T.I.M.E.R.S. FOR FOOT ULCERS – CURRENT MANAGEMENT STRATEGY

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ABSTRACT

Managing venous ulcers poses significant challenges for nursing personnel. This article outlines the current strategies employed in addressing venous ulcers, with particular emphasis on the updated T.I.M.E.R.S. wound assessment tool and compression therapy. Diagnosis should consider risk factors associated with chronic venous disease as well as other conditions such arterial ischaemia, ulcers related to diabetic neuropathy, or cancer. Doppler duplex ultrasound is typically conducted to validate the diagnosis. In the treatment of chronic wounds, implementing the updated wound assessment strategy T.I.M.E.R.S. is recommended. Optimal wound management requires tailored dressings and usage of antimicrobial agents. Application of local antibiotics on wounds should be avoided, with the exception of gentamicin embedded in a collagen matrix presented in the form of a sponge. Correctly adjusted compression therapy is a gold standard of treatment. Pentoxifylline is advised as an oral treatment to expedite the rate of ulcer healing.

Key words: venous ulcers, chronic venous disease, compression, hard-to-heal wounds.

INTRODUCTION

Chronic wounds are characterised as skin injuries where the healing process is hindered or delayed. In Poland, it is estimated that approximately half a million individuals are afflicted by chronic wounds [1]. Venous ulcers stand out as a primary cause of such wounds, accounting for about 80% of the cases. In Europe and North America, approximately 10% of the population suffers from venous insufficiency, with venous ulcers developing in approximately 0.2% of the population [2]. Other contributing factors include arterial and diabetic ulcers, as well as wounds stemming from cancer [3, 4].

Despite significant advances in medical science, patients with chronic wounds remain a considerable challenge for healthcare professionals, often encountering difficulties in accessing appropriate assistance. Caring for patients with chronic wounds can be a demanding task for nurses due to the complexity of both the patients' health conditions and the wounds themselves, often requiring a significant amount of time and attention from the nurse.

In this article, our aim is to outline the current management strategy for venous ulcers, incorporating an examination of the updated wound assessment tool known by the acronym T.I.M.E.R.S. (Tissue, Infection/Inflammation, Moisture, Wound edge, Repair/Regeneration, Social) [5].

DEFINITION OF VENOUS ULCERS

Venous ulcers represent one of the most severe complications arising from chronic venous disease. These ulcers are characterised by persistent wounds involving the epidermis, dermis, and subcutaneous tissue, failing to heal due to impaired venous blood flow [6].

During physical examination, deep defects are often noticeable, primarily located in the distal part of the lower extremities, particularly around the malleolar area. These lesions may manifest as singular or multiple wounds and are frequently accompanied by telangiectasias and hyperpigmentation, which are characteristic signs of chronic venous disease. Within the wound, one might observe necrosis, pus, or the presence of a fibrous or biofilm layer [7].

The healing process for these ulcers is notably protracted, lasting from several months to several years. Research indicates that approximately half of all ulcers require an average of 9 months to heal, with 20% of cases extending up to 2 years and 8% exceeding 5 years. Moreover, recurrence is common, occurring in about 50% of cases within 12 months [8].

Untreated chronic venous disease can lead to severe complications, causing persistent pain and reducing quality of life. Managing lower leg ulcers poses a multifaceted challenge in terms of both treatment and care, especially in advanced stages of the disease.

PATHOMECHANISM OF VENOUS ULCERS

Venous ulcers are a manifestation of chronic venous disease, which is the cause of venous hypertension, i.e. increased blood pressure in the venous vessels. Primary chronic venous disease (resulting in venous hypertension from varicose veins with idiopathic valvular insufficiency) is more common than secondary venous disease (resulting in venous hypertension usually from venous thrombosis and valvular insufficiency and/or obstruction). In both primary and secondary, damaged valves of the deep venous vessels, which normally regulate blood flow, fail to circulate the blood from the lower legs back to the heart [9].

