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Application of autologous peripheral blood-derived stem cell/progenitor cell (CD34+) + stem cells and hyperbaric oxygen therapy for patients with severe limb ischemia

Submission date
18/09/2017

Recruitment status
Stopped

Registration date
03/10/2017

Overall study status
Stopped

Last Edited
22/05/2023

Condition category
Circulatory System

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Peripheral arterial occlusive disease (PAOD) is a narrowing of the arteries other than those that supply the heart or the brain, most commonly affecting the legs. It affects up to 15% of adults over the age of 55. Without appropriate and aggressive treatment, the one-year mortality (death) rate of PAOD has been reported to be as high as 25%. Patients with PAOD may develop critical limb ischemia (CLI) at the late stage of the disease (reduced blood flow) and lose their limb. Current treatment of PAOD consists of lifestyle changes, medication, or surgery. Treatment failure can lead to limb loss and a high economic/family burden for care following amputation. In fact, about 30% of patients cannot be treated with any of abovementioned methods and the only option is amputation, especially in diabetic patients. Currently, although surgery has been used for the treatment of CLI with an acceptable success rate, the overall clinical outcomes remain dismal. Therefore, there is still an unmet need for treatment of PAOD at present. The aim of this study is to find out whether a combination of stem cells and hyperbaric oxygen (HBO) treatment may be a treatment option for patients with limb ischemia. The combined treatment may promote blood vessel growth (angiogenesis) and prevent disease progression and amputation.

Who can participate?
Patients aged 20-80 with severe limb ischemia

What does the study involve?
Participants are randomly allocated to either the control group or the experimental group. The control group is treated with standard antiplatelet drugs plus HBO treatment. The experimental group is treated with HBO treatment combined with a transfusion of their own stem cells. HBO treatment involves breathing pure oxygen at high pressure for 100 minutes once daily for ten days.

What are the possible benefits and risks of participating?
The stem cell treatment may help to save the affected limb. The risks of stem cell infusion are irregular heart rhythm, heart attack, heart failure, brain ischemia, bleeding, anemia, worsening kidney function, electrolyte imbalance and malignancy. However, the reported rate of these side effects is less than 1%. The possible side effects from HBO treatment are serous otitis media (glue ear; 2%), tympanic rupture (eardrum rupture; <1%), nasal congestion, temporary reversible blurred vision, cataract and seizure.

Where is the study run from?
Kaohsiung Chang Gung Memorial Hospital (Taiwan)

When is the study starting and how long is it expected to run for?
December 2016 to May 2023

Who is funding the study?
Ministry of Science and Technology (Taiwan)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
Combination autologous peripheral blood-derived stem cell/progenitor cell (CD34+) + stem cells and hyperbaric oxygen therapy for the treatment of severe limb ischemia: investigate the safety and efficacy

Study objectives
The combination autologous peripheral blood-derived stem cell/progenitor cell (CD34+) + stem cells and hyperbaric oxygen therapy for severe limb ischemia may be a therapeutic option for patients with limb ischemia.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Chang Gung Memorial Hospital, 08/02/2017, ref: 201601217A0

Study design
Prospective single-center interventional 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 the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Severe limb ischemia

Interventions
Patients will be randomized in a 1:1 ratio. The randomization procedure is stratified by the research department and the permuted block design within strata is utilized. The study treatment is randomly assigned according to the randomization list held by a biostatistician and using sealed envelopes provided to the core laboratory. The envelopes will be opened only when the next study subject is enrolled. Concealment is realized in a way that only team members of the research department will have access to the randomization code. All members have signed an agreement that the randomization code will be kept confidential.

Control group: standard antiplatelet plus HBO therapy (n=20)
Experimental group: HBO therapy combined with intraarterial transfusion of autologous peripheral blood-derived stem cell/progenitor cell (CD34+) stem cells: 1 x10^7 - 3x10^7 cells

Hyperbaric oxygen (HBO) therapy will be arranged at the time of admission with a dose of 2.5 Bar for 100 minutes, frequency once daily and duration ten days.

