Study protocol: a pilot clinical trial of topical glyceryl trinitrate for chronic venous leg ulcer healing

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ABSTRACT

Background Chronic venous leg ulcers (VLUs) are costly to the healthcare system and a burden to patients, significantly reducing quality of life. Nitric oxide (NO) is important to wound healing, with a small study demonstrating a NO donor, topical glyceryl trinitrate (GTN), was effective for VLU healing. The aim of this study is to examine the application of topical GTN in relation to VLU healing.

Methods A pilot double-blinded randomised controlled clinical trial will be undertaken. Participants in the control group (n=20) will receive a placebo ointment (ointment base) and participants in the treatment group (n=20) will receive a NO donor (base ointment with 2% GTN) weekly for 4 weeks. The inclusion criteria will be adults >18 years of age with a chronic VLU. Rate of healing will be determined by planimetry (ulcer tracing) using the Gillman equation.

Significance This clinical trial aims to provide proof of concept of a novel treatment, topical GTN, which may accelerate wound healing through improvements to vasodilation and antimicrobial properties at the wound bed.

What is already known

- Chronic VLUs are a burden to patients and the healthcare system.
- NO is important to wound healing.
- GTN is a NO donor.

What this study aims to contribute

- Pilot a double-blind clinical trial of topical GTN.
- Examine the effect of 2% topical GTN on wound healing in VLUs.

BACKGROUND

Chronic venous leg ulcers (VLUs) are a burden to patients, especially in terms of poorer quality of life[1]. These ulcers tend to recur, even after an initial healing[2], with up to half of all

new ulcers lasting more than 1 year[3]. VLUs adversely affect quality of life in many ways, including via pain and other skin symptoms, disturbed sleep, and restriction in social activities and mobility[1,4]. There is a significant relationship between delayed VLU healing and severely reduced quality of life symptoms[1] leading to longer term insomnia, depression and even suicidal ideation[5]. These factors are also linked to non-adherence to treatment, further increasing VLU burden[6].

VLUs are also a burden to the community, particularly in terms of increasing healthcare costs[3]. While there are no recent Australian costing studies, the cost to the Australian health budget was estimated to be $365 million per annum in 1994[7], while the cost for the UK in 2012–13 was £941 million[8]. Each VLU in the UK in 2015–16 averaged £7600 over 12 months, which varied from £3000 per healed VLU to £13500 per unhealed ulcer, highlighting that unhealed VLUs are 4.5 times more costly[3]. Although VLUs can occur in patients as young as 30 years, affecting a person's work productivity[9], prevalence of these ulcers increases with age. This takes on significance in Australia due to an aging population[10]. There is limited current Australian information on point prevalence of chronic leg ulcers; however, a literature review by Bishop and White[11] found it varies between 0.1% and 1.1% in the UK. Suffice to say there is a need for novel treatments to decrease the burden and costs of VLUs to patients and society.

While there are many causes of chronic leg ulcers, venous disease is the most common, accounting for nearly 80% of cases[9]. However, while venous insufficiency is the problem[3], the exact pathogenesis of venous ulceration is still under investigation. The multiple theories postulated – venous hypertension, fibrin cuff theory, growth factor trap theory, ischaemia/reperfusion injury, leukocyte trapping theory[12] – indicate the cause is a multifactorial process[3].

In chronic wounds like VLUs the wound healing process is interrupted during the inflammatory phase with failure to move towards the repair and remodelling phases. In the inflammatory phase, a wound is predominantly infiltrated by macrophages which, when activated, synthesise nitric oxide (NO)[13]. The wound healing effects of NO at this time include vasodilation, antimicrobial activity, antiplatelet effects and induction of vascular permeability[13,14]. NO production is catalysed by enzymes, including inducible NO synthase (iNOS)[14], with peak production occurring within the first 48–72 hours of wound healing, indicating it is predominantly active during inflammation[13]. Impaired wound healing has been linked to deficient NO synthesis[13].

A Tasmanian study[15] demonstrated that the enzyme iNOS, which drives the production of NO, was elevated in patients with faster healing VLUs. This suggests that application of a topical NO donor might accelerate the healing process by releasing NO into the wound to improve blood flow to the affected area and potentially kill unwanted microbes in the wound[15]. The use of a topical NO donor, glyceryl trinitrate (GTN), strongly demonstrated this, but results were inconclusive due to a small sample size[15]. Given that 30% of ulcers are clinically infected on presentation[3], the antimicrobial properties as well as vasodilation from NO may be relevant to healing[13]. While NO has been trialled in various forms for wound healing[14], it has not been used as a topical VLU treatment. GTN is a NO donor which stimulates an increase in the production of NO[16] – it is already available in an ointment formulation approved for human use (Rectogesic, Care Pharmaceuticals). Therefore, the aim of this clinical trial is to examine the application of topical GTN ointment in relation to the healing of VLU.

