Protocol

CIVIL study

Copper Impact on Venous Insufficiency and Lipodermatosclerosis

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Full title: Randomised Controlled Trial on the Impact of Copper Impregnated Stockings on lipodermatosclerosis secondary to venous insufficiency

Background

Chronic venous disease (CVD) has various clinical presentations and the most commonly known symptom is varicose veins. Other symptoms include pain, oedema, and cutaneous changes of the lower legs such as hyperpigmentation, eczema, atrophie blanche (white scar tissue) and lipodermatosclerosis (induration caused by the fibrotic process of the subcutaneous fat). Chronic venous disease can be classified with the clinical, aetiologic, anatomical, and pathophysiological classification (CEAP-classification) in which the clinical signs are graded into six classes; C0-C6 (Table 1). CVD includes all symptoms and signs, whereas chronic venous insufficiency (CVI) refers to a more advanced stage of CVD (i.e. C4-C6) (12).

CEAP Clinical classification of chronic venous disease

C0	No visible or palpable signs of venous disease
C1	Telangiectasies or reticular veins
C2	Varicose veins
C3	Oedema without skin changes
C4a`	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C5	Healed venous ulcer
C6	Active venous ulcer

The prevalence of CVD varies among the different stages of the disease. A large worldwide study of the Vein Consult Program showed a prevalence of clinically significant CVD of more than 60% in the general population (4). Varicose veins are the most common manifestation

of CVI with a prevalence up to 30% in adult population (1,2,3). The prevalence of active and healed ulcers is approximately 1% of the adult population (5). Since delayed healing and recurrence are very common, the prognosis of venous ulceration is poor (6).

The high prevalence and the chronic nature of venous disease have a considerable socio-economic impact. A study conducted in the United States and the United Kingdom showed that venous ulcers cause a decrease of 2 million working days per year (7) and the National Health Service (NHS) spends approximately 1-3% of the total health care budget on the treatment of CVD (8,9).

Graded compression stockings are the primary conservative treatment in patients with CVI. A significant improvement can only be achieved with a good compliance (10). Reduced adherence to compression therapy is a well-known and major issue in the treatment of patients with CVD (13). Patients with clinical CEAP classification C4 venous disease, or higher, have an increased risk of venous ulceration. Non-compliance with compression hosiery and deterioration of the skin condition increases this risk. In literature the non-compliance ranged from 22%-67% (13 - 17). The most common reasons for non-compliance are inapplicability, the perception of inefficacy and the lack of comfort (13). However,the strategy to properly address non-compliance remains unknown.

Standard compression stockings reduce the symptoms of pain and oedema, facilitate the healing of ulcers, and prevent the recurrence of venous ulcers (11), but they do not improve the skin condition. Copper has been shown to promote angiogenesis and therefore it could support wound healing and possibly improve skin condition. Copper has also been shown to have strong antimicrobial properties. It has been shown in observational, non-randomised trials that improvement of the skin condition could be seen within two weeks (33,34). When no change in skin condition is seen within four weeks, it is unlikely to be seen at all.

Antimicrobial copper

Copper was primarily known for its antimicrobial effect and has been used for hygienic purposes for centuries (18). With the increase in antibiotic resistant bacteria causing nosocomial infections, copper has become a popular subject of recent research. There are many laboratory studies showing the biocidal effect of copper on a wide range of microbes such as bacteria, fungi and viruses (21,22). Copper has also been proven to be effective against Methicillin-resistant Staphylococcus aureus (MRSA) (19) and Vancomycin-resistant Enterococci (VRE) (20). The use of copper surfaces in the hospital has been evaluated in several clinical studies showing significant reductions in bacterial colonisation on copper surfaces compared to standard materials (23). After the use of copper as a biocidal contact surface, the use of copper impregnated textiles was explored. Currently, there is a great variety in products available containing copper impregnated textiles such as socks, pyjamas, underwear, bed linen, face masks, stockings and wound dressings, but there is a paucity of clinical research. There has been a clinical study on the effect of copper impregnated socks in patients suffering from tinea pedis showing a significant improvement or resolution of the infection after wearing these socks for two weeks (24).

Wound healing

It has also been proven that copper is essential for the process of wound healing. Copper is assumed to be involved in several processes crucial for wound healing (25). A key role in wound healing is angiogenesis. It has been shown that copper induces the production of vascular endothelial growth factor (VEGF) and therefore stimulates angiogenesis (26). Furthermore, copper promotes wound healing due to an elevation in integrin expression (27); enhancement of fibrinogen stabilisation (28) and up-regulation of several enzymes essential for matrix remodelling and cell growth (29). Several laboratory studies have

demonstrated an association between a copper dependant enzyme, lysyl oxidase (LOX), and skin ageing and pathological skin conditions (30).

Safety

The dermal exposure to copper is considered safe as copper is not only an essential element for normal skin function but also essential for the immune system and blood coagulation (31). In contrast to microorganisms, human skin cells have the ability to metabolise and utilise copper (32) and therefore the development of adverse reactions are unlikely (33,35).

Our hypothesis is that copper impregnated stockings promotes wound healing and improves the skin condition in patients with lipodermatosclerosis secondary to CVI.

Aim

To investigate the impact of copper impregnated stockings on subjective and objective outcomes in patients with lipodermatosclerosis secondary to venous insufficiency.

