NEGATIVE PRESSURE WOUND THERAPY IN THE MANAGEMENT OF TYPICAL CHRONIC LOWER LIMB ULCERS

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Summary

Chronic lower limb ulcers are defined by a long-standing evolution, with no tendency to heal after three months of proper treatment or still not completely healed after twelve months. Chronic wounds may be classified as typical and atypical. The majority of the typical chronic ulcers are localized on the lower limbs and are caused by chronic venous insufficiency, followed in frequency by other wound types: arterial, of mixed etiology- arterial and venous, pressure, neuropathic and diabetic foot ulcers. Standard therapy of chronic ulcers begins with a few general principles which are applicable regardless of the lesions' cause: tissue debridement, control of the infection, moisture balance and management of the edges of the wound. Negative pressure wound therapy is an alternative method shown to be effective in the treatment of wounds of various etiologies. The appropriate negative pressure therapy type is chosen according to the clinical situation of the patient, the characteristics of the wound and the objective of the treatment. We aim to review the applications of negative pressure wound therapy in the management of typical chronic lower limb ulcers, its impact on skin healing, its adverse reactions, as well as to provide information from our experience with this device.

Keywords: *typical chronic wounds, typical chronic ulcers, lower limb ulcers, delayed healing, negative pressure wound therapy.*

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1. Introduction

Chronic lower limb ulcers are defined by a long-standing evolution, with no tendency to heal after three months of proper treatment or still not completely healed after twelve months [1].

Chronic lower limb ulcers affect 0.6-3% of those aged over 60 years and 5% of those aged over 80 years and represent an important cause of morbidity [2]. The incidence of chronic lower limb ulcers is increasing, especially due to the ageing population and the influence of certain risk factors for atherosclerotic occlusion such as diabetes, obesity, smoking and others [3]. It was estimated that in the course of a lifetime, almost 10% of the population may develop a chronic wound, with a wound-related mortality rate of 2.5% [3]. Data from the Wound Healing Society shows that approximately 15% of the adults in the United States suffer from chronic wounds, predominantly pressure ulcers, diabetic (neuropathic) foot ulcers and venous ulcers [4]. Chronic wounds may be classified as typical and atypical.

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Typical ulcers include ischemic, neurotrophic and hypostatic ulcers, while atypical ulcers refer to those caused by autoimmune disorders, infectious diseases, vasculopathies, neoplasms, metabolic and genetic disorders, external factors, psychiatric disorders, drug related reactions and others [5]. Multiple systemic diseases may present with atypical wounds; the primary causes of the wounds may be represented by the systemic disease (e.g., Crohn's disease) or an abnormal immune response of the host due to the systemic disorder (e.g., paraneoplastic syndrome) [5]. Concerning typical chronic wounds, about 80% localized on the lower limbs are caused by chronic venous insufficiency; in 5-10% of cases the etiology is arterial, while the remainder are due to neuropathic disorders [5].

Standard therapy of chronic ulcers begins with a few general principles which are applicable regardless of the ulcer type: tissue debridement, control of the infection, moisture balance and management of wound edges [6, 7]. Afterwards, considering the type of the wound, the therapy may vary. Compression in the form of bandages, stockings or mechanical devices, specific wound dressings and elevation of the lower extremities are recommended for venous ulcers [6, 7]. For arterial ulcers, patients should be referred to a vascular surgeon for proper intervention. Pressure ulcers require offloading of the affected area as a primary measure. Management of diabetic foot ulcers includes offloading pressure and, when necessary, treating the underlying peripheral arterial disease [6]. Neuropathic wounds may require, as well, offloading, identification of the sensory neuropathy, assuring adequate-fitting footwear, monitoring for signs/symptoms of Charcot arthropathy/fracture, osteomyelitis, cellulitis [8]. Non-healing ulcers of the lower extremity may require vascular assessment, as well as palpation of pedal pulses and measurement of the ankle-brachial index [6]. Regarding atypical non-healing ulcers, a biopsy should be performed to exclude malignancy [6].

