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Study Protocol

The Evaluation of Pain Severity in the Lower Limb Caused by Chronic Venous Insufficiency

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Abstract

This protocol describes the use of advanced technologies for the assessment of pain severity in patients with chronic venous insufficiency pre and post intervention and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator. This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate. Aim: To investigate the effectiveness of surgical intervention plus exercise on the severity of leg pain. To identify the accuracy of CHEPS in the assessment of leg pain associated with CVI. To evaluate the reliability of Visual scale analogue in measuring the severity of pain in CVI? To evaluate the effectiveness of PPG, a non-invasive technique in the diagnosis and treatment of patients with CVI. The evaluation of pain severity in the lower limb caused by Chronic venous insufficiency. Design: Cohort observational study. Outcome Measures: Reflux flow, varicose veins, chronic venous insufficiency, leg pain, objective tool CHEPS, PPG. U/S: SFJ, LSV Diameter (Cm), Velocity (Cm/Sec), PPG: Rf Refilling Time (Sec), Vas, Pain Severity: Mild, Moderate, Severe. CHEPS measures: latency W/m2, amplitude (M). Population: Adult patients with chronic venous insufficiency. Eligibility: Adults (>18years) with chronic venous insufficiency. Duration: 18 months

Key words:Ultrasound, varicose vein, leg pain, chronic venous insufficiency, vascular imaging, medical imaging, CHEPS, PPG

Introduction

Background

Chronic Venous Insufficiency (CVI) is a condition that is characterised by having venous walls or valves in the lower limbs that are inefficient. As a result, the veins do not adequately return blood to the heart, and it pools in the veins, creating a kind of blockage or static state [1]. This leads to varicose veins, enlarged, twisted, and often painful veins in the lower limb [2]. While technically, this can occur in any vein in the body, it is most common in the legs because of the increased pressure that occurs in veins during standing or walking activities. This is a condition that affects primarily superficial veins and can cause significant discomfort [2]

Chronic venous insufficiency occurs in approximately 40% of the population [1] .Correspondingly, varicose veins of the lower limbs are a significant problem for a large percentage of the population. In fact, an estimated third of the UK population, or between 10 and 40 % of adults between the ages of 30 and 70 years of age, are affected by venous insufficiency and related varicose veins [1]. This is significant because it can introduce more than discomfort. Additionally, are indicators of poor blood flow or vascular insufficiency. The current literature review will seek to determine the current, most promising treatments and what gaps exist in the existing literature as it relates to the assessment of pain with venous insufficiency as it relates to treatment.

Risk factors for the development of CVI and Varicose Veins include age, gender, pregnancy, family history, obesity, and lifestyle [2]. More specifically, as a person ages they become in-

creasingly likely to suffer from varicose veins. Women, and especially women who are pregnancy, are also at increased risk. The hormonal changes that women experience, throughout their lifetime, increase the pressure inside veins while relaxing vein walls. Pregnancy also increases blood volume, enlarging the veins in the legs and increasing the risk of varicose veins [4]. Obesity, standing for long periods of time and a sedentary lifestyle can increase the pressure on the veins and decrease flow, resulting in an increased risk [4]. Finally, family history, or a genetic predisposition to CVI, increases the risk [4].

Early symptoms of venous insufficiency, more specifically, include feelings of heaviness in the limbs, discomfort and tension in the legs, or persistent itching. Additionally, as symptoms and severity advance, the symptoms include changes in the skin and venous ulceration. l If allowed to go untreated, Venous insufficiency can cause serious, if rare, complications as well [3]. These include ulcers, blood clots, and bleeding. Venous disease, which leads to venous insufficiency and varicose veins is a problem because it is not entirely understood, and further research is, as a result, required, especially as it relates to the practical improvement of venous tone and function.

Pain

The most common complaint related to venous disease and related insufficiency is pain [5]. This is important because it is directly related to patients' reduced quality of life [6]. However, there remains a fundamental lack of understanding of the mechanisms of pain or a lack of a way to measure pain in a way that is consistent from patient to patient.

Pain mechanisms relevant to vascular disease

A complex range of mechanisms underpins pain in patients with vascular disease. Nociceptive, inflammatory, and neuropathic mechanisms may all occur. Recognition of the predominant pathophysiological process driving pain in individual vascular disease patients is essential for successful pain management because the varied mechanisms warrant specific approaches to analgesic choice [7].

