Investigating effects of Aspirin in people with Venous Leg Ulcers: The ASPiVLU randomised controlled trial

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ABSTRACT

Background: Venous leg ulcers (VLUs) are a common problem that impact on quality of life and are a costly health care burden. Cost-effective strategies to heal and prevent recurrence are required to address this growing burden. Whilst compression therapy has the potential to heal some ulcers, new treatments are needed to address those wounds that are more challenging to heal. Targeting the inflammatory processes underlying venous ulcers is a possible strategy. Limited evidence suggests that low-dose aspirin may be an effective adjunct to aid ulcer healing and reduce recurrence. The Aspirin in Venous Leg Ulcer study (ASPiVLU) will seek to investigate if daily low-dose aspirin improves time to healing.

Design: This randomised, double-blinded, multicentre, placebo-controlled clinical trial will recruit 268 participants with a chronic VLU from wound clinics across Australia. Participants will be randomised to receive either daily oral aspirin (300 mg) or placebo, in addition to best practice compression therapy.

Discussion: This study will provide a robust evaluation of the benefits and harms of aspirin as an adjunct therapy to compression in the management of VLUs. Recruitment commenced in March 2015 and study completion is anticipated in June 2018.

BACKGROUND

Venous leg ulcers (VLUs) are a common and costly problem, managed in community settings with variability in clinical practice[1,2]. Age-related venous leg ulceration is the most common cause of lower limb ulceration in developed countries with an overall prevalence between 1.65 and 1.74%, which is higher in adults aged 65 and older[3,4]. In 2010, an estimated 400,000 Australians were treated for a VLU, translating to costs of A$3 billion per year[3]. The natural history of venous ulceration is a cycle of healing and recurrence[5], which has a considerable impact on an individual's health, quality of life and socio-economic costs[6].

Estimated increases in life expectancy means that more people will be living with VLUs in the future, increasing the financial and health care burden of this already costly chronic disease[7,8].

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Adults over 60 years of age represent the fastest growing segment of the population in developed countries, and retaining health, mobility and independence at this age has become a major goal of preventive medicine[9,10].

Best practice treatment is compression therapy to aid venous return[11]. Data shows that VLUs heal better with multi-component compression than without[12], although treatment inconsistency has been reported as a limiting factor to healing[2,13].

There is a need for better treatment and prevention strategies. Aspirin is a widely used and relatively well-tolerated drug and its potential to reduce inflammation associated with VLUs may achieve better healing and decrease the frequency of ulcer recurrence[14].

Signs of inflammation have been observed in experimental models of venous disease. The inflammatory cascade begins with increased vascular permeability, and progresses to adhesion of leukocytes and platelets[15]. Chronic VLUs persist in an inflammatory state characterised by ongoing presence of leukocytes and a failure to properly generate vascularised granulation tissue. This perpetual inflammatory state may be a significant contributor to these difficult-to-heal chronic wounds.

Aspirin may be capable of influencing the progression of VLUs through suppression of inflammation as it inhibits the enzyme cyclo-oxygenase (COX), thereby blocking synthesis of several stimulators of inflammation[16].

Two randomised controlled trials (RCTs) have reported the impact of aspirin on VLUs, both with a small number of participants.

An RCT conducted by Layton (n=20) reported daily oral administration of aspirin (300 mg) with compression bandaging increased both the rate of healing (p<0.01) and the proportion of participants healed when compared to placebo with compression bandaging, over a four-month period[14,17]. Thirty-eight per cent of the aspirin participants reported complete healing, compared with 0% in the placebo group (p<0.007). Improvement, assessed by reduction in wound size, occurred in 52% of the aspirin group, compared with 26% with the placebo (p<0.007). The potential benefits of aspirin as an adjunct to compression was identified, but the study sample size was small and the mechanism by which aspirin improved healing or the effect on recurrence was not reported.

A more recent RCT conducted by del Río Solá (n=51) compared daily oral administration of aspirin (300 mg) in addition to compression with compression alone over a five-month period[18]. There was little difference in complete healing rates between groups (21/28 aspirin and 17/23 compression bandage alone) and the average time to healing was 12 weeks shorter in the aspirin group versus 22 weeks in the compression only group. The average recurrence rate was lower in the aspirin group; 39 days [SD 6.0] for aspirin versus 16.3 days [SD 7.5] for compression alone.