Additionally, the activity of the calf muscles during walking is crucial for facilitating the upward movement of venous blood in the legs. Restricted mobility in the ankle joint can lead to sustained elevation of lower limb venous blood pressure, contributing to the development of venous hypertension. Individuals with veno-venous ulcers often exhibit limited mobility in the ankle joint [10].

When these mechanisms fail, superficial veins widen and stretch in an attempt to accommodate the increased blood flow, resulting in venous stasis and heightened pressure within the blood vessels. While venous hypertension is frequently linked to issues such as venous valve dysfunction or inadequate calf muscle function, numerous theories exist regarding the underlying causes of venous ulcers. However, due to the complexity of these processes and the multitude of factors involved, a comprehensive understanding of the pathophysiology of ulcers remains elusive, and the exact cause of venous ulcers remains incompletely understood [2].

RISK FACTORS OF VENOUS ULCERS

Current research suggests that we can distinguish several risk factors for venous ulcers, the identification of which can stop development of further disease. Venous ulcers mostly occur in patients over 55 years old, with history of chronic venous insufficiency, pulmonary embolism, increased body mass index (BMI), with lack of physical activity, in diseases with decreased mobility of the ankle, and in individuals who have had multiple pregnancies [3].

DIAGNOSIS

Venous ulcers demand a comprehensive approach from medical personnel. Diagnosis should be approached by considering the overall health condition of the patient, taking into account risk factors associated with chronic venous disease, and conducting a thorough medical, nursing interview. When making a differential diagnosis, it is important to consider conditions such as arterial ischaemia, ulcers related to diabetic neuropathy, injuries, skin diseases, and cancer.

Several imaging tests aid in diagnosing chronic venous disease, but the most commonly utilised method is noninvasive duplex ultrasound. It enables the evaluation of blood flow within veins and the extent of backflow in both surface and deep veins as well as to pinpoint the locations and severity of obstruction and incompetence within the veins [11].

Other recommended examinations include measurement of ankle-brachial index and arterial pulse examination to exclude arterial pathology [7]. An ankle-brachial index ranging from 0.9 to 1.3 is considered within the normal range [12].

COMPRESSION THERAPY

The gold standard for treating chronic venous ulcers is compression therapy. Conducted research indicates that compression therapy can effectively reduce oedema and pain, significantly decrease venous reflux, and enhance venous outflow [13].

Correctly adjusted compression therapy aims to reduce venous hypertension. Patients undergoing compression therapy are less likely to experience recurrence of venous ulcers [3]. According to current guidelines, it is recommended that the pressure exerted by compression around the ankle should be approximately 40 mmHg, while in the area under the knee it should range from 17 to 20 mmHg [14]. It is crucial to note that arterial occlusive disease, heart failure, and an ankle-brachial pressure index < 0.5 are absolute contraindications to compression therapy [15].

The main types of compression therapy include sustained elastic and inelastic bandages, elastic compression stockings, adjustable compression garments, and pneumatic compression to obtain intermittent treatment [16].

Various systems of compression therapy are available, with multi-layered therapy, which is not vastly influenced by the stretching of muscles during walking, now considered more effective compared to single-layer therapy [7]. These systems should be applied by trained personnel. Two commonly used systems are the two-layer compression method, which involves using a backing and a low-stretch bandage, and the four-layer compression method, which includes a layer of cotton, a layer of crepe bandage, an elastic bandage, and an outer cohesive layer [17].

Compression stockings are a beneficial factor in reducing the risk of ulcer recurrence after healing and

are currently recommended for use. They are easy for patients to manage independently.

ORAL TREATMENT

The treatment of chronic venous ulcers primarily focuses on wound management strategies, but there is increasing recognition of the importance of pharmacological therapy. Numerous studies emphasise the significance of systemic medications as adjunctive treatments, particularly pentoxifylline. Pentoxifylline possesses anti-inflammatory properties and can enhance microcirculation in blood vessels by decreasing blood viscosity and inhibiting platelet aggregation [18]. A meta-analysis of randomised controlled trials has shown that pentoxifylline significantly increases the rate of ulcer healing while also reducing the duration of treatment and the diameter of the ulcer [19, 20].