Nociceptive pain

Nociceptive pain occurs after thermal, chemical, or mechanical stimulation of peripheral nociceptors on unmyelinated C fibres or tiny myelinated Aδ fibres. It constitutes a physiological response to real or threatened non-neuronal tissue damage and reflects normal adaptive functioning of the somatosensory nervous system. It is typically a reversible type of pain that sub- sides when the insult is removed. In vascular patients, nociceptive pain is a key component of intermittent claudication (pain and cramping after repeated muscle action or exercise). A range of peripheral receptors (ion channels and G-protein- coupled receptors) found on Aδ and C fibres is involved in the generation of nociceptive pain. These include acid-sensing ion channels, responsive to calcium, and the transient receptor potential (TRP) channel family. The acid-sensing ion channels are important in the initial pain response but are also vital in con- version to chronic pain states and may therefore serve as targets for analgesic drug development [8,9].

Inflammatory pain

This type of pain constitutes the response of the somatosensory nervous system to tissue damage and inflammation. In the periphery, increased inflammatory mediators, such as cytokines and chemokines, sensitize local nociceptors, lowering their threshold for responsiveness (peripheral sensitization). This increased responsiveness results in potential stimulation of pain pathways after innocuous input and in exaggerated responses to noxious stimulation [9].

Pain modulated by the inflammatory response involves activation of a number of receptors and ion channels, with interactions between peripheral immune cells, alterations in local blood flow, and changes in the chemical and electrical activity of the peripheral afferent neurones [9,10].

The plasticity that underpins these changes is rapid (occur- ring in minutes) and is an almost inevitable consequence of surgery and tissue trauma. This upregulation of nociception should normally resolve as wound healing occurs. Maladaptive responses, including inadequate resolution of these changes after inflammation, are likely central to conversion from acute to chronic pain [10].

Neuropathic pain

Pain resulting from a lesion or disease of the somatosensory nervous system is termed neuropathic. The lesion may occur at the molecular, cellular, or tissue level and impact on function and structure of the somatosensory nervous system. The result is a combination of sensory loss and increased responsiveness to both noxious and innocuous stimuli. Positive phenomena, such as allodynia (pain after non-painful stimuli), hyperalgesia (heightened pain after painful stimuli), and hyperpathia (an eruptive pain extending beyond the duration of a stimulus), are common clinical features of neuropathic pain. In vascular patients' neuropathic mechanisms may underpin much of the chronicity in pain presentations. In particular, neuropathic pain is a key component in critical limb ischaemia, the associated ischaemic pain, and the persistent pain that may occur after surgery. There are characteristic changes in neuropathic pain, which include alterations in ion channels, G-protein- coupled receptors, neurotransmitters, and central activation [10,11].

Summary

This study will look at complex phenomena of pain. However, lack of consistency between Pain Symptoms and Clinical Severity Treatment. The present study is designed to investigate the factors associated with pain and any improvement following treatment.

Rationale for Current Study

The individual's quality of life is significantly influenced by chronic venous insufficiency. The present study is therefore aimed at evaluating the effectiveness of surgical intervention and exercise on the level of pain and the impact of early diagnosis upon the quality of life of CVI patients. Identifying, if CHEPS could be used as a significant tool for measuring the severity of pain in a patient with CVI.

Research Questions

Principal research questions

Does surgical intervention plus exercise improve the severity of leg pain

Secondary research questions

Is a novel (CHEPS) tool considered reliable for the assessment of pain in a patient with chronic venous insufficiency?

Research Hypothesis

Primary hypothesis

Surgical intervention plus exercise will improve leg pain in patients with CVI

Secondary hypothesis

Contact heat evoked potential (CHEPS) is a reliable tool to assess pain in a patient with chronic venous insufficiency.

Study Objectives

1-. To compare the outcome of pain threshold and quality of life between the group A conservative treatment (compression stocking and exercise) and the group B (surgical treatment: Laser ablation and exercise) To identify the accuracy of CHEPS in the assessment of leg pain associated with CVI.

2- to compare results of Ultrasound, PPG, CHEPS, VAS and MCGILL questionnaire, between group A and group B

Secondary Research Objectives

1.Predicting pain-related improvement in patients with venous insufficiency after endo-venous ablation plus exercise.

