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Healing of venous ulcers using compression therapy: Predictions of a mathematical model

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HIGHLIGHTS

- Healing of venous ulcers under treatment investigated with a mathematical model.
- Clinical data was used to calibrate the model.
- Three layered bandages predicted to heal wounds faster than standard bandages.
- The model can be used as a predictive tool to estimate the time needed for a wound to heal.

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ABSTRACT

Venous Leg Ulceration (VLU) is a chronic condition for which healthcare systems worldwide face rising treatment costs. VLU can be due to sustained venous hypertension which causes the veins to become cuffed with fibrin, inhibiting the supply of nutrients to the wound site. For patients that cannot tolerate compression therapy with an inelastic short stretch (SS) bandage, the mainstay treatment, an elastic three layered (3L) bandage is an alternative. In this paper, a mathematical model is developed to investigate whether the healing of venous ulcers under SS and 3L bandages occurs at different rates and to postulate the reason for any difference. The two treatments were applied to a simplified wound geometry, under the assumption that the rate limiting step of healing is the supply of oxygen to the wounded tissue. Clinical data of wound size over time under the two treatments from Weller et al. (2012) was used to fit key, unknown, model parameters using a least squares approach. Numerical results are presented for the oxygen distribution within the wound space, using the fitted parameter values. The 3L bandage allows more oxygen flow into the wound than the SS bandage and, hence, the 3L bandage results in faster healing, however the difference is more significant for wounds of larger initial size. The model can be used as a predictive tool in a clinical setting to estimate the time to heal for a wound of a given initial size, treated with either a SS or 3L bandage.

1. Introduction

Venous Leg Ulceration (VLU) is a chronic, relapsing and remitting condition with 30–70% recurrence within five years (Nelson et al., 2006). Healthcare systems worldwide are faced with rising costs associated with treating VLU. A 2003 systematic review revealed that these wounds occur in up to 1.8% of the general population in industrialised countries (Graham et al., 2003). Since prevalence of VLU increases with age, obesity and diabetes (Australian Institute of Health and Welfare, 2009), treatment costs will increase in the coming decades. Wounds of this nature cause the patient a significant reduction in mobility and a general decreased quality of life (Chase et al., 2000). These ulcers represent a significant cost to community services as they are slow to heal and the majority of patients require nursing care at least once per week plus general practitioner consultations (Weller and Evans, 2012). To make matters worse, VLUs commonly undergo a cycle of healing and recurrence (Moffatt et al., 2007), which impacts significantly on the patient's quality of life and the financial burden of treatment (Gottrup et al., 2010).

The healing of VLU is notoriously slow, with average healing times ranging from 12 to 30 weeks (Chase et al., 2000), however it is important to note that venous ulcers do not always heal. Wound

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dressings alone are usually not enough to heal a chronic VLU; it is also important to deal with the associated venous insufficiency (Curran and Plosker, 2002). The therapeutic mainstay in management of venous ulceration is graduated compression bandaging (changed once weekly) or stockings (removed daily) (Grey et al., 2006; Brown and Maloy, 2005). No single system of compression is more effective than other systems, although multi-component systems are superior to single component systems and systems that contain an elastic layer are better than those with inelastic components. However, 30–60% of patients still remain unhealed after 12 weeks of treatment with compression therapy (Weller, 2013; Franks et al., 2004). The pressure applied by a short stretch bandage to the lower limb forces venous return of blood to the heart (Trent et al., 2005), improving circulation and supply of nutrients to the wound site. The compression required to reverse venous hypertension is around 40 mmHg at the ankle (Ramstadius, 1997). Different levels of pressure, depending on the ulcer size, type and patient requirements may need to be applied (London and Donnelly, 2000), but, in general, higher compression has been shown to aid healing better than low compression (Fletcher et al., 1997). Patients that cannot (or will not) tolerate compression therapy in its standard short stretch (SS) form pose a clinical problem for medical staff (Bale and Harding, 2003). As an alternative, Bale et al. used a graduated bandage with three layers (3L) and reported improved patient comfort and convenience (Bale and Harding, 2003; Weller et al., 2013). One possible mechanism of action of the 3L bandages is that the bandage supplies a pressure gradient (lower at points higher up the leg) that improves blood flow (Weller et al., 2010). The impact of the two different bandage types on the wound healing mechanism thus requires exploration.