Another group of drugs widely used in pharmacological treatment of ulcers are flavonoids. Conducted research suggests that this group of medication may lead to reducing symptoms of chronic venous disease. Studies have demonstrated that compared to a placebo, flavonoid usage can decrease oedema and alleviate symptoms such as cramps or paraesthesia. However, there is limited research conducted in this area, and the evidence regarding improved ulcer healing with flavonoids is insufficient [7, 11].

TREATMENT OF CHRONIC WOUNDS

Specially designed tools for wound management can be utilised to treat chronic wounds effectively. The treatment strategy for local chronic wounds, initiated by the European Wound Management Association in 2004, is known by the acronym T.I.M.E. In 2018 group of specialists updated it to T.I.M.E.R.S., which consists of 6 key stages:

- T (tissue debridement) – tissue debridement,
- I (infection and inflammation control) – infection and inflammation control,
- M (moisture balance) – maintaining adequate moisture levels,
- E (edges, epithelialisation stimulation) – stimulation of epidermis and protection of wound edges,
- R (regeneration) – stimulating cell activity,
- S (social factors) – the importance of patient engagement in increasing the likelihood of healing [5].

It should be emphasised that each of these stages should be implemented simultaneously, with emphasis on the one that is most challenging at the time.

"T" for tissue debridement

The first step in wound treatment is to clean wounds, i.e. debridement. Careful removal of necrotic tissue and biofilm plays a key role in the wound healing process and minimises the risk of infection. Biofilm poses a significant threat to proper healing. Surgical debridement remains the gold standard, but alternative methods such as enzymatic and larvicide-assisted biosurgery can be effective and selective [21-23].

"I" for infections and inflammation control – lavaseptics and antiseptics

Lavaseptics, such as saline or Ringer's fluid, are used to clean the wound before applying antiseptics. Antiseptics, on the other hand, are key to fighting infection and destroying biofilm, preventing further infection development [21, 23]. The subsequent section presents a comprehensive elucidation of antimicrobial agents.

"M" for moisture balance

The choice of the appropriate dressing should be tailored to the characteristics of the wound and its stage of healing. Lower limb ulcers are rarely wounds without features or risk of infection; thus, especially in early stage of the treatment, the dressings must have antimicrobial properties and exudate sequestration.

The dressing must be sufficiently absorbent to prevent maceration, but also to protect the wound from infection. In infected dry wounds with low to moderate exudate, gel dressings with octenidine or polyhexanide are recommended. They absorb the exudate if present, turning into a semi-liquid form. If the wound stays dry, they provide lubrication for optimal healing conditions. Wounds with moderate to heavy exudate should be treated with highly absorbent dressings such as hydro-fibre or foam dressings. In non-infected wounds with low to moderate exudate, the use of hydrocolloid dressings is recommended, which, due to their active colloid layer, stimulate the processes of autolysis in the wound, and stimulate angiogenesis and granulation. In the situation of infected ischaemic wounds, dressings with iodopovidone are highly recommended. Dressings that incorporate a lipid colloid (TLC) healing matrix are distinguished by their high absorbency and, thanks to their antimicrobial content, can be used as early as the debridement stage of an infected wound. Recently, there have also been dressings equipped with a healing TLC-NOSF matrix, which, after reacting with wound secretions, transforms into a gel, shortening the healing process by reducing the damaging effects of extracellular matrix metalloproteinases [5, 21].

In wound management, the selection of dressing materials is critical, aiming to uphold moisture balance, mitigate bacterial proliferation, minimise odour generation, and ensure patient comfort. Nevertheless, it is imperative to acknowledge that individuals

with chronic wounds often endure heightened discomfort during dressing changes and wound cleansing procedures [24].

The removal of adhesive dressings can evoke not only pain and tissue trauma but also incite the inflammatory cascade and compromise granulation tissue integrity. Consequently, dressings with reduced adhesiveness and designed to minimise trauma are frequently favoured and advocated to alleviate pain and minimise tissue injury during dressing changes [25].