Negative pressure wound therapy (NPWT) is a device-based treatment developed in the 1990s whose uptake in the healthcare system has been dramatic in the developed countries [7]. A wound dressing is applied on the ulcer, then, using a negative pressure (or vacuum), the tissue fluid is drawn away and collected in a canister (Fig. 1, fig. 2). NPWT may represent a cost-efficient alternative to the standard management of chronic lower limb ulcers for both the patients and the healthcare providers [7].

We aim to review the applications of NPWT in the management of typical chronic lower limb ulcers, its impact on wound healing, as well as its adverse reactions.

2. Standard management of typical chronic lower limb ulcers

2.1. Venous lower limb ulcers

It is believed that the primary underlying mechanism which leads to the development of chronic lower limb ulcers is represented by venous hypertension, which may appear due to venous reflux or venous obstruction. Along with venous hypertension, multiple risk factors may enhance the formation of chronic lower limb wounds: age (55 years or older), high body mass index, physical inactivity, family history of chronic venous insufficiency, history of pulmonary embolism or superficial/deep venous thrombosis, higher number of pregnancies, severe lipodermatosclerosis and venous reflux in deep veins [9]. Patients with chronic lower limb ulcers present with heaviness, aching, itching, which may develop before venous ulcers appear [9]. Clinically, a venous ulcer has irregular well-defined borders, is exudative with granulation base and fibrin deposits, often located over the medial malleolus [10]. Associated findings are represented by edema, telangiectasias, atrophie blanche, and lipodermatosclerosis [10]. Current evidence supports management with compression therapy, exercise, dressings, pentoxifylline, and others. A prophylactic approach with early venous ablation and/or surgical intervention to correct venous reflux may decrease recurrence rates [10].

A proper management of venous lower limb ulcers begins with patient counselling regarding activities which promote good hygiene and skin care, good nutrition, obesity reduction and, overall, improvement in general health [11]. Guidelines based on several randomized controlled trials show that compression therapy

(a system of elastic or non-elastic garments or devices which provide graduated compression pressure) are a mainstay of treatment to promote venous lower limb ulcers healing [12-14]. Dressings and multiple layers of bandage promote healing without macerating the skin [11]. Skin grafting accelerates the healing of large ulcers which are already in the process of healing, with good vascularity and infection-free [11]. Regarding drugs used in the management of chronic venous ulcers, systemic antibiotic therapy should be used only when there is clear clinical evidence of wound infection; the efficacy of pentoxifylline, flavonoids, aspirin, sulodexide, mesoglycan and prostaglandins to aid healing is variable [11]. Incompetent superficial veins may be successfully treated with either endovenous LASER techniques, open surgery, or a combination of both [11].

2.2. **Arterial lower limb ulcers**

Arterial lower limb ulcers account for approximately 22% of ulcers. Their formation is mainly due to inadequate blood supply to the skin because of luminal narrowing secondary to atherosclerosis of the medium and large sized arteries [15]. Other causes include diabetes, vasculitis, thromboangeitis, thalassemia and sickle cell disease which may predispose to the formation of atheroma [16]. Risk factors for the formation of arterial lower limb ulcers are represented by: smoking, hypertension, hyperlipidemia, diabetes and obesity. Patients may have a history of myocardial infarction, stroke, angina or intermittent claudication [16]. On clinical examination, a chronic arterial wound is usually located over the toes, foot or ankle, its edges have a „punched-out" appearance, the wound bed is often covered with adherent necrotic crusts, the exudate level is usually low, pain is severe even without the presence of infection, edema is not common and associated features such as gangrene may be present [16]. Buerger's test (a delay of more than 10-15 seconds in return of the normal color of the skin after raising an ischemic lower limb to 45 degrees for one minute) may indicate vascular compromise [16]. A detailed management of arterial lower limb ulcers will be further described; however, it should be primarily aimed at increasing blood flow by either angioplasty or reconstructive surgery, along with lifestyle changes (control of underlying conditions, smoking cessation) [16].