Intervention Type
Mixed

Primary outcome measure
Limb salvage, defined as alive without amputation within 12 months

Secondary outcome measures
1. Relief of rest pain was measured using Canadian cardiovascular society grading of angina pectoris (CCS) score at 1 week, 1 month, 3, 6, 9 and 12 months after hospitalization or enrollment
2. Ankle brachial index (ABI) was measured by duplex echography at 1, 3, 6 and 12 months after hospitalization or enrollment
3. New collateral vessel formation measured by magnetic resonance angiography (MRA) at 6 and 12 months
4. The amount of O2 diffused from capillaries through the epidermis of diseased foot, measured using transcutaneous oximetry (TcPO2) at 6 and 12 months
5. Walking distance and cardiopulmonary function measured using six-minute walk test (if possible), and quality of life measured using Short Form-36 (SF-36) at 1, 3, 6 and 12 months after hospitalization or enrollment

Safety endpoint: adverse events and severe adverse events (death or hospitalization) of study patients measured using case report form at clinical visit every three months or as necessary

Overall study start date
20/12/2016

Completion date
31/05/2023

Reason abandoned (if study stopped)
A total of 5 patients were selected in the phase I trial, 1 patient was failed in the screen stage, and others were enrolled. Due to not testing the TcPO2 measurement, 4 patients were unable to be treated and followed up, and this trial period will expire on 31/05/2023. Therefore, the clinical trial will be terminated.

Eligibility

Key inclusion criteria
Age between 20-80 with severe limb ischemia due to diffuse atherosclerosis. Inclusion criteria for the study were all of the following:
1. Ischemic peripheral vascular disease with rest pain defined as pain that occurs at night and at rest. Clinical evaluation by Fontaine classification (Fontaine stage III: rest pain, stage IV: ulcer and/or necrosis)
2. Ankle–brachial index (ABI)<0.7
3. A non-surgical candidate for revascularization, for example, diffuse multi-segment disease, inability to locate a suitable vein for grafting, or extensive infra-popliteal disease not amenable to a vascular graft
4. The image analysis includes the MRA or angiocardiography by diagnostic intravascular catheter (depended on clinical results). The above results show that obstruction more than 75%

stenosis will considerate into this test
5. Use of contraception
6. The trialists accept the laboratory data within 3 months since initial screening
7. TcPO2<45mmHg

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
40 patients (20 patients treated with HBO only and the other 20 patients treated with HBO and EPC)

Key exclusion criteria
1. Age <20 y/o or >80 y/o
2. Pregnant or feeding women
3. Adventitious agents (HIV, syphilis, hepatitis B virus, hepatitis C virus, will be excluded. If the examination result is positive, Centers of Disease Control will be notified by law)
4. Infective disease
5. Myocardial infarction within 3 months, heart failure, or functional class IV
6. Malignant or hematologic disease, or severe disease with life span less than one year
7. End stage renal disease or eGFR less than 30 ml/min
8. Patients after treatment improved in the case using bypass surgery or stenting ischemic cardiac catheterization
9. Receiving other clinical trials monitor
10. Patients can’t receive therapy or examination in this study
11. Blood sugar and blood pressure control poorly (SBP>160 mmHg, AC F/S>200mg/dL and PC F/S>300mg/dL)
12. Not suitable for cardiac catheterization
13. Contraindications to G-CSF or HBO
14. Patient is unconscious
15. Untreated active infection
16. Those who undergo major surgery within one month
17. Patients with stroke or unstable angina within 3 months
18. Unsuitable candidates after initial evaluation
19. Those of unsuitable for HBO therapy, e.g., active pulmonary tuberculosis, spontaneous pneumothorax etc
20. TcOP2 ≥46mmHg

Date of first enrolment
01/10/2017

Date of final enrolment
31/03/2020

Locations

Countries of recruitment
Taiwan

Study participating centre
Kaohsiung Chang Gung Memorial Hospital
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Sponsor type
Government

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Funder(s)

Funder type
Government

Funder Name
Ministry of Science and Technology, Taiwan

Alternative Name(s)

Ministry of Science and Technology, R.O.C. (Taiwan), Ministry of Science and Technology of Taiwan, MOST

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Taiwan

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
30/09/2021

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date