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A 3 month clinical trial of herbal medicine combination intended for topical application in patients with leg symptoms complaints due to chronic venous insufficiency: a double-blind randomized controlled trial

Submission date	**Recruitment status**	[X] Prospectively registered
05/01/2016	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
14/01/2016	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
04/01/2022	Circulatory System	

Plain English summary of protocol

Background and study aims

Chronic venous disease (CVD) is a common condition that affects the veins of the legs. These veins carry blood from the legs to the heart. Veins have a series of valves that open and close to direct blood from the surface of the legs into the deep leg veins, which is then pumped back to the heart. If these valves don't work properly, blood can flow backwards in the veins and pool in the legs. These can result in a variety of symptoms. Some are mild (legs feeling heavy, aching and /or unsightly veins) to more severe (swelling, changes in skin colour, skin rashes, infections and chronic ulcers). People with more severe symptoms are said to suffer from chronic venous insufficiency (CVI). It has been reported that, in Thailand, varicose veins are common among women factory workers (33%). A study has confirmed that over 70% of hospitalized leg and foot ulcer patients were due to CVD. In addition, investigations by groups of Thai vascular (vein) specialists looking at different clinical presentations (signs and symptoms) and patterns of Thai patients with CVI, concluded that it can happen in young people. The progression of CVI can be prevented if diagnosed early. Bandaging is the most common method of managing the condition. However, many patients don't stick to the treatment as its inconvenient and costly long term. Drug therapies could be an alternative, but searching through electronic databases brought up limited options that were mostly herbal medicines and the evidence that was available was conflicting. The active herbal extracts asiaticoside (from titrated extract centenella asiatica), acetyl salicylic acid (from willow bark extract) and acemannan (from aloe vera) were identified and selected based primarily on their combined potential anti-inflammatory, anti-fibrosis and anti-coagulating (stopping blood clots from forming), antibacterial and immunomodulation (modifying the immune system) effects. This study is investigating whether these medicines are an effective treatment for CVI.

Who can participate?

Patients diagnosed with CVI suffering with leg symptoms.

What does the study involve?
Participants are randomly allocated into one of two groups. Those in group 1 are given a herbal medicine combination gel formulation containing acetyl salicylic acid, asiaticoside and acemannan to use once in the morning and once in the evening continually for 3 months. Those in group 2 were given a placebo (dummy) gel to be applied in the same way as the herbal one for 3 months. Each patient's CVI is assessed before the start of treatment, and then after week 1, week 2, week 3, week 4, week 8 and week 12.

What are the possible benefits and risks of participating?
The treatment may alleviate symptoms and help prevent the progression of CVI. The herbal medicine gels are safe to use, the only risks being a localized skin reaction similar to that of what may occur when using the control gel.

Where is the study run from?
Wiang Chai Somdej Prayanna Sangworn Hospital (Thailand)

When is the study starting and how long is it expected to run for?
February 2016 to December 2016

Who is funding the study?
National Research University Project, Chulalongkorn University (Thailand)

Who is the main contact?
Mr Anan Udombhornprabha

Contact information

Type(s)
Scientific

Contact name
Mr Anan Udombhornprabha

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
CR0032.115 Date 10 November 2015 #4400 EC_Chiangrai_Wiang Chai SDPY Hospital

Study information

Scientific Title
Herbal medicine combination containing acetyl salicylic acid and asiaticoside plus acemannan in topical gel formulation for chronic venous insufficiency: a 3 month double-blind randomized placebo-controlled trial among Thai patients diagnosed as mild-to-moderate chronic venous insufficiency

Acronym
AS ASIA

Study objectives
Current hypothesis:
Is the response to treatment of mild-to-moderate chronic venous insufficiency with a herbal medicine combination topical application containing 2% acetyl salicylic acid, 2% Asiaticoside plus 1% acemannan 35% better when compared to a control.

Previous hypothesis:
Is the response to treatment of mild-to-moderate chronic venous insufficiency with a herbal medicine combination topical application containing 2% acetyl salicylic acid, 2% Asiaticoside plus 1% acemannan 50% better when compared to a placebo.

Ethics approval required
Old ethics approval format

Ethics approval(s)
College of Public Health Science, Chulalongkorn University, 10/11/2015, ref: CR0032.115

Study design
Interventional, prospective randomized, double-blind, controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Chronic venous insufficiency

Interventions
Current interventions as of 15/12/2017:
Participants fulfilling the eligibility criteria were randomly allocated into one of two arms.
1. Active treatment arm: each participant was given a herbal medicine combination gel formulation containing 2% acetyl salicylic acid in bees wax encapsulation and 2% asiaticoside plus 1% acemannan. It was applied to the leg with symptoms once in the morning and then again at bedtime continuously for 3 months.
2. Control treatment arm: each participant was given a controlled-gel with identical odour and colour with no active herbal drugs. It was applied to the leg with symptoms once in the morning and then again at bedtime continuously for 3 months.

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Participants fulfilling the eligibility criteria were randomly allocated into one of two arms.
1. Active treatment arm: each participant was given a herbal medicine combination gel formulation containing 2% acetyl salicylic acid in bees wax encapsulation and 2% asiaticoside plus 1% acemannan. It was applied to the leg with symptoms once in the morning and then again at bedtime continuously for 3 months.
2. Control treatment arm: each participant was given a placebo-gel with identical odour and colour with no active herbal drugs. It was applied to the leg with symptoms once in the morning and then again at bedtime continuously for 3 months.

