Investigation of plaque vulnerability: Identification of atherosclerotic plaque angiogenesis using Bevacizumab-800CW and optoacoustic imaging: a single center proof of concept study (CAROTID-OPTOLIGHT)

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* To investigate whether it*s feasible to detect within the carotid artery the carotid plaques using optoacoustic imaging with the innovative MSOT Acuity Echo in patients with symptomatic carotid stenosis. * To investigate whether the VEGF-targeted...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular therapeutic procedures
Study type	Observational non invasive

Summary

ID

NL-OMON45786

Source
ToetsingOnline

Brief title
Carotid Optolight

Condition

- Vascular therapeutic procedures
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
atherosclerotic plaque, Carotid plaque

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Tracer

Intervention

Keyword: Carotis, fluorescence, fluorescence guided imaging, optoacoustic imaging

Outcome measures

Primary outcome

- To investigate whether it*s feasible to detect the carotid arteries and carotid plaques using optoacoustic imaging with the MSOT Acuity Echo in patients with symptomatic carotid stenosis.

- Pre-operative detection of atherosclerotic plaques in carotid stenosis with VEGF-targeted Bevacizumab-800CW using NIRF, to evaluate if upregulated VEGF within the atherosclerotic plaque can be detected non-invasively, in which duplex findings and patients history are considered the gold standard.

Secondary outcome

- Presence of fluorescent signal when endarterectomy is performed.

Study description

Background summary

This project consists of the realization followed by the clinical validation of a procedure dedicated to detect vulnerable atherosclerotic plaques in symptomatic carotid stenosis. If in the future it would be possible to detect a symptomatic carotid atherosclerotic plaque non-invasively (i.e. those plaques resulting in cerebrovascular accidents and/or transient ischemic accidents), this would strongly improve risk assessment among this large cohort of

patients. At the moment, indications for intervention are primarily based on degree of stenosis, and not on degree of vulnerability. Symptomatology is considered, but clinicians are not capable of predicting the consequences of a first event, while two thirds of all patients with a major stroke are not preceded by previous minor symptoms. Previous trials (NASCET and ECST) showed a significant absolute risk reduction for symptomatic patients with a stenotic lesion of the internal carotid artery greater than 70% after the performance of a carotid endarterectomy (CEA; excision of the atherosclerotic plaque). However, surgery can be associated with significant morbidity and even mortality. On the other hand, reliable prediction prior to surgery whether an atherosclerotic plaque is going to become symptomatic could also prevent unnecessary surgery, which again significantly reduces morbidity and mortality. In literature and our preliminary ex vivo data with a nuclear imaging tracer 89Zr-Bevacizumab, it appears that vulnerable atherosclerotic plaques (i.e. those likely to become symptomatic) have an increased rate of angiogenesis at the site of the rupture (i.e. the site of the vulnerable plaque) which expose highly upregulated Vascular Endothelial Growth Factor-A (VEGF-A) production as part of the inflammatory response within the plaque and subsequently which can be visualized with a tracer targeting specifically VEGF-A.
An intraoperative near-infrared fluorescence (NIRF) imaging camera, among a NIR fluorescence endoscopy system, and the use of the optical contrast agent Bevacizumab-800CW in now more than 250 patients has been evaluated for its feasibility to detect tumor lesions in patients with colorectal cancer, colon polyps, Barret*s esophagus, peritoneal carcinomatosis of colorectal cancer origin and breast cancer. These studies showed that bevacizumab-800CW is safe in clinical use and feasible to detect even small tumor lesions with a high sensitivity. While Bevacizumab-800CW can also detect the soluble ligand VEGF-A, as shown by ex vivo analyses of excised CEA specimen, we aim to investigate whether systemic administered Bevacizumab-800CW can be applied to patients preoperative for the detection of vulnerable plaques by non-invasive optoacoustic imaging and subsequently ex vivo mesoscopic imaging for validation purposes. The primary objective for the proposed study is to achieve pre-operative detection of the atherosclerotic plaque for patients with a symptomatic carotid artery stenosis by non-invasive optoacoustic imaging. In this study we will introduce the following concept: a preoperative non-invasive optoacoustic-scan guided by the Bevacizumab-800CW targeted VEGF-A. This will help us to detect if and at what time point within the atherosclerotic plaque there is an upregulation of angiogenesis which can cross-correlated by ex vivo analyses of characteristics of the vulnerable plaque (i.e. atheroma, foam cells, influx of activated macrophages and angiogenesis as a result of pro-inflammatory responses present in the plaque). The end-goal of the proposed dual pre- and intra-operative imaging procedure is to prove that the symptomatic carotid atherosclerotic plaque can be accurately and safely detected by VEGF-A targeted optical imaging agents. In addition, this study serves as a step-up to a larger non-invasive VEGF-A targeted optical imaging study expanding the detection technology by using a new non-invasive multispectral optoacoustic detection system. Ultimately, VEGF-A targeted