METHODS

Study design

This pilot study will utilise a double-blinded randomised controlled clinical trial design. Participants in the control group (n=20) will receive a placebo ointment (ointment base) applied weekly for 4 weeks directly to the VLU. Participants in the treatment group (n=20) will receive the NO donor (ointment base with 0.2% GTN) applied weekly, also for 4 weeks. Both ointments have been manufactured to clinical grade by Care Pharmaceuticals. Participants and research nurses involved in treatment will not know if the product applied is the placebo or the GTN donor. The rate of healing over 4 weeks will be measured by planimetry (ulcer tracing), with the understanding that complete ulcer healing is not likely in the timeframe being examined. The trial is prospectively registered with the Therapeutic Goods Administration (TGA) (Clinical Trial Number (CTN) 2014/0114) and the ANZ Clinical Trial Registry (Universal Trial Number U1111-1153-9849). Ethics and site specific governance approval have been obtained (HREC/13/QPCH/68; SSA/15/QPCH/244).

Hypothesis

Participants receiving the GTN donor ointment will have a statistically higher linear healing rate (LHR) compared to patients that receive only the placebo ointment.

Setting and sample

The setting is a 630-bed tertiary referral hospital in southeast Queensland. Participant recruitment will be drawn from patients (adults >18 years old) in the hospital's medical wards who are medically diagnosed with a chronic VLU and who consent to participate. Participants with a leg ulcer of non-venous origin such as arterial, pressure or diabetic will be excluded. Other exclusions include patients with malignant ulcers, other forms of malignancy, active autoimmune disease, or who have had organ transplantation or have an active exacerbation of cardiac disease.

Study procedure

Both ointments will be aliquoted by a biochemist into separately coded (coloured dot) sterilised jars. Blinding will be achieved with one member of the research team using

an online random number generator to prepare a set of randomised numbered labels which will be attached to the jars as per coding and numerical sequence. Ointments will be stored with the hospital pharmacy and dispensed following recruitment as per a medically ordered trial prescription according to numbered sequence.

Usual medical management for patients with VLUs, along with weekly ointment application, will be used for both groups. All treatment will be provided by research nurses who have received specialised training for this trial.

Photographs of the wound, collected at baseline and weekly, will be used with digital software (PictZar® 7.6.1QS) and planimetry (ulcer tracing) to measure ulcer size and ascertain LHR. Rate of healing will be calculated using the Gilman[17] equation LHR=Δ A/PxT (cm/week), where Δ A=change in ulcer area (2nd area – 1st area), P=mean perimeter of ulcer (1st perimeter + 2nd perimeter/2), T=time between the visits. Weekly treatments will continue for 4 weeks in hospital or in participants' homes if discharged. Participant characteristics and demographic data, as well as type of medical management in place for each participant, will also be collected.

Data analysis

Data will be entered into a statistical database (SPSS Version 25, IBM Corp) for analysis and used to compare treatment and control group outcomes to determine if there is any difference in healing rates between the groups. Digital images will be analysed using electronic software (PictZar® 7.6.1QS).

POTENTIAL LIMITATIONS

Slow and difficult recruitment has been noted in previous chronic VLU trials[6], including ones with which the researchers have been involved. Patients admitted to hospital with VLUs as a co-morbidity are often too unwell to consent and/or participate in a trial and are usually later discharged to a community provider for VLU treatment. Those whose primary reason for admission is for their VLU usually have an infection or cellulitis[3] and may thus be ineligible to participate in a research trial. In addition, many patients are reluctant to return to hospital for a 'research visit' which is most likely a reflection on how a chronic VLU affects mobility and mood, with fatigue and depression being common disabling symptoms[1]. Non-adherence to treatment has also been associated with lack of a trusting relationship with healthcare providers[6], a factor which is also likely to affect recruitment. Thus, research grant funding will be used to fund research nurses to visit participants in their home for weekly visits if discharged before completion of the four weekly treatments.

SIGNIFICANCE

Given the lengthy healing rate of VLUs[3] and the long-term effects of these ulcers on a patient's quality of life[1], novel treatments for VLUs are needed. An earlier trial suggested that the topical application of GTN had a significant effect on increasing the healing rate of chronic VLUs, although results were inconclusive due to a small sample size. This clinical trial aims to provide proof of concept of this novel treatment in preparation for a larger clinical trial. It is anticipated that GTN will accelerate wound healing through improvements to vasodilation and blood flow as well as to antimicrobial properties at the wound bed. However, the burden of VLU on patient quality of life may affect the likelihood of patients consenting to participate in research trials; this should be taken into consideration for future trial planning.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest. Products used in this trial have been provided by companies with no input into research design or processes.

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