New research and innovations in venous leg ulcer management

This paper describes the latest research and areas of interest in the management of venous leg ulcers. Among many interesting lines of investigation are further research into the effects of different forms of compression therapy and an examination of the hypotheses put forward for the causes of delayed wound healing. These include wound infection, and how these problems may be overcome.

RESEARCH DEVELOPMENTS

Compression
A recent in-depth study of 18 different brands of therapeutic hosiery outlines the essential knowledge that can help underpin our day-to-day management of people with venous disease, including leg ulcers[1]. This provides insight into the effect pressure has on the affected limb in both static and dynamic circumstances.

An important new development is calculating static and dynamic parameters such as pressure changes and measuring the dynamic stiffness index of medical elastic compression stockings. Previous randomised studies have shown that stockings of the same compression class have different acute effects on venous haemodynamics[2]. The explanation for this could be the variations in stiffness of the products used.

Direct in vivo imaging techniques allow clinicians to see the effect of the various compression methods on tissues. This includes bandaging, stockings and intermittent pneumatic compression devices. This has led to new insights into the pressures needed to achieve traditional treatment goals: the reduction of oedema and improved deep or superficial vein diameters and venous flow.

Delayed wound healing
Several risk factors have been identified as correlating with the failure of venous leg ulcers to heal with compression therapy. These comprise longer ulcer duration, large surface area, fibrinous deposition present on >50% of the wound surface and an ankle brachial pressure index (ABPI) of <0.85.

An open prospective single-centre study was undertaken in order to determine possible risk factors associated with the failure of venous ulcers to heal when treated with a multilayer high compression bandaging system for 52 weeks[3]. In total, 189 patients (101 women and 88 men with a mean age of 61 years) with venous leg ulcers (ulcer surface >5cm² with a duration of more than three months) were included. After 52 weeks of compression therapy, 24 (12.7%) venous ulcers had failed to heal. The study concluded:

1. Prognostic factors for ulcers that healed without problems were a small ulceration...
area (<20cm²), venous ulcer duration of less than 12 months, a decrease in calf circumference of more than 3cm, and the emergence of new skin islets on >10% of the wound surface during the first 50 days of treatment.

- Indicators of slow healing were a large body mass index (BMI) >33kg/m², a short walking distance covered during the day of less than 200 metres, previous wound debridement, and ulcers with the deepest presentation (>2cm).
- A calf ankle circumference ratio of <1.3, a fixed ankle joint, and reduced ankle range of motion were the only independent parameters associated with non-healing (p<0.001).

The results of this study suggest that non-healing venous ulcers are related to the impairment of the calf muscle pump[3].

Wound infection

Wound infection and biofilm formation have been hot topics for the past few years and are discussed by Percival and Cutting[4], who highlight strategies that could be used to treat chronic wounds containing biofilms, including antibiotic agents. However, the task of designing the necessary randomised clinical trials to prove their effectiveness in vivo will not be easy given the fact that wound healing may be influenced by many other factors.

A recent update of the Cochrane Review on antibiotics and antiseptics for venous leg ulcers by O’Meara and colleagues[5] led to the conclusion that, at present, there is no evidence to support the routine use of systemic antibiotics to promote healing in venous leg ulcers. However, the lack of reliable evidence means that it is not possible to recommend the discontinuation of any of the agents reviewed. For this review, 25 trials reporting 32 comparisons of treatments were identified[6].

In terms of topical preparations, there is some evidence to support the use of cadexomer iodine. However, further good quality research is required before definitive conclusions can be made about the effectiveness of systemic antibiotics and topical preparations in healing venous leg ulceration. In light of the increasing problem of bacterial resistance to antibiotics, current prescribing guidelines recommend that antibacterial preparations should be used only in cases of clinical infection and not for localised infections[7].

Debridement

Debridement is a way of removing colonised tissue in a leg ulcer. Larval therapy is one technique that has been used for a decade, but requires further assessment of its cost-effectiveness.

In one such study, Dumville et al compared the clinical and cost-effectiveness of larval therapy with a standard debridement technique using a hydrogel[8]. The study was a pragmatic, three-arm, randomised controlled trial with an economic evaluation. Community nursing services, community leg ulcer clinics and hospital outpatient leg ulcer clinics took part in a range of urban and rural settings.

