

Review Article

Negative Pressure Wound Therapy for the Diabetic Foot Treatment: A Literature Review

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Abstract: Diabetes mellitus is one of the most common chronic metabolic diseases. Diabetes mellitus can cause many complications such as obesity, stroke, coronary heart disease, diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy. Studies show that compared to the cost of treating diabetes, more costs are incurred for the treatment of complications of diabetes. One of the most common chronic complications is diabetic foot ulcers (DFU), which are disabling and affect about 15% of diabetic patients which leading to infection, gangrene, and eventually leading to amputation. DFU care requires a cross-disciplinary and systematic approach consisting of blood glucose control, surgical debridement, vascular recanalization, decompression, and supportive treatment. Controlling wound infection and performing tissue repair is very important to prevent or reduce amputation rates. The concept of negative pressure wound therapy (NPWT) was first established and applied in clinical practice by a German physician, Fleischmann, in 1993 and has been recognized for its remarkable effects in increasing perfusion, improving wound drainage, and promoting the growth of granulation tissue. Currently, NPWT is widely used for various acute and chronic wounds, such as DFU and considered effective to reduce limb amputation rates. NPWT is safe for the treatment of neuropathic, nonischemic, and noninfected plantar ulceration in patients with diabetes mellitus. However, special attention should be given to proper patient selection and intraoperative assessment to ensure wound closure and avoid undue complications.

Keywords: Diabetic foot ulcers, diabetes mellitus, negative pressure wound therapy, VAC, literature review.

Introduction

Diabetes mellitus is one of the most common chronic metabolic diseases. Diabetes mellitus has been estimated to affect more than 200 million adults worldwide, and its incidence is still increasing.¹ Diabetes mellitus can cause many complications such as obesity, stroke, coronary heart disease, diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy.² Studies show that compared to the cost of treating diabetes, more costs are incurred for the treatment of complications of diabetes.

One of the most common chronic complications is diabetic foot ulcers (DFU), which are disabling and affect about 15% of diabetic patients. DFU is thought to be associated with diabetic neuropathy and peripheral vascular disease, leading to infection, gangrene, and eventually leading to amputation.^{1,2,3}

According to the International Working Group on the Diabetic Foot (IWGDF), amputations for DFU are performed every 20 seconds and in more than 1 million people every year. Globally, in 2017 there were 425 million people with diabetes, and by 2045 it is expected to increase to 629 million. According to an expert opinion published in the New England Journal of Medicine, 19-34% of diabetic patients will develop diabetic foot ulcers, the 5-year mortality rate after amputation is greater than 70%, and the 2-year mortality rate after amputation in those on kidney dialysis reaches 74%.^{4,5}

The risk of death in DFU patients is much higher than those with multiple malignant tumors. DFU has become one of the main killers associated with high morbidity and mortality. Therefore, its prevention and treatment have become an urgent clinical problem. DFU care requires a cross-disciplinary and systematic approach consisting of blood glucose control, surgical debridement, vascular recanalization, decompression, and supportive treatment. Controlling wound infection and performing tissue repair is very important to prevent or reduce amputation rates.^{3,6-7} However, due to various factors, such as occlusive arteriosclerosis, multi-drug resistant bacterial infections, neuropathy, and inappropriate treatment methods of debridement and dressing change, limb salvage treatment in DFU cases has resulted in delayed wound healing, prolonged treatment cycles, and heavy economic burden on families and communities.⁷⁻⁹

The concept of negative pressure wound therapy (NPWT) was first established and applied in clinical practice by a German physician, Fleischmann, in 1993 and has been recognized for its remarkable effects in increasing perfusion, improving wound drainage, and promoting the growth of granulation tissue. Currently, NPWT is widely used for various acute and chronic wounds, such as DFU. In 2016, NPWT was recommended with class I evidence by the Wound Healing Society of the United States in its DFU treatment guidelines. Improving wound healing by reducing edema, removing bacterial products, and approximating wound edges should be considered as a treatment strategy when others fail.^{3,10} Although NPWT is expensive, the IWGDF for the prevention and management of DFU recommends considering the use of NPWT to reduce wound size, in addition to the best standard of care after surgery. NPWT appears to stimulate granulation tissue formation and wound contraction.¹¹

Discussion

Diabetic Foot Ulcer

DFU is one of the main chronic complications caused by diabetes mellitus and results from peripheral disease of neurological and vascular changes. Ulcers are a dreaded complication of the diabetic foot that can lead to limb amputation. The prevalence of DFU in the diabetic population is 4%-10%, and this condition is more common in older patients. According to the World Health Organization (WHO) and IWGDF, DFU is described as a condition in which the feet of a patient with diabetes is at potential risk of pathological consequences, including ulceration, infection and/or damage to deep tissues, associated with neurological abnormalities and varying degrees of peripheral arterial disease and metabolic complications of diabetes in the lower extremities.¹²

The common underlying causes of DFU are poor glycemic control, calluses, foot deformity, improper foot care, ill-fitting footwear, underlying peripheral neuropathy, poor circulation, and dry skin. About 60% of people with diabetes will develop neuropathy, which eventually causes foot ulcers. The risk of foot ulcers is increased in individuals with flat feet because they have disproportionate pressure across the foot, leading to tissue inflammation in high-risk areas of the foot.¹³

There are five staging of the diabetic foot, and the stages are superficial ulcer for the first stage, deep ulcer involving the tendon, bone, or joint for the second stage, deep ulcer with abscess or osteomyelitis for the third stage, gangrene involving the forefoot for the fourth stage, and gangrene involving the entire foot for the fifth stage.¹³