imaging in carotid stenosis could be used to predict vulnerability of the atherosclerotic plaque non-invasively in order to select those patients who will benefit the most of a surgical procedure.

Study objective

* To investigate whether it*s feasible to detect within the carotid artery the carotid plaques using optoacoustic imaging with the innovative MSOT Acuity Echo in patients with symptomatic carotid stenosis.
* To investigate whether the VEGF-targeted optical imaging agent Bevacizumab-800CW is able to detect VEGF upregulation as a characteristic of the vulnerable plaque in carotid tissue by means of pre-operative Bevacizumab-800CW optoacoustic imaging in patients with symptomatic carotid stenosis cross-correlated by ex vivo microscopic analysis.v

Study design

Study design: Interventional phase 1 technical feasibility study: non-randomized, open label, uncontrolled with single group proof of concept study. This study will be carried out at the University Medical Center Groningen, Department of Surgery and Department of Nuclear Medicine and Molecular Imaging. Further analysis of sections of the plaques will be done at the Department of Pathology at the UMCG and by the Helmholtz Institute, Biomedical Research Centre, München.

Study burden and risks

Burden - Time-investment: for most surgeries, patients are usually submitted one day prior to planned surgery. Patients will have to visit the UMCG one extra time for the tracer injection and the imaging procedure three days preoperative.
The burden associated with participation consists of: an intravenous injection of Bevacizumab-800CW 3 days before the surgical procedure. Additionally, the optoacoustic imaging procedure will take around 20-30 minutes.
Burden * Extra procedures: Patients will undergo intravenous injection of Bevacizumab and have to undergo one extra imaging procedure preoperative. The estimated time for imaging preoperative is 20-30 minutes.
Risks: The possible most likely adverse event for injection of Bevacizumab-800CW is a short elevation of blood pressure or an allergic and/ or anaphylactic reaction, as described in the IMPD. Most adverse events are transient and mild (nausea, vomiting, flushing, chest discomfort).
Risk * Medical Device: The optoacoustic imaging device uses a class IV laser and therefore is a risk for cornea and skin. Several measurements described below, are taken to reduce the risk of injuries to an absolute minimum.
Benefit: Patients will have no direct benefit from this study.

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

1) Patients with significant and symptomatic carotid stenosis who are scheduled for carotid endarterectomy as decided by the Multi-Disciplinary Carotid Board

Exclusion criteria

1) Medical or psychiatric condition that compromise the patient*s ability to give informed consent
2) Pregnant or lactating women
3) Significant renal (creatinine >110 µmol/L) dysfunction
4) History of iodine allergy or anaphylactic reactions to insect bites or medication or previous allergic reaction to bevacizumab

5) Presence or history of hyperthyroidism

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-04-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab-IRdye800CW
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	06-11-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Not approved

Date:	04-12-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2018-002662-39-NL
CCMO	NL66696.042.18