The first step in the management of arterial ulcers should be finding and treating its underlying cause, which may include vascular bypass, dilation, stents by a vascular surgeon. Wound care is essential and tissue debridement, local moisture balance and infection control should be performed. Emollients may be applied to assure that the surrounding skin is pliable [6]. A review by Weir GR et al. from 2014 clearly describes the optimal local wound care regimen by classifying arterial ulcers into healable and non-healable arterial wounds [17]. Carefully cleaning the ulcer, controlling infection and inflammation are the main issues which should be addressed from the beginning [17]. A debris-free wound is necessary for healing to occur. Povidone-iodine, chlorhexidine, hydrogen peroxide may interfere with fibroblast formation and epithelial growth, therefore, they should be used in wounds in which bacterial burden is more important than the potential cytotoxicity of antimicrobials [17]. Water or 0.9% saline solution are considered the safest wound cleansers [17]. Dry gangrene or eschars should be kept dry since adding moisture to devitalized tissue creates an ideal medium for bacterial growth [17]. Before initiating debridement, the clinician should have an objective evidence that the ulceration is healable [17]. Debridement can be surgical, mechanical, enzymatic, or with autolytic methods, along with alginates, hydrogels and hydrocolloids dressings [17]. Surgical interventions should be considered if conservative treatment does not improve ulcer healing in 4 to 6 weeks [18].

2.3. **Diabetic ulcers**

Diabetic foot ulceration is a severe complication of diabetes mellitus and is the most common cause for hospitalization in this particular category of patients [19]. Risk factors leading to the formation of diabetic foot ulcers can be divided into three main groups [19]. First-degree risk factors are represented by senso-

rimotor diabetic polyneuropathy, patients age and previous ulceration, while peripheral arterial occlusive disease and structural deformities in the skeleton of the foot are considered second-degree risk factors [19]. Third-degree risk factors are the duration of the disease, male gender and late complications of type 2 diabetes (retinopathy, nephropathy) [19]. Most authors agree that diabetic foot ulcerations are caused by a combination of both neuropathy and angiopathy [19-23]. Clinical features of diabetic ulcers include: typical predisposed locations, such as the metatarsal I, a circular shape, with hyper-keratotic borders (as a result of the local high-pressure load), with a large extension of depth and, when coinfection is present, erythema of the surrounding tissues may be seen. Pressure relief is mandatory to promote wound healing. Other management measures are represented by wound cleansing, which includes debridement with radical necrosis removal; modern wound dressings. Non-occlusive, moist wound therapy is usually recommended [24-26].

Management of diabetic leg ulcers represents a challenge, since this particular type of chronic wound combines dramatically decreased circulation and chronic infection [27]. A systematic review from 2015 by Andrews KL et al. states that the management of diabetic leg ulcers includes the following steps: off-loading by limiting walking and wearing special footwear; debridement and biofilm disruption; the use of modern dressings: either hydrating, debriding or antimicrobial (the topical agent is chosen by taken into consideration the wound location, size, depth and presence of drainage); the use of cellular and/or tissue-based products (agents derived from animal, human or synthetic tissues that have been altered in order to activate the senescent cells in the chronic diabetic ulcer and promote healing – the wound bed and local perfusion should be optimized prior to their application) [28]. Topical antimicrobial therapy (creams, ointments, gels) may impair wound healing, despite their widespread use [29]. An optimal management of diabetic leg ulcers includes the participation of a multidisciplinary integrated team [28].