The ASPiVLU study has sought to address methodological and clinical limitations of previous studies to produce conclusive results with an appropriately powered, randomised, double-blinded, placebo-controlled trial. A daily dose of 300 mg aspirin was selected as current evidence is derived from studies using this dose with minimal reported adverse events, and the data that aspirin doses of 300 mg daily appear to be as effective in suppressing inflammation as higher doses with lower risk of haemorrhagic or gastrointestinal side effects. Confidence in its use will require a study such as ASPiVLU to demonstrate substantial benefit and acceptable level of side effect rates.

OBJECTIVES

The primary objective is to determine whether aspirin as an adjunct to compression therapy improves the time to healing of the target ulcer in a 12-week treatment period. The secondary objective is to investigate the effects of aspirin on the rate of target ulcer recurrence over 12 months from date of randomisation.

METHODS

Study design

ASPiVLU is a randomised, double-blinded, multicentre, placebo-controlled clinical trial designed to assess the clinical effectiveness of a daily 300 mg oral dose of aspirin as an adjunct to three-layer (3L) compression in healing VLUs in adults, over a one-year period.

Study setting and participants

Participants will be recruited from six speciality wound clinics in the states of Victoria, New South Wales, Queensland and Tasmania, Australia. All consecutive eligible patients who attend study wound clinics for VLU management and fulfil selection criteria will be invited to participate in the study.

The ASPiVLU study is recruiting participants at the following sites:

- Austin Health; Alfred Health; Western Health, **Victoria**
- Royal Hobart Hospital, **Tasmania**
- Westmead Hospital Vascular Clinic, **New South Wales**
- Prince Charles Hospital Wound Clinic, **Queensland**

Inclusion criteria

- Age 40 years or older.
- Have one or more VLUs in the presence of venous insufficiency, confirmed by clinical assessment and/or duplex ultrasound.
- The target ulcer (largest ulcer) must have the following characteristics:
  - Present for six weeks or more.
  - Total surface area between 1 cm^2 and 20 cm^2.
  - Separated from other ulcers by at least 1 cm.
- Ankle Brachial Pressure Index [ABPI] of ≥ 0.7 or systolic toe pressure ≥ 50 mmHg.

Exclusion criteria

- Unable or unwilling to wear compression bandage.
- Aspirin intolerance.
- Current, regular aspirin use or regular aspirin use for any reason within the last six weeks.
- Concurrent use of any other anticoagulation therapy.
- Bleeding disorder, including thrombocytopenia (platelets <100 x 10^9/L).
- History of peptic ulcer, gastrointestinal bleeding or intracranial bleeding.
- Severe liver disease as assessed by physician.
- Severe hypertension >180/110 mmHg (once managed, patient can participate).
- Undiagnosed anaemia, anaemia in setting of haemodynamic instability or Hb<80 g/L.
- Renal failure or severe impairment, defined as eGFR<15 mL/min or requiring dialysis.
- Pregnancy or breastfeeding.

INTERVENTION

Study medication

Participants will be allocated to either active treatment with daily aspirin or inactive placebo for one year from study enrolment. Both study medications are enteric coated, unscored white tablets with identical appearance, developed and provided by Bayer Pharma AG. Pharmaceutical packaging professionals will package the medication to maintain blinding.

Compression therapy

All participants will be treated with 3L compression therapy. The 3L compression will consist of a padding layer and three layers of

elastic, tubular bandage (Tubular-Form™; Sutherland Medical), applied over primary wound dressing. Compression will be applied by study-trained wound research nurses, and will be changed at weekly treatment visits. The safety and efficacy of 3L compression was demonstrated in our previous compression RCT[19,20].

Compression hosiery

Participants will be fitted with compression hosiery, *VENOSAN® compression stockings*, once ulcer healing is achieved. *VENOSAN® compression stockings* will be fitted for the secondary prevention of ulcer recurrence.

ENDPOINTS

Primary endpoint

The primary outcome of this study is the time to complete healing of a participant's target ulcer up to 12 weeks after randomisation. Proof of healing will be confirmed by independent expert review of digital photos of the ulcer and must meet the criteria of complete epithelialisation, no scab and no exudate.

Secondary endpoints

A range of secondary endpoints will be assessed, either at clinic visits or with phone calls made by research study staff.

- Recurrence of target ulcer.
- Wound pain score.
- Health-related quality of life and wellbeing index (EQ-5D-5L).
- Adverse events.
- Serum inflammatory markers.

ASSESSMENT OF PROCESS MEASURES

Other assessments will be carried out as part of the ASPiVLU study, including:

- Adherence to medication.
- Adherence to compression treatment or secondary prevention compression hosiery.