VLU are the most common type of lower leg ulcer and are typically a surface manifestation of underlying venous disease (Brown and Maloy, 2005). VLU is often due to sustained venous hypertension which results from chronic venous insufficiency (Grey et al., 2006). To ensure one-way flow of blood from the lower limbs to the heart, veins have valves to prevent back-flow (Brown and Maloy, 2005). When these valves fail to work properly, blood can flow backwards in the veins, increasing pressure in the veins at the extremities of the lower limbs, and the surrounding tissue (Trent et al., 2005). Severe cases are referred to as chronic venous insufficiency and can lead to VLU. Sustained chronic venous insufficiency leads to hypertension (elevated pressure) in the lower limb peripheral circulation (Chen and Rogers, 2007). This hypertension leads to dilation of veins, edema (swelling caused by excess fluid trapped in the tissue) and further damage to the valves in the veins (Brown and Maloy, 2005). Furthermore, venous hypertension causes the vasculature to become cuffed with fibrin (a protein involved in blood clotting) and this is thought to lock the wound in a chronic inflammatory state of healing although the pathogenic steps leading from venous hypertension to ulceration are unknown (Agren et al., 2000). The formation of these fibrin cuffs has been suggested to prevent the diffusion of oxygen and nutrients to the wound (Trent et al., 2005; Chen and Rogers, 2007; Agren et al., 2000).

In order to heal, a wound must proceed through a set of four overlapping and interconnected stages: haemostasis, inflammation, proliferation and remodelling (Enoch et al., 2006). During haemostasis, the primary goal is to prevent further blood loss. Chemical stimuli released during haemostasis regulate the inflammation process, which begins when leukocytes (white blood cells) are attracted into the wound to control bacteria and remove debris. The proliferation phase is signalled by rapid proliferation of fibroblasts, which replace the wounded tissue with a collagen matrix (Enoch et al., 2006). Angiogenesis, the formation of new blood vessels from pre-existing vasculature, allows nutrient support to be provided to the healing tissue. The remodelling phase lasts for several months (Sheffield and Smith, 2002), during which time the tensile strength of the wound is increased. During all stages of successful healing, nutrient support, including oxygen, is critically essential. Without sufficient oxygen, the wound will not heal and many processes are detrimentally affected by chronic hypoxia, including bacteria killing (Babul and Rhodes, 2000), angiogenesis (Knighton et al., 1981) and collagen synthesis (Gordillo and Sen, 2003). For a review of the biology of wound healing, non-healing wounds and their treatments see Thackham et al. (2008).

Mathematical and statistical models, varying in nature, complexity and purpose, have been developed to investigate the rate of closure of healing wounds. Cukjati et al. derived a formula for the advance of the wound margin toward the wound centre, assuming a delayed exponential decrease in wound area over time (Cukjati et al., 2001). The model of Cukjati et al. is not mechanistic in that no attempt is made to model why the wound area changes over time. Margolis et al. use logistic regression to model the probability of healing, based on the characteristics of a patient and their ulcer, such as age, gender, the severity of the wound and size of the wound (Margolis et al., 2004). The statistical models of Margolis et al. are useful in determining the risk factors for wounds that do not heal, but again the models are not mechanistic in that the physical drivers of wound area change are not considered.

Several authors have adopted a free-boundary approach to model wound healing. Early work by Gaffney et al. modelled the closure of a corneal epithelial wound due to electric stimulus with a moving boundary (Gaffney et al., 1999), for which Chen et al. later provided a detailed, formal, mathematical analysis (Chen and Friedman, 2000). In 2009, Xue et al. developed a model of a circular skin wound as a free-boundary problem (Xue et al., 2009), where the wound was modelled on $0 \le r \le R(t)$, partially healed tissue on $R(t) < r \le R(0)$ and normal tissue on $R(0) < r \le L$. In recent work, Ben Amar et al. modelled the advancing epithelium front during the reepithelialisation of healing by considering a cell species and an interacting chemical morphogen (Ben Amar and Wu, 2014). The role of the morphogen is to restore the cell population, by acting as a chemoattractant for directed motion of epithelial cells. The wound radius is modelled as an internal moving interface between the inner wounded tissue and the outer healed epithelium. Numerical simulations of the evolution of a circular wound suggest that a circular geometry of the wound cannot be maintained. Valero et al. have published a recent review of mechanistic models of wound healing, in which they outlined future challenges for theoretical modelling of wound healing (Valero et al., 2014). They identified computational models that provide insight into impaired wound pathologies in order to propose novel treatments as an open research field. There have been several mechanistic mathematical models of chronic wounds and their treatments developed (Flegg, 2009; Flegg et al., 2009, 2010, 2012; Friedman and Xue, 2011), however, to date, there have been no mathematical models developed specifically to gain insight into venous leg ulcers and their treatments.

As it is difficult to conduct *in vivo* investigations into the wound healing process in VLU in a non-invasive manner, realistic mathematical models that are based on known behaviours provide a useful framework for studying the healing process, its dysregulation and potential treatments to stimulate healing. A crucial component of a useful mathematical model is validation of parameters and testing against experimental and/or clinical data. In this paper, a mathematical model of compression therapy, formulated as a free-boundary problem, to treat VLU is developed to investigate whether the healing of venous ulcers under SS and 3L bandages occurs at different rates and to postulate the reason for any difference.