2.4. **Pressure ulcers**

Pressure ulcers represent a significant problem of the healthcare system worldwide with an overall prevalence in hospitalized patients that ranges from 5% to 15 [30]. Patients with impaired mobility or sensation have the greatest risk for the appearance of pressure ulcers, since they are usually long-term bed- or wheelchair-bound [30]. Natural skin aging with dermal and epidermal thinning, flattening of the dermo-epidermal junction and decreased epidermal turnover are additional risk factors for pressure ulcers in elderly patients [30]. Classification of pressure ulcers includes the following stages: stage 1 – non-blanchable erythema of the intact skin; stage 2- partial-thickness skin loss, exposing underlying the dermis; stage 3- full-thickness skin loss; stage 4- full-thickness skin loss and tissue loss; unstageable pressure injury – obscured by an eschar full-thickness and tissue loss; deep tissue pressure injury – persistent, non-blanchable deep red, brown or purple discoloration [31].

Standard therapy for pressure ulcers includes careful cleansing with saline or tap water and debridement in order to reduce the bacterial burden (stage 4 pressure ulcers are at risk for the appearance of osteomyelitis), dressings which maintain a moist wound-healing environment with the goal to promote a fine balance between exudate absorption and moisture retention [32]. Topical agents which contain growth factors may be an alternative for pressure ulcers which do not respond to standard therapy [32]. Negative pressure wound therapy may accelerate healing time in stage 3 or 4 pressure wounds; moreover, it may help optimize the wound bed before surgical closure. The main surgical method of wound closure for pressure ulcers is represented by skin flaps with or without muscle transfer [32].

2.5. **Neuropathic ulcers**

Neuropathic ulcers represent a frequent condition especially with diabetes mellitus on the rise, with significant morbidity [33]. Neuropathic ulcers may also be seen in patients with end-stage renal disease, alcohol abuse, vitamin deficiency, spinal cord injury, syringomyelia and tabes dorsalis [33]. Clinically, neuropathic ulcers

usually affect the metatarsal heads, great toes and heels; they are painless round or oval ulcers with well-defined borders within either hyperkeratotic or macerated skin [33]. Neuropathic wounds are associated with decreased sensation to the foot, normal capillary refill palpable pulses, xerosis.

Prophylactic measures include patient education, proper skin care and use of an adequate footwear. Once the neuropathic ulcer has developed, the standard of care involves debridement, offloading and treatment of concurrent infection [33]. If these above-mentioned measures fail, then skin grafts or hyperbaric oxygen therapy may represent therapeutic alternatives [33]. Nevertheless, the clinician should always take into consideration other factors which may influence the response of the neuropathic wound to the standard of care, such as chronic infected wounds, nutrient deficient patient or wounds subjected to persistent trauma [33].

3. Negative pressure wound therapy

Negative pressure wound therapy (NPWT) is an efficient method employed in the treatment of wounds of many different etiologies [34-36]. Synonyms for NPWT include topical negative pressure or vacuum therapy or vacuum-assisted closure therapy (VAC) [34]. NPWT was introduced in the clinical practice in the early 1990's and has become widely used in the management of non-healing, complex chronic wounds in both inpatient and outpatient care, in order to reduce the reliance on hospital-based care [34]. The technique of NPWT consists in a foam dressing shaped to properly cover the wound, on top of which a transparent adhesive membrane is placed to periwound skin and then connected to the vacuum source through a drain tube. The vacuum source exerts a subatmospheric pressure which may be either intermittent or continuous, the wound exudate being collected in a canister (Fig. 1, fig. 2) [37]. However, in spite of the therapy's promising potential for widespread clinical use, studies showing high-level evidence of its effectiveness and economic benefits are sparse [38-40].

NPWT exerts its healing benefits through multiple mechanisms, which include: changes in perfusion, microdeformation, macrodeformation and exudate control [41]. However, these mechanisms of action should to be discussed considering the clinical context in which NPWT is applied. For instance, for chronic wounds (diabetic foot ulcers, pressure ulcers, radiation-induced wounds, venous stasis ulcers, wound dehiscence and others), Argenta and Morykwas found in a clinical study from 1997 that the volume of exudate which was removed from the wound site varied directly with the size and chronicity of the ulceration [42]. Removal of exudate led to the formation of granulation tissue [42]. Moreover, it seems that chronic wounds differ from healing wounds regarding the local

Figure 1. Required materials for the proper application of NPWT.