2.To evaluate the reliability of Visual scale analogue in measuring the severity of pain in CVI

3.To evaluate the effectiveness of the PPG non-invasive technique in the diagnosis of patients with CVI.

4.To evaluate the level of pain in patients with CVI before and after treatment

Study Design

Methods

Cohort observational study

Duration: 18 months.

The Initial sample size of this study will be 84 participants.

This study will take place in the vascular departments at Imperial College Healthcare NHS Trust, Hammersmith hospital Campus.

We plan to recruit 84 patients who meet the inclusion criteria and have chronic venous insufficiency, and who have an appointment for routine vascular assessment.

Whilst patients are reviewed routinely post-surgery at 12 weeks and 16 weeks, we arranged to carry out 3 assessments via outpatient clinic at 0, 12 and 16 weeks

These participants will be divided into two groups as follows:

Group A (Conservative treatment: compression stockings and exercise)

This group of patients will be from those who are offered vein intervention (Laser Ablation) but refused this option. 42 Participants will be assessed by using venous blood flow tools (ultrasound and PPG) and pain severity tools (MCGILL questionnaire, VAS, and CHPES).

The timeline will be as follows:

A) Baseline 0 week before conservative treatment

B) 12 weeks measurements (routine post treatment appointment)

C) 16 weeks after undergoing conservative treatment

Group B (Surgical treatment: Laser ablation and exercise)

42 Participants with chronic venous insufficiency and who have been accepted for surgical intervention with laser ablation will be assessed by using venous reflux tools (ultrasound and PPG) and pain severity tools (MCGILL questionnaire, VAS, and CHPES) as mentioned above.

This assessment will also be performed during three times periods:

A) Baseline 0 week before surgical treatment

B) 12 weeks measurements

C) 16 weeks

Recruitment Process

Suitable patients who meet the inclusion criteria in the outpatient department will be approached by their primary vascular team with an offer to participate in the study. If a patient is prepared to discuss their potential role in this research, then the researchers will discuss the study details at the patient's convenience. Recruitment will be completely voluntary and will not affect their routine care. This will be made clear during the discussion regarding the research, and again during the consenting process. Time will be made available for any questions and for the patient to consider recruitment in their own time. Patients will be required to sign their consent before any study-related procedures are carried out. Once done, their personal identifiable data will be coded and pseudonymised

Study group protocols

Protocols for varicose veins

A.Ultrasound protocol chronic venous insufficiency (CVI):

Reflux Assessment:

Ultrasound assessment will be involving:

B - mode = compressibility.

Colour mode = filling.

Pulse wave. = positive or negative.

Superficial Deep Venous Systems and perforators are performed with Multi-frequency 3- to 9-MHz linear transducer for more superficial Image and 2- to 5-MHz sector/curved array transducer for deeper field imaging. The exam will be done with the patient standing position. The limb being examined is externally rotated and the knee is slightly bent, the sapheno-femoral junction (SFJ), frequent femoral vein (CFV), and the origin of each femoral veins are identified, and guide compression of the calf or thigh is carried out to examine reflux. The Valsalva maneuver can be used for the equal purposes however this check is negated by means of a proximal competent valve. Automated rapid inflation/deflation cuffs may additionally also be used for eliciting reflux. They are essential when a preferred stimulus is needed to evaluate reflux parameters.

Next, the femoro-popliteal and calf veins are examined in the sitting position. Distal compression of the calf or foot (Lejar's Plexus) is used to check reflux in these areas. The superb saphenous vein (GSV) inside the saphenous compartment and small saphenous vein (SSV) within the triangular fascia are examined with intermittent calf compressions. Foot compression is used when examining the distal extent of the veins. All tributaries when incompetent is observed and their direction and connections are registered.

B -PPG protocol for venous assessment:

will assess overall venous blood flow in the leg. It will also give information about your muscle pump power, i.e. the ability of the calf muscles to pump venous blood back to heart.

Pain assessment protocols

A -cheps protocols

Contact heat evoked potential (CHEP) scan is an objective tool to measure small nerve fibre function. This device will assess the pain threshold using thermal sensitivity.

C: Pain Scoring

C1: VAS Protocols

Visual analogue scale (VAS): a tool used to measure intensity of pain. patients will be asked to record their maximum and average pain score before and after the treatment using a validated Visual Analogue Scale (VAS) by placing a mark on a 100-mm VAS.