Negative pressure wound therapy

NPWT is a noninvasive system creating a localized controlled negative pressure environment. NPWT utilizes the control of applying negative pressure to the wound, where a specially designed open pore foam dressing is cut into the wound shape, and the vacuum unit provides continuous or intermittent sub atmospheric pressure.¹

In 2017, the European Wound Management Association reported that NPWT-assisted treatment for DFU increases granulation tissue proliferation and accelerates wound healing.^{3,14} The IWGDF recommends using NPWT to promote ulcer healing in international guidelines on the prevention and management of DFU.⁴ Since NPWT is an important adjunct treatment for DFU, NPWT should be standardized in terms of its use, parameter adjustment, evaluation, and other important aspects. The success of treatment for DFU depends on the mechanism of action of therapy, chronicity of the ulcer, and patient compliance. Due to the complexity of DFU treatment, medical treatment of DFU remains challenging.¹

The Association and Effectiveness of NPWT in the Treatment of Diabetic Foot

NPWT has been used as an adjunct treatment for DFU, and its potential influence on local gene expression and epigenetic methylation in the wound bed was recently described.^{15,16} However, the novel mechanism of action of NPWT can be attributed to processes involving the whole organism in which signals are transmitted through molecules circulating in the tissues and organs of the organism. This inter-tissue signaling, for example, via circulating microvesicles (MV), has been associated with wound healing pathomechanisms. MVs represent a heterogeneous population of vesicles that grow from the plasma membrane and express specific antigens from their host cells. The main source of circulating MV is derived from different cell populations such as platelets, endothelial cells, neutrophils, and lymphocytes.¹⁵

The main function of MV is to transfer bioactive molecules including proteins, lipids, DNA, mRNA, and miRNAs, some of which have important signaling functions. The cellular components are selectively recruited by a highly regulated process into the MV. Among these bioactive components, angiogenesis regulatory factors are of greatest interest, especially in patients who have complicated diabetes. MVs contain various factors that contribute to their angiogenesis-promoting function, such as angiogenin, vascular endothelial growth factor (VEGF), monocyte chemotactic protein-1 (MCP-1), and also receptor proteins including urokinase-type plasminogen activator (UPAR), receptor- 2 for VEGF (VEGF R2), and Tie-2/TEK.^{17,18}

The NPWT technique is a noninvasive system in which foam is placed on the wound and uses negative pressure controlled by a vacuum-connected device that promotes stimulation and healing of the wound. However, despite the existing evidence regarding the use of NPWT in the healing of surgical, vascular, or other types of wounds, there are only a few studies analyzing its effectiveness in DFU. In several systematic reviews, investigators agreed that there is moderate to strong evidence for the use of NPWT in DFU.¹² However, some of the results have highlighted certain negative aspects associated with NPWT. Some of the potential side effects of NPWT include wound maceration, wound infection, bleeding, and retention of dressings. Besides that, NPWT systems appear to be expensive, which may preclude their widespread use. However, if the therapy accelerates wound healing, substantial reserves can be made for the costs associated with the dressing.^{12,15}

Previous studies showed that the time to complete wound healing was significantly better in the NPWT therapy group compared to conventional dressings. Similar results were obtained when comparisons were made between the two groups of patients stratifying by ulcer size. Time to complete healing in the NPWT group was significantly better in both DFU < 10 cm and 10 cm compared to the conventional group; However, its efficacy was more pronounced at DFU < 10 cm ($P < 0.0001$) than at DFU 10 cm ($P = 0.0042$).¹⁹

There are some studies that compared the effectiveness of NPWT and conventional dressing. In a study by Armstrong and Lavery, the median time to complete closure was 56 days in the NPWT therapy group compared with 77 days in the conventional saline dressing group.²⁰ Blume et al. showed that a greater proportion of DFUs receiving NPWT therapy achieved complete skin closure or 100% re-epithelialization.²¹

Singh et al. showed the mean time to complete wound closure 41.2 days and 58.9 days in the NPWT therapy and the conventional groups.²² According to Vaidya et al. sixty patients with DFU showed a cure time of 17.2 days in the NPWT therapy group compared to 34.9 days in the conventional dressing group.²³

NPWT causes mechanical tension at the foam-wound interface, which damages the cytoskeleton activating a cascade that causes cell proliferation and angiogenesis. Increased levels of fibroblast growth factor, altering growth factor- β , fibroblast proliferation, smooth muscle actin, interleukin-8, and vascular endothelial growth factor are involved in the increased formation of granulation tissue in NPWT. NPWT also creates an environment by reducing edema and bacterial load, which would otherwise inhibit granulation.¹⁹

NPWT safety assessment

The side effects of NPWT treatment can be infection, pain, edema, bleeding, and death. Adverse events were reported in 16 studies that made comparisons between NPWT and other treatments. Generally, most of them did not achieve a significant difference in the serious side effects associated with the NPWT system compared with other standard treatments.¹²

NPWT cost-effectiveness assessment

Regarding the high expenditure of NPWT and the lack of full coverage by insurance companies, the cost-effectiveness of this therapy can be influenced by other factors such as faster healing time, shorter duration of hospitalization, number of treatment sessions, and number of dressing changes. In a recent meta-analysis by Liu et al. a significantly faster healing time was detected by NPWT technology compared to other standard dressings.²⁴ This finding may justify the cost benefits of the NPWT.¹²

Conclusion

Diabetic foot ulcers require a multidisciplinary approach and are difficult to treat. NPWT is useful and should be considered to reduce limb amputation rates. NPWT is safe for the treatment of neuropathic, nonischemic, and noninfected plantar ulceration in patients with diabetes mellitus. However, special attention should be given to proper patient selection and intraoperative assessment to ensure wound closure and avoid undue complications.

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