Figure 2. Negative pressure wound therapy system: foam dressing shaped to properly cover the wound, on top of which a transparent adhesive membrane is placed to perilesional skin and then connected to the vacuum source through a drain tube.

proinflammatory status. Non-healing chronic wounds showed a great amount of tumour necrosis factor alpha (TNF-α) and interleukin-1 (IL-1); high levels of the proteases matrix metalloproteinase-2 (MMP-2), MMP-3 and MMP-9; and low levels of tissue inhibitor of metalloproteinases-1 (TIMP-1) [43]. A study by Stechmiller JK et al. from 2006 which analyzed the effect of VAC therapy on the expression of cytokines and proteases in the wound fluid of patients with pressure ulcers demonstrated that throughout a 7-day course of NPWT, there was a significant decrease of TNF-α during day one, three and seven, compared to baseline [43]. NPWT also increases the delivery of albumin at the wound site, thereby changing the environment of a chronic wound into that of an acute wound, making it more favorable for wound healing [44].

In summary, NWPT aids in the development of granulation tissue, cell hyperplasia leading to epithelization and favors microcirculation. NWPT precipitates the wound's healing process by reducing interstitial wound fluid, bacterial burden and by increasing the expression of cytokines involved in cicatrization. NWPT should be performed on debrided skin and edges [45].

When describing the NPWT, complications of this therapeutic method should also be included. Bleeding may occur when a coagulation disorder of the patient is overlooked or when the device is placed directly over an exposed blood vessel. Infection may also occur [46]. NPWT powered by continuous electricity removed exudate, kept the wound clean and facilitated healing; however, when power was off, sponges covering the wound were foreign and acted as the source of infection [46]. Pain was usually experienced by wounded patients, especially during dressing changes. Patients treated with NPWT needed fewer dressing changes and thus suffered less pain theoretically [46]. Anxiety may be another complication experienced by some of the patients treated with NPWT, which may be due to the presence of pain, restrictions of activities and unfamiliarity with this particular therapy [46]. A prospective study by Hourigan LA et al. from 2010 showed that NPWT led to wound-related protein loss more than burn wounds; therefore, optimal nutrition is recommended in this category of patients [47].

The adequate NPWT type is chosen according to the clinical situation of the patient, the characteristics of the wound and the objective of the treatment [45]. It is mandatory to monitor progress and acknowledge the suitability from one NPWT to another and balance the needs such as progress and stage of wound healing (Fig. 3, Fig. 4) [45].

4. Negative pressure wound therapy in chronic lower limb ulcers

Standard design NPWT is currently mostly used for VLUs (Venous Leg Ulcers) and DFUs (Diabetic Foot Ulcers) because of the amount of exudate removed and the reduction of pain due to the gauze or foam applied on the wound before covering it with the device. A study by Mohammed AH et al. from 2020 showed the safety of NPWT and its potential of decreasing edema, pain, bleeding and local wound infection [48].

Figure 3. Chronic ulcer on the antero-lateral aspect of the lower left limb, the day before NPWT.

Figure 4. Improved aspect of the wound after seven days of NPWT with reduction in size of the ulcer and formation of granulation tissue

Other types of NPWT have appeared during the last decade and are being studied and monitored in order to assess a methodology of use.

The single-use NPWT device (sNPWT device) has a good portability and a smaller size, patients benefiting from more freedom and less discomfort; patients can have normal daily activities such as bathing, walking, dressing-up, while caregivers may also help them easier. Therefore, hospital-based care is more short-termed, which leads to a favorable impact on the quality of life of the patient and on the healthcare costs [49].

