Could you briefly discuss the Aspirin in Venous Leg Ulcer (ASPiVLU) study?

The aim of ASPiVLU is to ascertain whether low-dose aspirin should routinely be given to people diagnosed with a VLU to improve wound healing and decrease ulcer recurrence. This research is important because VLU is a common and costly condition that results in significant patient suffering. If an already approved drug could be used to reduce healing time, this would significantly reduce resource use and improve patient quality of life. Since aspirin is generally safe, cheap, well tolerated and widely available, the potential impact on this population is important.

The primary objective of this study is to determine whether aspirin, as an adjunct to compression, improves venous ulcer healing. The secondary aim is to determine the effects of aspirin on venous ulcer recurrence after healing. We will measure serum inflammatory markers and hospitalisations to shed light on the mechanism of aspirin’s effect and to explore its impact on other important health outcomes.

Can you elaborate on the possible causes of VLU and how the condition affects everyday life?

Chronic VLUs are wounds of the lower limb caused by a diseased venous system resulting in chronically swollen legs and damage to the tissues around the ankles. VLUs take several months and sometimes years to heal, during which time they result in significant patient suffering and substantial cost to the health system.

Many patients do not adhere to compression therapy – a tight bandage applied to the lower limb – mainly because it can be painful, inconvenient for everyday life and may prevent the use of normal shoes. If aspirin could reduce the time of healing, this would be a significant breakthrough.

Could you describe the methodology you propose to use in your double-blind, multicentre, placebo-controlled trial on the effect of aspirin treatment?

We will recruit participants to investigate the effect of aspirin when combined with compression, compared to placebo combined with three-layer compression in adults confirmed to have a VLU.

We will assess the effect of aspirin on healing and ulcer recurrence. The primary outcome will be assessed at 12 weeks and, once healed, all participants will be followed monthly up to 52 weeks to measure the number of VLU recurrent episodes. We will recruit 286 patients over the next three years from hospital outpatient wound clinics in Australia.

By what means will you assess proof of healing?

The primary endpoint will be the time to complete healing of a participant’s target ulcer at or before 12 weeks after randomisation. Proof of complete healing will be measured by an independent expert, review of digital photos of the ulcer taken at baseline and fortnightly to 12 weeks or until healed, whichever occurs first.

The ulcer will be photographed using a digital camera to allow independent verification of ulcer size and proof of healing – 100 per cent epithelialisation with no scab and no exudate. A paper ruler with mm/cm markings will be used in each photo next to the ulcer to verify size.

Do you foresee any major challenges associated with this study? If so, what actions will you take to mitigate them?

The main challenge that we might have is recruiting sufficient participants into the trial. To ameliorate this, we have identified additional wound clinics across Australia that we can incorporate into the trial if necessary to ensure that the required number of patients can be recruited within three years.

Are you collaborating with any other researchers or laboratories in the course of your investigations?

Researchers based at Monash University are collaborating internationally on the largest trial conducted in Australia. An individual patient data meta-analysis with research groups from the UK and New Zealand is being discussed by principal researchers from Monash University, the University of Auckland and St George’s, University of London. The study will assess the potential advantages of daily low-dose aspirin for healing VLUs.
Ulcer healing

Researchers at Monash University in Melbourne, Australia, may have found an affordable and accessible new treatment for the most common type of leg ulcer, which causes pain and incapacitation in the elderly.

VENOUS LEG ULCERS (VLUs) are painful sores, most often on the inside of the leg just above the ankle, which can take many weeks to heal. In over 90 per cent of cases they are due to the improper functioning of the venous valves in the legs. This condition becomes more prevalent with age, and thus represents an increasing burden on healthcare systems as a consequence of population ageing, and as the risk factor-associated epidemics of obesity and diabetes continue to expand.

In Australia, this condition affects an estimated 400,000 people, with an annual economic burden of billions of dollars. Dr Carolina Weller is a senior research fellow in the Department of Epidemiology and Preventive Medicine at Monash University, where she is working to address this problem; developing and testing interventions to improve the quality of care received by those with such chronic wounds.

Weller wants to improve the treatment of VLUs which, in its existing state is not only costly, but also ineffective. The current standard is the use of compression bandaging to counteract the elevated pressure in the leg veins and allow the ulcer to heal. Two to four layers of bandage are usually placed over a dressing, with high pressure particularly applied at the ankle.