C2: Questionnaire MCGILL

The McGill Pain Questionnaire will be used to evaluate a person experiencing significant pain. It will be used to monitor the pain over time and to determine the effectiveness of any treatment.

Data management

Study specific data, which is non-identifiable, will be collected at Hammersmith - Vascular Laboratory on the Redcap case report form (CRF). Each participant will have a unique identification allocated to them which will be recorded on the CRF for reporting purposes. The only chief of investigator and Coinvestigators will have access to the code that links the pseudonymised study data to the patient's identifiable information to maintain participant confidentiality. The only chief of investigator and Coinvestigators at Hammersmith- Vascular Laboratory will have password-protected access to the study database. CRFs, clinical notes and administrative documentation will be kept on a confidential file cabinet in the files room at Hammersmith - Vascular Laboratory and held for 5 years after the end of the study. During this period, all data will be accessible to the competent authorities and the sponsor with suitable notice.

Clinical procedures

- Consent prior to scan
- Clinical data collection immediately after scanning.
- US and PPG
- CHEPS
- Peak systolic velocity (cm/s)
- Blood pressure (unit)
- Vessel diameter (mm).
- BMI

Participant Entry

Pre-registration evaluations PRE

venous disease.

Inclusion criteria

≥ 18 years age

- patients being treated in the Vascular Department (chronic venous insufficiency patients who have an appointment for the routine vascular assessment)

- ability to provide informed consent.

Exclusion criteria

-pregnant patients

-cancer

- Exclude anyone who is taking part in any other research

-Unable to give consent

Withdrawal criteria

Patient's choice

Adverse events

Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

None are expected during this study.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

•Results in death

•Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

•Requires hospitalization, or prolongation of existing inpatients' hospitalisation

•Results in persistent or significant disability or incapacity

•Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Reporting procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

Non-serious AEs

All such events, whether expected or not, should be recorded.

Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, death due to end-stage renal failure related conditions and hospitalizations for elective treatment of a pre-existing condition does not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

•'related', ie resulted from the administration of any of the research procedures; and

•'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office. Contact details for reporting SAEs RGIT@imperial.ac.uk; m.aslam@imperial.ac.uk

Assessment

The exam will be performed at the time when patients are attending their routine outpatient appointments. This procedure is expected to take approximately 45 minutes in addition to their normal scan time. There will be no follow-up appointments.

Reporting incidental finding during this research will depend on the participant preference.

Incidental findings in research participants who want to be informed of any incidental abnormalities that might affect their health will be reported by a physician in the research team. If the findings will have a major impact on patient's medical management then the doctor treating her/him will be informed and participant removed/withdrawn from the study. On the other hand, incidental findings in participants who do not want to be informed of any incidental abnormalities will not be reported. Results from this study will not have a direct benefit to the patient, but lay summary of aggregated results can be provided to all patients.

Study closure

The study will be closed (end of study definition) when patient recruitment is completed and all data have been received.

Study outcome measures

Primary outcome measures

- Ultrasound: SFJ, LSV diameter (cm)
- Peak systolic velocity (cm/s).
- End diastolic velocity (cm/s).
- PPG: RF REFILLING TIME (SEC).
- VAS, PAIN SEVERITY: MILD, MODERATE, SEVERE.

Secondary Outcome Measures

- Pulsatility index (PI).
- Acceleration time (AT) (ms).
- Acceleration ratio (AR).
- Measured length (cm).
- Measured width (cm).

Statistics and Data Analysis

Sample Size

Group A = 42

Group B = 42

Total = 84

We will plan to recruit 84 patients with chronic venous insufficiency who have an appointment for the routine vascular assessment. This study will take place in the vascular departments at Imperial College Healthcare hospital Hammersmith hospital.

Initially we seek to recruit approximately 84 participants.

Analysis plan

All analyses will be performed based on the parameter's values. The analysis population will include all participants enrolled in the study.

This calculator uses a number of different equations to determine the minimum number of subjects that need to be enrolled in a study in order to have sufficient statistical power to detect a treatment effect. 1

Before a study is conducted, investigators need to determine how many subjects should be included. By enrolling too few subjects, a study may not have enough statistical power to detect a difference (type II error). Enrolling too many patients can be unnecessarily costly or time-consuming.