Negative pressure wound therapy device with instillation (NPWTi) allows the continuous application of various solutions, with anti-microbial action or that act as accelerators of wound healing. A clinical study by Giri P et al. on 48 patients with extremity ulcers (25 patients included in group one, in which NPWT was combined with saline instillation and 23 patients included in group two, in which NPWT was used alone) showed that wound healing is significantly better when saline instillation is combined with NPWT [50].

4.1. **NPWT in chronic venous ulcers**

Regarding the efficacy of NPWT used as an adjunct to compression therapy in chronic venous ulcers, a clinical study from 2011 by Kieser DC et al. on seven patients with a total of 12 chronic venous ulcers showed the following results: after four weeks of NPWT combined with compression bandaging, non-healing wounds began to develop into healthy, granulating wounds. The patients were monitored for a total of twelve weeks and a statistically significant reduction in ulcer surface area during the first weeks of NPWT was found [51]. This is in accordance with another clinical study from 2014 by Kucharzewski M et al. which aimed to assess the applicability of NPWT in the management of chronic venous lower limb ulceration. Results showed that in 10 out of 15 patients the ulcers healed within six weeks and in the remainder five cases, the ulcers healed within 20 weeks [52].

4.2. **NPWT in diabetic and neuropathic wounds**

A multicenter randomized control trial on 342 patients with diabetic foot ulcers by Blume P et al. from 2007 aimed to compare the safety and efficacy of NPWT to that of the advanced moist wound therapy (AMWT). Results demonstrated that that 43.2% of patients achieved complete ulcer closure with NPWT, and only 28.9% of the patients under AMWT achieved complete epithelization [53].

A randomized, multicenter control trial by Armostrong DG et al. from 2005 on 162 patients affected by diabetes with partial foot amputation showed that more patients achieved complete healing in the NPWT group (56% vs. 39%); the rate of granulation tissue formation was faster in the NPWT group compared to the control group; however, the frequency and severity of complications (predominantly wound infection) was similar between the NPWT group and the control group [54].

4.3. **NPWT in pressure wounds**

A systematic review by Ploumis A et al. from 2019 aimed to assess the efficacy of vacuum assisted closure in patients with spinal cord injury which develop pressure ulcers due to prolonged immobility. It seemed that the use of negative pressure indeed promoted the healing of pressure ulcers in this particular category of patients [55]. A review by Gupta S and Ichioka S from 2012 concluded that NPWT seemed to be reliable, user-friendly and efficient in treating pressure ulcers [56].

In a prospective, randomized-controlled trial from 2002 by Ford CN et al., 28 patients with 41 full-thickness pressure ulcers were enrolled in order to compare the efficacy of NPWT against wound gel products regarding wound healing for a minimum of four weeks. An interim analysis of the results showed two cases of healing in the NPWT group and two in the group treated with wound gel products. Pressure ulcer volume was reduced by 51.8% with NPWT compared to 42.1% using gel products. The authors concluded that NPWT was a superior therapeutic measure for reducing inflammation at the wound site of pressure ulcers [57].

A systematic review from the Cochrane database from 2015 about the use of NPWT in pressure ulcers which included four studies with a total of 149 participants concluded that there is still scarce available data on positive outcomes such as wound healing or on negative aspects such as adverse effects in pressure ulcers [58].

5. Conclusions

Chronic lower limb ulcers represent an important condition for the healthcare system in terms of proper management and high costs, with a major impact on the quality of life of the affected patients. In some cases, standard therapeutic approach of typical chronic lower limb ulcers does not lead to the desired outcome of proper healing. Consequently, negative pressure wound therapy may represent a feasible alternative in the management of typical, chronic wounds. Most authors consider negative pressure wound therapy an adjunct to the standard approach of chronic wounds. Nevertheless, concrete evidence concerning the efficacy of negative pressure wound therapy in different types of chronic lower limb ulcers is yet to be established through future studies.

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Conflict of interest
NONE DECLARED

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