Patients with venous or mixed venous/arterial ulcers with a minimum ABPI of 0.6 and where a minimum of 25% of ulcer area was covered by slough and/or necrotic material were recruited into the study. Loose larval therapy and bagged larval therapy techniques were compared to a hydrogel dressing. The primary endpoint was complete healing of the largest eligible ulcer. The primary outcome was time to complete healing of the reference ulcer. Secondary outcomes were time to debridement, cost of treatments, health-related quality of life (including ulcer-related pain), bacterial load, presence of methicillin-resistant Staphylococcus aureus and staff and patient attitudes to and beliefs about larval therapy.

During the three years of the trial, a total of 267 people (aged 20–94 years) were recruited. The study concluded that larval therapy significantly reduced the time to debridement of sloughy and/or necrotic chronic venous and mixed venous/arterial leg ulcers, compared with the hydrogel. However, larval therapy did not significantly increase the rate of healing of the ulcers and it was impossible to distinguish between larval therapy and hydrogel in terms of cost-effectiveness[9].

The authors concluded that future research should investigate the association of debridement and healing and the value of debridement as a clinical outcome for patients and clinicians. To inform decision-makers’ selection of debriding agents where debridement is the treatment goal, decision-analytic modelling of all alternative debridement treatments is required.

References

Aetiological approaches
New interventions for treating the underlying cause of venous leg ulcers aim to be less ‘aggressive’ and yet have similar long-term effectiveness as traditional surgical approaches. They may also have fewer side effects and complications and less of an impact on quality of life. Some of these interventions have yet to be evaluated.

Surgical correction of superficial venous reflux in addition to compression bandaging has been found not to improve ulcer healing but to reduce ulcer recurrence at four years. In the ESCHAR study, 112 legs were randomised to compression bandaging and 102 legs received compression bandaging plus surgery. Venous surgery provided an increased haemodynamic benefit versus compression alone[9].

PAPERS THAT CHANGED PRACTICE
In recent years, several papers have reviewed scientific research on our understanding of the mechanisms of chronic ulceration in venous disease and, as a consequence, the factors that may contribute to impaired healing.

In one paper, Chen and Rogers state that, in order to develop effective treatment regimens, a clearer understanding of the underlying biological and pathological processes that lead to skin breakdown is required[8]. By bringing together relevant aspects of diverse subjects such as inflammation, cardiovascular and connective tissue biology, they aim to provide an insight into how circulatory abnormalities that are caused by the underlying venous disease, can induce local tissue inflammation resulting in tissue breakdown. This is an extensive and clearly written review of the biological events leading to ulceration in venous disease, with a link to ulceration in other situations such as pressure ulcers and diabetic foot complications. This article is supported by a comprehensive list of interesting literature references.

A paper by Raffetto also summarises current advances and known facts on the pathophysiology of venous leg ulcers, placing emphasis on tissue/cellular interplay and alterations in venous fibroblast regulation on a cellular (nuclear) level, pointing to regulatory mechanisms of fibroblast behaviour in venous disease[9].

As a consequence, potential therapeutic targets are indicated, although the author recognises that clinical studies involving the modulation of cytokines, MMPs and cell-cycle proteins are lacking to support or to confirm the basic scientific evidence for intervention.

Using contemporary, standardised terminology and reporting the latest insights into compression bandages and stockings will help the interpretation of reviews, RCTs and the results of smaller studies and will promote the standardisation of practice between clinicians in different countries.

Partsch et al’s objectives were to propose terms to describe both simple and complex compression bandage systems and to offer a classification based on in vivo measurements of sub-bandage pressure and stiffness[10]. The aim was to overcome the lack of agreement on their classification and confusion over the use of important terms/characteristics such as pressure, layers, components and elastic properties of the final bandage once in place.

The new and now largely accepted terminology is explained in detail in reports such as that of Partsch et al[10], which have led to the development of best practice statements such as those published by the Union Internationale de Phlébologie (UIP) and the World Union of Wound Healing Societies (WUWHS)[11].