Objectives

Primary:

To assess the effect of copper stockings on symptoms in patients with lipodermatosclerosis secondary to venous insufficiency.

Secondary:

To assess the effect of copper stockings on skin condition in patients with lipodermatosclerosis secondary to venous insufficiency.

Methodology

This is a randomised controlled pilot study to assess the feasibility of copper impregnated stockings. All patients with CEAP classification 4 in both legs and venous disease identified by venous duplex will be recruited from the vascular clinics within Croydon Health Services over a period of three months. All patients will be given a patient information sheet describing the study prior to consent (Appendix 1 Patient Information Sheet). Patients will be giving adequate time to read the information. Informed consent and the agreement for photography of their legs will be obtained (Appendix 2 Informed Consent). Patients will be assessed at baseline and at 2, 4 and 8 weeks follow-up.

The inclusion criteria are:

- Male or female patients
- CEAP classification 4 in both legs
- Venous disease identified by venous duplex
- Ability to understand and read the patient information sheet (in English)
- Ability to give informed consent

The exclusion criteria are:

- Inability to give consent
- Pregnancy
- Current ulceration
- Wilson's disease
- Allergy to copper
- Arterial insufficiency of the lower extremities

<u>Copper impregnated stockings</u>

All patients will be asked to wear compression stockings (14-18mmHg). These closed-toe and below-the-knee stockings are made of 88% nylon, 5% elastin, and 7% spandex and come in various sizes. One of the pair will have copper oxide ions permanently attached to

the nylon fibres and these stockings will contain 2-3% copper ions. The patients will wear a copper stocking on one leg (study leg) and a non-copper stocking on the other (control leg). Both the patients and the clinicians will be blinded to the copper impregnated stocking.

Randomisation

All stockings are marked with an 'L' for the left or 'R' for the right foot. The manufacturer has randomly marked the copper stockings with an 'L' or 'R' and paired these with a non-copper stocking. A closed envelope will contain the unique numbers of all the pairs of stockings and the information on which sock contains the copper. This envelope will remain closed for the whole recruitment period.

Patient data, history and physical examination:

Demographic data such as age, ethnicity, height and weight will be collected (Appendix 3 Datasheet). Past medical history such as concomitant (chronic) diseases and the use of medications will be obtained. At each visit, subjective symptoms will be obtained using the Aberdeen Varicose Veins Questionnaire (AVVQ). For obtaining objective signs, the CEAP classification and the Venous Clinical Severity Scoring (VCSS) will be performed for grading the severity of the venous insufficiency per leg individually, and photographs with the Eykona® 3D camera will be taken. All datasets will be coded and anonymised. The data will be stored in a secure room within the Trust. All electronic data will be stored within password protected IT system within the Trust, which is only accessible by the clinical and research team.

Aberdeen Varicose Veins Questionnaire

This questionnaire is specific for varicose vein disease but it also addresses important elements of venous insufficiency in general. The AVVQ (appendix 4 Datasheet) is a validated questionnaire and it consists of 13 questions on signs and symptoms such as pain, oedema, itching, purple discoloration, eczema and skin ulceration. It also addresses social

issues such as compression stocking usage and the effect of the disease on daily life. The AVVQ is the only validated questionnaire on vascular disease where most questions address each leg separately and therefore provides the ability to compare the two legs. The scoring of the questionnaire is from 0, which indicates no effect on the patient, to 100, which indicates a severe effect.

CEAP

Chronic venous disease can be classified with the clinical, aetiologic, anatomical, and pathophysiological (CEAP) classification (appendix 4 Datasheet). The clinical element is scored from 0 to 6 with increasing disease severity. The aetiological element indicates if the venous disease has a congenital, primary or secondary origin. The anatomical element denotes if the veins involved are superficial, deep or perforating. The pathophysiological element indicates the presence of reflux or obstruction.

Venous Clinical Severity Scoring (VCSS)

The VCSS is an extension of the CEAP classification and has been designed as an evaluative tool for the assessment of CVD. The VCSS (appendix 4 Datasheet) consists of 10 categories, pain, varicose veins, oedema, skin pigmentation, inflammation, induration, ulceration (number, size and duration) and use of compression therapy, which are scored on a severity scale from 0 to 3.

Eykona® Wound Measurement System

Skin changes associated with lipodermatosclerosis such as erythema, induration, hyperpigmentation and white atrophy, will be measured using the Eykona® Wound Measuring System (Type EYK10001). This system (Appendix 4 Datasheet) contains a 3D portable camera with software that enables precise measurements of wound size and tissue condition. Photographs will be taken at each visit. The length and width are measured and the surface area of the different skin changes will be calculated.

Statistical analysis

Statistical analysis will be performed using SPSS version 20.0 or higher. The CEAP classification, the Venous Clinical Severity Score and the AVVQ score at the 2, 4, and 8 weeks assessment will be compared with the baseline scores. The length, width and surface area of the skin condition from the leg with the copper will be compared with the control leg and the measurements at the 2, 4, and 8 weeks assessment will be compared with the baseline measurements. Paired t-test will be used for continuous data at baseline and a multilevel (mixed) regression model will be used to analyse the change over time.

Sample size calculation

The sample size for this study will be 15. This number is based on the prevalence of the disease in this hospital over three months' time. There is no existing data available to allow a sample size calculation. The data collection of this pilot study will enable power calculation for a larger multicentre study.

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