Data Analysis

All analyses will be performed based on the parameter's values. The analysis population will include

All participants enrolled in the study. Dividing 84 participants in to two main groups and Comparisons between the groups.

Participants will be divided into two clinical groups, each group composed of 42 patients.

1. Group A control (Conservative treatment: compression stocking and exercise)

2. Group B (surgical treatment: Laser ablation and exercise)

The methodology will be used Linear Mixed Models for repeated measures adjusting for group, gender and age. Bonferroni correction will used for the comparisons between groups. The data will be analysed by an experienced statistician using appropriate statistical package. 0.05 will be considered to indicate statistical significance.

Statistical power is determined by the following variables:

Baseline Incidence: If an outcome occurs infrequently, many more patients are needed in order to detect a difference.

Population Variance: The higher the variance (standard deviation), the more patients are needed to demonstrate a difference.

Treatment Effect Size: If the difference between two treatments is small, more patients will be required to detect a difference.

Alpha: The probability of a type-I error -- finding a difference when a difference does not exist. Most medical literature uses an alpha cut-off of 5% (0.05) -- indicating a 5% chance that a significant difference is actually due to chance and is not a true difference.

Beta: The probability of a type-II error -- not detecting a difference when one actually exists. Beta is directly related to study power (Power = 1 - þ). Most medical literature uses a beta cut-off of X0% (0.X) -- indicating a X0% chance that a significant difference is missed.

Abbreviations

ABPI: Ankle-Brachial Pressure Indices; BMI: Body mass index; B-mode: Brightness Mode; CFV: Common femoral vein; DVT: Deep Vein Thrombosis; DM: Diabetes Mellitus; DUS: Duplex Ultrasound; LSV: Long Saphenous Vein; LSV: Long saphenous vein; PSV: Peak systolic velocity

Regulatory Issues

Ethics approval

The Chief Investigator has obtained approval from the xxxxx Research Ethics Committee and the HRA. The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the provisions of the Data Protection Act 2018 and the General Data Protection Regulation. All patient identifiable data collected from the study will be kept on a password protected file on a password protected NHS computer logon in the vascular laboratory in Hammersmith hospital – Imperial College London Healthcare NHS Trust. This data will only be available to the researchers. Any patient identifiable data extraction from medical notes will be performed in the clinical storing area. The notes and data will be stored in the vascular laboratory in similar fashion to study data. This data will only be available to the researchers. All patient identifiable data on manual files will be stored in the Vascular laboratory confidential file cabinet at Hammersmith Hospital-Imperial College London Healthcare NHS Trust. This data will only be available to the researchers. All researchers accessing identifiable patient data owe an equivalent duty of confidentiality to a health professional. All data outside the vascular laboratory will be fully coded with no patient identifiers (completely pseudoanonymised) and this pseudoanonymised data will only be available to the researchers and statistical team. A study code will be allocated to the patients and this will occur at consenting. This code will help protect confidentiality and will be stored on a password protected file on a password protected NHS computer logon in the vascular laboratory in Hammersmith Hospital-Imperial College London Healthcare NHS Trust. This data will only be available to the researchers.

Acknowledgements

Indemnity

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Resolution for NHS Trusts in England, which apply to this study

Sponsor

Imperial College Healthcare NHS Trust will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study. Sponsor's/protocol number: 21HH6669. NRES reference: XXXX. NCT number: NCT04794712. IRAS Project ID 310190

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Saudi Arabian Cultural Bureau in London is funding this study. No payment will be made to participants and to researchers.

Audits

The study may be subject to inspection and audit by Imperial College London Healthcare NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

Study Management

The day-to-day management of the study will be co-ordinated through Dr Mohammed Aslam (CI).

Publication Policy

The results of this study may be published in peer-reviewed scientific journals or conference presentations.

Study Management Group

Chief Investigator: Dr Mohammed Aslam; Co-investigators: Mrs Bedor Alsoliman; Statistician: Joseph Eliahoo; Study Management: Dr Mohammed Aslam.

Sponsor

Imperial College Healthcare NHS Trust is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact: Research Governance and Integrity Team. Imperial College London and Imperial College Healthcare NHS Trust. Funder: Saudi Arabia Cultural Bureau.

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