"E" for epithelialisation stimulation – protecting the wound edges and stimulating epidermis

It is also important to take care of the wound edges and stimulate epidermination, which speeds up the healing process. The use of preparations containing substances that support this process, such as paraffin or epidermal activators, can help to ensure optimal conditions for wound healing [5, 23].

"R" for repair and regeneration

Effective treatment of hard-to-heal wounds requires addressing risk factors before therapy can yield significant results. These risk factors include underlying pathology, presence of infection, biofilm formation, and patient-related factors [5].

A wide range of treatment choices and technologies are available, based on their suitability for the specific wound and the patient's individual characteristics. Among the available options are both locally and systemically administered treatments, such as oxygen therapy, growth factor preparations, substances like nitric oxide and sucrose octasulphate, tissue substitutes, negative pressure wound therapy (NPWT), systemic pharmaceutical treatments, and protein-based nutritional supplements. Each of these interventions offers unique benefits and may be employed depending on the nature of the wound and the patient's overall health status [5].

"S" for social situation and patient-related factors

In the very beginning of holistic assessment of the patient, alongside the clinical, the non-clinical risk factors such as social situation and patient-related factors must be identified.

Manageable risk factors may involve patient education utilising appropriate language and materials tailored to their level of comprehension. Conversely, uncontrollable risk factors may include aspects such as the patient's living conditions and the presence of conditions like dementia. When evaluating social and patient-related risk factors, it is imperative to distinguish between those amenable to intervention by healthcare professionals and those that are immutable and necessitate acknowledgment.

Non-clinical social and patient-related risk factors can be categorised into various domains, encompassing psychosocial determinants, factors influencing treatment adherence, physical health status, comorbidities, and extrinsic environmental influences. A comprehensive understanding of these factors facilitates the development of individualised care strategies tailored to the specific needs of each patient [5].

Antimicrobial agents

Polyhexanide (PHMB) acts analogously to the peptides produced naturally by keratinocytes and neutrophils in the wound.

It is a membrane-active agent that also binds to the bacterial outer membrane of gram-negative bacteria, destroys it, and then selectively damages microbial DNA [25]. It effectively penetrates biofilm, and its broad spectrum of activity covers both gram-negative and gram-positive bacteria, including resistant strains: MRSA and VRE, spore-forming bacteria, intracellular bacteria, fungi, and human immunodeficiency virus (HIV). It is characterised by prolonged activity [26].

Octenidine dihydrochloride damages the cell walls and leads to subsequent death of microorganisms by binding to fatty acids. It is suitable for wound cleansing as well as use as a rinse and a gel.

Its spectrum covers vegetative forms of bacteria, gram-negative and gram-positive bacteria, including also MRSA, ORSA, VRSA, and VRE, as well as fungi, viruses, and protozoa. Octenidine effectively penetrate biofilm structures, also the one formed by, e.g., *Pseudomonas aeruginosa*, *Staphylococcus aureus* (including MRSA), and *Acinetobacter baumannii*, including multidrug-resistant strains. In antiseptic products used for wound treatment, octenidine hydrochloride is usually combined with phenoxyethanol. Because it is practically not reabsorbed, preparations containing octenidine dihydrochloride should only be used for small superficial wounds; no insertions to the skin or fistulas are allowed. It should also not be combined with dressings containing silver [26, 27].

Hypochlorites used in antisepsis are primarily a mixture of sodium hypochlorite and hypochlorous acid in low concentrations. They are recommended for hard-to-heal deep wounds, traumatic wounds, and chronic wounds, including bedsores or diabetic foot syndrome. If sterile, in low concentrations not exceeding 0.006%, are also safe for use in the peritoneal cavity and on tendons and bones. At concentration of 0.00025-0.5%, their antimicrobial activity is only partial. These compounds exhibit broad anti-

microbial activity, covering gram-positive and gram-negative bacteria (including MRSA, ORSA, VRSA, VRE), viruses, fungi, and bacterial spores [27].