The aim of another study by Partsch et al[11] was to review published literature concerning the use of compression treatments in the management of venous and lymphatic diseases and establish where reliable evidence exists to justify the use of medical compression and where further research is required to address areas of uncertainty.

Papers were classified in accordance with the recommendations of the GRADE group to categorise their scientific reliability. The review includes papers on compression stockings, bandages and intermittent pneumatic compression devices. A wide range of compression levels was reported to be effective. While good evidence for the use of compression is available in some clinical indications, there is still much to be discovered. Little is known about dosimetry in compression, and for how long and at what level compression should be applied. The exact differences in the effects of elastic and short-stretch or inelastic compression bandages are also little understood.
IMPORTANT SCIENTIFIC INNOVATIONS

Another hypothesis for delayed healing in leg ulcers is impaired neo-angiogenesis in the scar tissue surrounding a longstanding wound. Researchers have studied the possibility of stimulating vessel formation in situ by applying inductive skin substitutes or engineered artificial skin constructs to the wound\(13\).

In search of an autologous vascularised skin substitute, the authors treated full-thickness wounds with autologous platelet-rich plasma gel (APG) in which they embedded endothelial progenitor cells (EPCs) and basal cell keratinocytes (KCs). All APG-treated wounds showed more vascular structures (p<0.001), and the addition of EPCs further improved neovascularisation. Applying APG + KCs resulted in the highest re-epithelialisation rates (p<0.001). No differences were found for wound contraction when examined by planimetry. The authors concluded that in this porcine full-thickness wound model, APG acts as a supportive biomatrix that, along with the embedded cells, improves extracellular matrix organisation, promotes angiogenesis, and accelerates re-epithelialisation.

In a study investigating cellular responses to injury, including the angiogenesis of wound healing, Herman and Leung developed a three-dimensional skin equivalent comprising multiple cell types found in normal human skin or chronic wound beds\(14\).

The in vitro model contains a microvascular component within the dermis-like extracellular matrix and has an intact epithelial covering composed of skin-derived epithelial cells. Capillary endothelial cells are labelled with fluorescent tracers before being embedded within a 3D matrix and overlaid with a monolayer of keratinocytes. Once embedded in the matrix, the endothelial cells show capillary-like tube formation, mimicking the microvasculature of skin. Angiogenesis and re-epithelialisation, which occur in response to injury and during wound healing, can be quantified using fluorescence-based and bright-field digital imaging microscopic, biochemical, or molecular approaches.

FUTURE FOCUS

More research is needed on the impact of compression treatment at the cellular level – on the function and behaviour of endothelial cells, interstitial tissue cells such as fibroblasts, adipocytes and inflammatory cells, and keratinocytes. These cells react to mechanical forces in the tissues in which they reside and communicate with each other or interact with the matrix on which they rest. Such research could shed light on aspects of wound healing and of tissue inflammation caused by venous insufficiency. Well conducted clinical trials are still needed to document evidence of efficacy and cost-effectiveness in specific indications.

Future textile research and development in compression bandages and hosiery is focusing on smart textiles. Areas of interest include textiles that could monitor pressures or other biological parameters, those with improved durability or which contain antimicrobial properties.

Some authors\(15\) have emphasised the need for post-marketing medical device monitoring, as occurs for medicines, such as the reporting of side effects and adverse events of compression treatment, as well as for wound dressings and topical preparations for leg ulcer care.

Debridement techniques such as topical substances, biosurgery with larvae or mechanical hydrodebridement need further evaluation of their cost-effectiveness. One preliminary report suggests that Versajet (Smith & Nephew), used for hydrodebridement, may be equally if not more effective than conventional surgical debridement, by causing less damage to viable tissue\(16\). It may also be more cost-effective because it minimises surgery duration and length of hospital admission and may be deployed both in hospital and in the community. However, cost-utility studies are required to evaluate the technique from the patient’s perspective.

CONCLUSION

There are many fields of interest in the treatment of venous leg ulcers, with research bringing more knowledge to bear on leg ulcer management techniques such as compression and on the problems of slow-to-heal and non-healing wounds. Standardisation of practice is being encouraged through the publication of international best practice guidelines.

AUTHOR DETAILS

Mieke Flour, MD, Head of Clinic, Dermatology Department, University Hospital, Leuven, Belgium

References