Intervention Type
Supplement

Primary outcome measure
Current primary outcome measure as of 21/02/2019:
Venous disease severity, assessed by the venous clinical severity score (VCSS) measured at baseline, week 4, week 8 and week 12

Previous primary outcome measure:
Venous disease severity, assessed by the venous clinical severity score (VCSS) measured at baseline, week 1, week 2, week 3, week 4, week 8 and week 12

Secondary outcome measures
Current secondary outcome measures as of 21/02/2019:
1. Physician-rated disability, assessed by the Physician Rated Symptom Perception Score (PRSPS) at baseline, week 1, week 2, week 3, week 4, week 8 and week 12
2. Quality of life, assessed by the Chronic Venous Insufficiency Quality of Life Scale International Collaboration 14 questionnaires (CIVIQ-14) and the Health-related Quality of Life Score Assessed with a Short-form 12-item Health Related Questionnaire Self-Administered Survey (SF-12). Measured at baseline and week 12
3. Patient-rated disability, assessed by the Patient Self-Rated Symptom Score (PSSS) at baseline, week 1, week 2, week 3, week 4, week 8 and week 12
4. Symptoms reported by patients, assessed by the Patients Self-Rated Symptoms Scale (VAS) in a weekly diary report

Previous secondary outcome measures:
1. Disability caused by venous disease, assessed by the Venous Disease Disability Score (VDDS), measured at baseline, week 1, week 2, week 3, week 4, week 8 and week 12
2. Quality of life, assessed by the Chronic Venous Insufficiency Quality of Life Scale International Collaboration 14 questionnaires (CIVIQ-14) and the Health-related Quality of Life Score Assessed with a Short-form 12-item Health Related Questionnaire Self-Administered Survey (SF-12). Measured at baseline and week 12
3. Assessment of overall physical functions, measured at baseline, week 1, week 2, week 3, week 4, week 8 and week 12
4. Laboratory blood chemistry and alanine aminotransferase enzyme assessments, measured at baseline, week 1, week 2, week 3, week 4, week 8 and week 12
5. Symptoms reported by patients, assessed by the Patients Self-Rated Symptoms Scale (VAS) in a weekly diary report

Overall study start date
01/02/2016

Completion date
31/12/2016

Eligibility

Key inclusion criteria
Current inclusion criteria as of 15/12/2017:
Patients seeking advice at the surgery ambulatory clinics with at least 5 of the following symptoms:
1. Heavy leg
2. Pain in the leg
3. Sensation of leg swelling
4. Night cramp
5. Itching leg
6. Sensation of burning
7. Sensation of pins/needle in the leg
8. Presence of superficial varicose vein
9. Presence of spider veins 10. Presence of blood-clotting.

And must have been accurately diagnosed as chronic venous insufficiency by physician as per WHO- ICD10 Criteria and also being graded as appropriate staging of the chronic venous insufficiency stage as per the CEAP Criteria.

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9. Presence of spider veins 10. Presence of blood-clotting.

Plus these patients must have at least one risk factor as follows :
1. Sibling history with presence of swollen leg, spider & varicose veins and ankle/leg ulcer
2. Long hours standing per day (≥3 hours)
3. Long hours sitting per day (≥3 hours)
4. No regular exercise
5. Smoker
6. Taking hormone replacement therapy and/or contraceptive (oral/injectable)

And must have been accurately diagnosed as chronic venous insufficiency by physician as per WHO- ICD10 Criteria and also being graded as appropriate staging of the chronic venous insufficiency stage as per the CEAP Criteria.

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
150

Total final enrolment
42

Key exclusion criteria
Patients with known history of:
1. ASA-exacerbated respiratory disease (AERD) and/or asthma
2. ASA-sensitivity and Rhinitis/Nasal Polyps
3. ASA and NSAIDs induce cutaneous reactions with Urticaria, Angioedema
4. ASA-induced anaphylactoid reactions with Hypotension, swelling, laryngeal edema, generalized pruritus, tachypnea
also:
5. Patients with known sensitivity or allergic to centenella asiaticosa or asiaticoside.
6. Patients with known sensitivity or allergic to acemannan and the aloe vera products

Date of first enrolment
01/02/2016

Date of final enrolment
31/05/2016

Locations

Countries of recruitment

Thailand

Study participating centre
Wiang Chai Somdej Prayanna Sangworn Hospital, Chiang Rai
263 Tumbol Wiang Chai Amphoe Wiang Chai
Chiang Rai
Thailand
57210

Sponsor information

Organisation
National Research University Project, Office of the Higher Education Commission (WCU-58-034-AS)

Sponsor details
Ministry of Education
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Phyathai Road
Pathumwan
Bangkok
Thailand
10330

Sponsor type
University/education

Website
www.unisearch.chula.ac.th

ROR
https://ror.org/036nq5137

Funder(s)

Funder type
Government

Funder Name
National Research University Project of Thailand

Results and Publications

Publication and dissemination plan

1. The baseline reports shall be published during June -July 2016
2. Results will be published after completion of the trial during Sept -Oct 2016
3. Publisher to be decided later

Intention to publish date

31/07/2019

Individual participant data (IPD) sharing plan

Not provided at registration

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	25/12/2017		Yes	No
Results article	results	31/01/2018		Yes	No
Basic results		20/02/2019		No	No
Results article	results	28/02/2019		Yes	No
Results article	results	01/06/2019		Yes	No
Abstract results	Presented at KIOM-SAR 2020 International Research Conference	11/09/2020	04/01/2022	No	No