The application of contrast-enhanced ultrasound to facilitate thrombolysis in patients with acute peripheral arterial occlusions.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON46851

Source
ToetsingOnline

Brief title
MUST Trial

Condition

- Embolism and thrombosis

Synonym
thrombosis, Vascular occlusion

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,Lamepro

Intervention

Keyword: Microbubbles, Occlusion, Thrombolysis, Ultrasound

Outcome measures

Primary outcome

Main endpoints will be the duration of thrombolysis needed for uninterrupted flow in the thrombosed native artery or bypass graft with outflow through at least 1 crural artery and microcirculation of the lower limb as measured by Laser Doppler Flowmetry on the skin of the lower limb. Furthermore, Severe Adverse Events (haemorrhagic complications, allergic reactions, in hospital mortality directly related to the treatment) and amputation-free rate at 6 months.

Secondary outcome

Secondary endpoints will be the success rate, distal thromboembolic complications, other complications, 30 day mortality rate, conversion to open surgery, duration of hospital admission, serum fibrinogen concentrations, pain scores and quality of life.

Study description

Background summary

Acute peripheral vascular disease can be caused by a blood clot blocking an artery in an arm or leg. This is an emergency situation that can result in amputation or be life threatening if not treated promptly. Infusion of lytic agents, such as urokinase and alteplase, can restore blood flow by dissolving the clot as a less invasive alternative to conventional surgical reconstruction, i.e. thrombolysis. In comparison with the lysis of small

arterial occlusions in for example patients with myocardial infarction, larger arterial occlusions in vascular surgery patients require higher doses of lytic agents and infusion over a longer period of time. However, this technique is time consuming (days), requires repeated angiography for treatment evaluation risking kidney failure and most importantly is accompanied by the risk on major bleeding complications, such as stroke. As a result this leads to high morbidity and mortality rates and a large impact on patient burden. Improvement of this therapy is therefore highly needed.
A potential accelerater of thrombolytic therapy is contrast-enhanced ultrasound. Contrast-agents, initially used as diagnostic tool could also be applied therapeutically to speed up thrombolysis. Their oscillating behavior could induce mechanical forces on the clot surface making the thrombus more susceptible to thrombolytics. This could reduce therapy time and lower the required dose of lytic agents leading to a lower risk of bleeding complications and decreased patient burden.

Study objective

The primary objective is to test whether thrombolysis with additional contrast-enhanced ultrasound is applicable in patients with peripheral arterial occlusions. The secondary objectives are to investigate the safety of microbubble and ultrasound enhanced intra-arterial thrombolysis and if it is logistically feasible in our university hospital.

Study design

Phase-II trial: 20 patients will all receive the experimental protocol. The first 10 patients were evaluated with the use of urokinase as thrombolytic therapy. Because of manufacturing delivery problems, the Urokinase has been replaced by Alteplase.

Intervention

The experimental protocol consists of the standard thrombolysis protocol, i.e. the local placement of a catheter and sheath in the *angio-room* just near the occlusion or thrombus of the affected artery and infusion of alteplase and heparin. In this study additional ultrasound contrast-agents will be intravenously injected and local ultrasound will be applied at the site of occlusion during the first hour of therapy.

Study burden and risks

The additional burden for patients participating in this study are estimated to be minimal seen the fact that the experimental protocol is executed during the first hour of standard thrombolytic treatment. The risk of the application of ultrasound with contrast is estimated minimal, as the technique has been used

safely in clinical practice as diagnostic tool for years. Furthermore, the total dose we administer during one hour is lower then safely administered as bolus injections in humans as reported before without the occurence of adverse events. The additional measurements during treatment and follow up are minimally invasive and require little extra time of the patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Men and women older than 18 years and younger than 85 years old
* Patients with a maximum of 2 weeks complaints due to lower limb ischemia due to thrombosed/occluded iliofemoral, femoropopliteal or femorocrural native arteries or femoropopliteal or
femorocrural venous or prosthetic bypass grafts

* Anatomic suitability duplex ultrasound in case of iliac occlusion
* Patients fit for thrombolysis i.e. with acute lower limb ischemia class I and IIa according to the
Rutherford classification (see attachment II)
* Patients understand the nature of the procedure and provide written informed consent before enrolment
in the study

Exclusion criteria

* Patients with clinical complaints of acute lower limb ischemia due to thrombosis of the iliofemoral, femoropopliteal or femorocrural native arteries, or femoropopliteal or femorocrural venous or prosthetic bypass grafts more than 2 weeks
* Patients with iliac occlusions anatomically not suitable for duplex ultrasound
* Patients with thrombosed popliteal aneurysms
* Patients with contra-indications for the administration of antiplatelet therapy, anticoagulants or thrombolytics
* Recent (less than 6 weeks) ischemic stroke, cerebral bleeding or myocardial infarction
* Patients with recent (less than 6 weeks) surgery
* Severe hypertension (diastolic blood pressure greater than 110 mm Hg, systolic blood pressure higher than 200 mm Hg)
* Current malignancy or severe comorbid condition with a life expectancy of less than 6 months
* Patients with uncorrected bleeding disorders (gastrointestinal ulcer, menorrhagia, liver failure)
* Women with child-bearing potential not taking adequate contraceptives or currently breastfeeding
* Pregnancy
* Patients who are currently participating in another investigational drug or device study
* Patients younger than 18 years or older than 85 years
* Patients with contra-indications for Luminity microbubbles i.e.
* Hypersensitivity to perflutren or other components of Luminity
* Recent acute coronary syndrome or clinically unstable ischemic cardiac disease, including: evolving or ongoing myocardial infarction, typical angina at rest within last 7 days, significant worsening of cardiac symptoms within last 7 days, recent coronary artery intervention or other factors suggesting clinical instability (for example, recent deterioration of ECG, laboratory or clinical findings), acute cardiac failure, Class III/IV cardiac failure, or severe rhythm disorders
* Patients known to have right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure >90 mmHg), uncontrolled systemic hypertension, and in patients with GOLD Stage IV COPD, diffuse interstitial fibrosis or adult respiratory distress syndrome.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-07-2017
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	alteplase
Generic name:	activase
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	microbubbles
Generic name:	Perflurtren
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	urokinase
Generic name:	medacinase
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	02-07-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-003469-10-NL
CCMO	NL46636.029.14