Chlorhexidine binds to the cytoplasmic membrane of the cell causing disruption of the membrane. Due to its broad spectrum, efficacy, substantivity for the skin, and low irritation, it is widely used. The spectrum of antimicrobial activity of chlorhexidine includes gram-positive bacteria, fungi, enveloped viruses, and protozoa. Unfortunately, its efficacy depends on the pH of the environment – it increases with increasing pH, but decreases in the presence of organic matter [28]. It is also poorly efficient against gram-negative bacteria. At low concentrations (1 µg/ml) it features a bacteriostatic effect, while at higher concentrations (≥ 20 µg/ml) it shows a bactericidal effect. At higher concentrations, chlorhexidine inhibits tissue growth and can therefore slow down the wound healing process. Due to certain limitations, such as increasing resistance to this compound among bacteria isolated from wounds, the high risk of anaphylactic reactions, and the relatively high toxicity when compared with other agents, the validity of its use is currently being questioned [27].

Iodine povidone exerts its antiseptic effect by its ability to form pores in the bacterial cell membrane, enzyme inactivation, and damage to the DNA structure. The spectrum of antimicrobial activity includes gram-positive and gram-negative bacteria, fungi, viruses, and protozoa. It acts very rapidly but can only be used within 7 days. It inhibits inflammatory mediators and causes inactivation of enzymes that act destructively on host tissues. However, it is forbidden for use in children under 6 months of age, as well as in patients with hyperactive goitre, Hashimoto's disease, and dermatitis herpetiformis. It is not recommended for use during pregnancy. Unlike hypochlorites, it cannot be used inside the peritoneal cavity. Recently it has become available as a gel, which features prolonged bactericidal effect, no cross-resistance to antibiotics, no selection of resistant strains, and a stable prolonged release of the active substance [27].

Silver, as an antimicrobial agent, is widely used as an adjunct to the treatment of chronic wounds. Regardless of the form in which it is present, it damages the cell membrane, disrupts ion transport, and inhibits cell division. Despite its widespread use, resistance to silver is still very low [27].

Antibiotics

Chronic wound infections are often caused by bacteria forming a biofilm, a barrier that makes it difficult for antibiotics to penetrate the wound in sufficiently high concentrations, which promotes the selection of resistant strains. Current guidelines recommend avoiding local antibiotic use in the treatment of chronic wounds, with the exception of gentamicin embedded in a collagen matrix in the form of a sponge [21].

Gentamicin, when embedded in the collagen matrix, has shown efficacy against several pathogens, including *Pseudomonas aeruginosa*, *Proteus* spp., *Escherichia coli*, *Klebsiella-Enterobacter-Serratia*, *Streptococcus* spp., *Salmonella* spp., and *Shigella* spp. The antibiotic concentration at the application site reaches high values (300 to 9000 mg/l) within 1-2 hours and persists for 3-4 days, which exceeds the bactericidal concentration of gentamicin [21].

The decision to use systemic antibiotic therapy should be carefully considered. The choice of antibiotic should be dictated by microbiological findings and the ability to penetrate the skin and subcutaneous tissue.

CONCLUSIONS

In conclusion, managing venous ulcers requires a holistic approach, encompassing comprehensive assessment, evidence-based interventions, and consideration of patient-specific factors. Implementing updated hard-to-heal wound protocol management eventually guarantees a holistic approach. Attention to social and patient-related factors is imperative because they significantly influence treatment outcomes, but surgical debridement is still the cornerstone of chronic wound management. Antimicrobial agents play a crucial role in infection control; currently the most recommended are polyhexanide, iodine povidone, and octenidine (allowed only in superficial wounds). The application of local antibiotics on wounds should generally be avoided, with the exception of gentamicin embedded in a collagen matrix presented in the form of a sponge. Pentoxifylline and flavonoids serve as adjunctive treatments to expedite healing, while compression therapy remains the gold standard for reducing venous hypertension and preventing recurrence.

Implementing the T.I.M.E.R.S. wound assessment protocol guarantees that nursing personnel address all aspects of wound care comprehensively. This approach not only enhances patient outcomes but also leads to a reduction in the recurrence rate of venous ulcers. Additionally, it has the potential to alleviate the workload for nurses in the future.

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