SAMPLE SIZE

Data from our previous compression study shows that in the placebo group we can expect 50% of ulcers to have healed at 12 weeks[20]. Aspirin is expected to increase this proportion by another 20%, that is, we expect 70% of the aspirin group to be healed at 12 weeks. For 90% power in a two-sided (alpha=0.05) test for time to healing analysed by a log-rank test, we require 121 people per group. Allowing for a 10% loss to follow-up, we will recruit n=134 participants per group.

DATA MANAGEMENT

Results from trial assessments will be recorded in the electronic case report forms (CRF) via an electronic data capture (EDC) system. The REDCap EDC system is a secure, web-based system (www.projectredcap.org). Each clinical site will use a unique password to enter CRF data directly into the EDC system.

STATISTICAL METHODS

The trial will be analysed by statisticians based in the Biostatistics Unit, Department of Epidemiology and Preventive Medicine, Monash University.

ANALYSIS OF ENDPOINTS

The primary endpoint will be analysed with a log-rank test to compare the time to healing, up to the 12-week time point, between the two randomised treatment groups. A secondary analysis will use logistic regression to compare proportion of participants healed by 12 weeks between groups.

The secondary endpoint, proportion of patients healed by 12 weeks and remaining recurrence-free at 12 months, will be compared between the two groups using logistic regression. Suppression of inflammatory markers in plasma by aspirin will be compared between groups using a linear mixed model with a random effect for participants to allow for correlation among each individual's repeat measures over time, adjustment for biomarker level at randomisation, and an interaction between time since randomisation (12 weeks or 12 months).

The secondary outcomes of pain score and EQ-5D-5L[21] will be analysed in linear mixed models with random effect for participant, adjustment for the measure at randomisation, and an interaction between time since randomisation and randomisation group. Other secondary outcomes, time from healing to recurrence among those healed by 12 weeks and time from randomisation to adverse events, will be compared between groups using univariate Cox proportional hazards regression.

The primary and secondary endpoints will be analysed according to intention-to-treat principles. No statistical adjustments will be made for the multiple secondary endpoints in their analysis but the reporting of all secondary endpoint analyses will make clear whether the primary endpoint was statistically significant and will state the number of secondary endpoints proposed *a priori* in the study protocol[22].

RANDOMISATION AND BLINDING

Patients will be randomised centrally via a web-based randomisation system to a ratio of 1:1 active (aspirin) or placebo therapy. The randomisation list will be generated by an independent statistician and implemented together with medication number selection by the database programmer; this arrangement will ensure that the randomisation schedule remains inaccessible to all study staff and senior investigators. Randomisation codes will be allocated via this password-protected system. Staff will enter their unique ASPiVLU identification number, study site number, participant identification number, wound size, wound duration and confirmation of inclusion and exclusion criteria.

Allocation will be stratified by study wound clinic site and wound size as measured by the Margolis index (wound size and duration)[23]. Treatment allocation will occur after baseline assessment of the

target ulcer is completed. Participants, wound clinic practitioners, outcomes assessors and investigators will remain blinded to treatment allocation until after analysis of the trial results has been completed.

UN-BLINDING

Un-blinding will occur in the event of a clinical emergency in which the knowledge of medication taken is essential for the participant's clinical management. The code can be broken by contacting the trial pharmacist via the trial centre. This procedure will ensure that no staff involved in the management or the conduct of the study will have access to the randomisation code. The Data and Safety Monitoring Board (DSMB) will be informed of any emergency code breaks in tabular form.

STUDY MEASURES AND VISIT SCHEDULE

All participants will receive weekly ulcer management at the wound clinic for a maximum of 12 weeks (the treatment period) or until complete healing is achieved. This will include application of a wound dressing and 3L compression therapy.

Once ulcer healing is achieved, participants will enter the study follow-up period. This comprises monthly phone calls until 52 weeks (12 months) from the date of randomisation (Day 1). Participants will be fitted with compression stockings (VENOSAN®) as secondary prevention against ulcer recurrence, and will be provided with advice leaflets on how to prevent ulcer recurrence. If the target ulcer recurs during the study period, or fails to heal within the 12-week treatment period, the participant will be referred back to the wound clinic for ongoing standard care. They will continue as participants in the follow-up period of the study.

An overview of the study flow is provided in Figure 1.

SCREENING AND ENROLMENT

The wound clinic medical practitioner and/or wound clinic nurse will assess eligibility of patients as outlined in the inclusion/exclusion criteria. Patients who are eligible will be provided with a verbal study overview, a written plain language statement and will be invited to participate.

