying which pressure is most effective for which category of patients.

Conclusions

High negative pressure (–160 mmHg) resulted in a significantly higher healing rate and shorter healing time, and reduced major amputation rate and reduced the death rate when compared to standard negative pressure (–125 mmHg) in patients with non-ischaemic DFUs. Further studies are required to identify the levels of negative pressure that are more effective in specific disease entities.

References

Argenta LC, Morykwas MJ (1997) Vacuum-assisted closure: a new method for wound control and treatment: clinical experience. *Ann Plast Surg* 38(6): 563–76

Behan HA, Ewon EK, Reyzelman A (2017) A closer look at the WIfI Classification System for Threatened Limbs. *Podiatry Today* 30(5): 14–8

Borgquist O, Gustafsson L, Ingemansson R, Malmsjö M (2010a) Micro- and macromechanical effects on the wound bed of negative pressure wound therapy using gauze and foam. *Ann Plast Surg* 64(6): 789–93

Borgquist O, Ingemansson R, Malmsjo M (2010b) Wound edge microvascular blood flow during negative pressure wound therapy: Examining the effects of pressure from –10 to –175 mmHg. *Plast Reconst Surg* 125(2): 502–9

Bus SA, Armstrong DG, van Deursen RW et al (2016) International Working Group on the Diabetic Foot. IWGDF Guidance on Footwear and Offloading Interventions to Prevent and Heal Foot Ulcers in Patients with Diabetes. *Diabetes Metab Res Rev* 32(S): 25–36

Conte MS, Bradbury MW, Kolh P et al; Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia (2019) Writing Group for the Joint Guidelines of the Society for Vascular Surgery (SVS), European Society for Vascular Surgery (ESVS), and World Federation of Vascular Societies (WFVS). *Eur J Vasc Endovasc Surg* 58(1S): S1–S109

Kasai Y, Nemoto H, Kimura N et al (2012) Application of low-pressure negative pressure wound therapy to ischaemic wounds. *J Plast Reconstr Aesthet Surg* 65(3): 395–8

Lipsky BA, Berendt AR, Cornia PB et al (2012) 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 54(12): 132–73

Mills JL, Conte MS, Armstrong DG et al (2014) The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on Wound, Ischemia, and foot Infection (WIfI). *J Vasc Surg* 59(1): 220–34

Morykwas MJ, Faler BJ, Pearce DJ, Argenta LC (2001) Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine. *Ann Plast Surg* 47(5): 547–51

Othman D (2012) Negative pressure wound therapy literature review of efficacy, cost effectiveness, and impact on patient's quality of life in chronic wound management and its implementation in the United Kingdom. *Plas Surg Int* 374398

Rayman G, Vas P, Dhatariya K et al; International Working Group on the Diabetic Foot (2020) IWGDF Guideline on interventions to enhance healing of foot ulcers in persons with diabetes. *Diabetes Metab Res Rev* 32(Suppl 1): e3283

Schaper NC, Apelqvist J, Bakker K (2003) The international consensus and practical guidelines on the management and prevention of the diabetic foot. *Cur Diab Rep* 3(6): 475–9

Schaper NC, van Netten JJ, Apelqvist J et al (2020) Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 Update). *Diabetes Metab Res Rev* 36(Suppl 1): e3266

Zhan LX, Branco BC, Armstrong DG, Mills Sr JL (2015) The Society for Vascular Surgery lower extremity threatened limb classification system based on Wound, Ischemia, and foot Infection (WIfI) correlates with risk of major amputation and time to wound healing. *J Vasc Surg* 61: 939–44