Unfortunately, the previous two trials were small, in total assessing only 71 participants, and insufficient to meet the high standard of randomised controlled trial required to demonstrate aspirin’s potential. Hence, Weller set up the Aspirin in Venous Leg Ulcer (ASPiVLU) study to test the clinical effectiveness of aspirin as an adjunct to compression therapy for healing chronic VLUs. This randomised, double blind, placebo-controlled trial will provide robust evidence of aspirin’s action. “We have sought to address the methodological and clinical limitations of previous studies and produce conclusive results,” enthuses Weller.

AN UNLIKELY SOLUTION

There is evidence to suggest that aspirin – a common and readily available drug – could address this need. The therapy suppresses platelet aggregation and reduces inflammation to minimise pathogenicity and vessel permeability. Corroborating the theory, data from two clinical studies in the UK and Spain show that aspirin, when paired with compression therapy, can improve VLU healing rates, prevent recurrence and reduce treatment costs.

ASPIVLU IS INVESTIGATING THE EFFECTIVENESS OF ASPIRIN IN VLUs IN ORDER TO:

1. Improve healing in people with leg ulcers in Australia
2. Help policy makers to reach more informed decisions on VLU programme funding
3. Improve the treatment advice offered by clinicians
4. Help patients with VLUs make decisions about preventive treatment

One in three patients with a venous leg ulcer will experience over 10 episodes of ulcération in their lifetime.
STUDY DESIGN

In the trial, participants recruited from seven specialty wound clinics in Australia will be randomly assigned to use aspirin combined with three layer compression, or placebo pills and compression, every day for a year. The primary outcomes will be assessed at 12 weeks and once the participant’s ulcer has healed. After this time participants will be monitored for recurrence at monthly intervals until the year is up, but all participants will remain in the trial for wound management, regardless of whether their wound has healed.

The dosage of aspirin to be used is critical, and was carefully decided based on evidence. The previous trials showed that 300 mg of aspirin administered daily can effectively accelerate ulcer healing and reduce recurrence rate, with minimal adverse effects. Alongside this, in vivo studies have shown that this dosage can suppress inflammatory markers and promote ulcer healing, while taking more aspirin can be associated with a larger risk of bleeding and gastrointestinal side effects. Thus, those randomised to the aspirin arm will receive 300 mg of aspirin daily.

Many outcomes will be measured throughout the trial (see boxout right), to assess the effectiveness of the treatment but also to understand its mechanism. Using serum collected from patients, the team will measure their inflammatory cytokine profiles. This will help to explain aspirin’s effects on harmful pro-inflammatory macrophages, and perhaps shed new light on how inflammatory mediators impair healing in chronic VLUs.

A POWERFUL CONCEPT

If aspirin coupled with three-layer compression is found to be effective in this trial, it could have a significant impact on medical care and health policy worldwide. “The ageing of the population will progressively increase the numbers for whom these results are applicable,” hypothesises Weller. “A method of effectively improving the healing rates with an ageing population is a high priority.”

If the trial is successful, it could revolutionise the treatment paradigm for this common and painful ailment, improve healing rates, reduce the time to healing, and decrease ulcer recurrence. In addition, as aspirin is an affordable medication, its access will not be limited by the income or insurance status of a patient.

Following the ASPiVLU trial, Weller may be able to demonstrate a partial solution to the increasing burden of VLUs. Her study stands to increase confidence in the clinical use of aspirin, demonstrating not only that the drug works, but also that its benefits outweigh its risks. When the final results are published, attention will turn to clinical use. As aspirin is already an approved drug, the translation of this novel finding to the clinic should proceed rapidly, just as aspirin quickens the pace of recovery for VLU patients.

TRIAL ENDPOINTS

The primary endpoints of a clinical trial measure outcomes that will help answer the most important question being asked, in this case, does aspirin improve the healing of VLUs?

Ulcer size

The size of the ulcer will be measured at baseline and fortnightly until the ulcer is healed.

Proof of healing

Healing will be measured via an independent expert review of digital photographs.

Secondary

The secondary endpoints ask other relevant but less important questions, for example, does the therapy reduce the cost of treating patients?

Serum samples

At baseline and at week six, blood will be taken from participants for later assays of inflammatory markers.

Wound pain score

The participants’ assessment of pain will be measured on a standardised 0-100 scale.

Quality of life

Health-related quality of life and wellbeing instruments will be used.

Recurrence

The trial will assess ulcer recurrence in participants with healed VLU at monthly intervals.

Adherence to compression

Participants will report how often they adhered to wearing their bandage.

Adherence to medication

At treatment visits, participants will be asked to present medication containers for a pill count.

Adverse events

Each follow up visit will assess adverse events using open-ended questions and a checklist.