TRIAL MONITORING

The ASPiVLU Steering Committee will be responsible for the overall management and conduct of the trial, including finalising the protocol, approving the operational plan for the study and financial management of the trial. A Data and Safety Monitoring Plan (DSMP) for ASPiVLU has been prepared according to the DSMP Guidelines for Clinical Trials to be approved by the DSMB. The DSMB will have responsibility for monitoring quality control of the data and safety aspects of the trial.

ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the Declaration of Helsinki 1964 as revised in Edinburgh[24], *Good Clinical Practice Guide* (CPMP/ICH/135/95) and with the National Health and Medical Research Council Guidelines on Human Experimentation. Human ethics approval has been sought from Alfred Health, Austin Health, Melbourne Health, Monash University, University of Tasmania, Prince Charles Hospital QLD and Western Sydney Local Health.

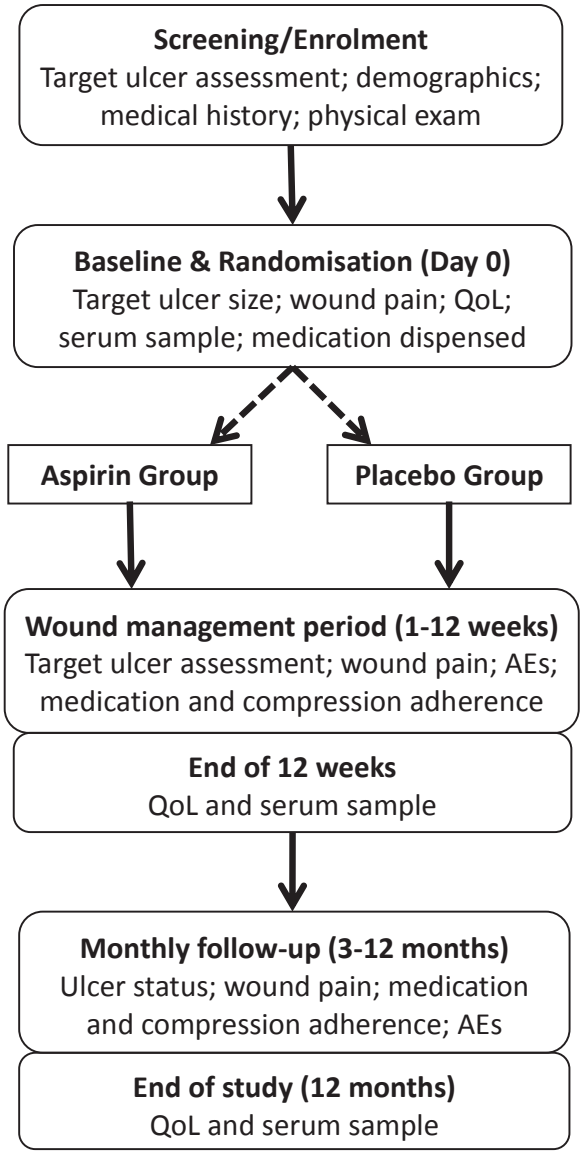

Figure 1: ASPiVLU study flow chart

DISSEMINATION

The ASPiVLU website (http://www.med.monash.edu.au/sphpm/aspivlu-study.html) will provide information to health professionals, the scientific community and the public regarding study results and recommendations. Study findings and recommendations will be published in peer-reviewed scientific journals, and print media, including consumer brochures, will be developed as appropriate.

DISCUSSION

A large-scale trial of aspirin is needed to evaluate the risk and benefit in people with VLUs. Two previous trials suggested that 300

mg of aspirin administered daily can accelerate ulcer healing and reduce recurrence rates, with minimal adverse effects. If aspirin coupled with 3L compression is found to be effective in this trial, it could have a significant impact on the medical care of VLUs, health care costs and health policy worldwide. It could revolutionise the treatment paradigm for this common and painful condition; improve healing rates; reduce the time to healing; and possibly decrease ulcer recurrence.

There are two other planned or ongoing RCTs relevant to the research question. **AVURT** (Aspirin for Venous Ulcers: Randomised Trial) in the UK and the **Aspirin4VLU** (Low Dose Aspirin for Venous Leg Ulcers) in New Zealand. Chief investigators of all three aspirin RCTs will work collaboratively to form the Aspirin for Venous Leg Ulcers Collaborative (AVLUC). The collaborative will collate individual patient data (IPD) meta-analyses of randomised controlled study data.

DECLARATIONS

The ASPiVLU investigator group is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12614000293662).

ASPiVLU has received funds from the National Health and Medical Research Council (Australia).

Bayer Pharma AG provided blinded aspirin and placebo for the ASPiVLU study.

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