Determination of Diagnostic Accuracy and Added Value of Vasovist®-Enhanced Peripheral MRA in Comparison to Intra-arterial Digital Subtraction Angiography (i.a. DSA) in Patients with Peripheral Artery Disease

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To determine the accuracy of Vasovist® enhanced MRA of the leg with regard to quantitative grading of stenosis (=50%) compared to digital subtraction angiography (DSA, standard of reference (SOR))

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Observational invasive

Summary

ID

NL-OMON32267

Source
ToetsingOnline

Brief title
Vasovist MA-01

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Peripheral Artery Disease

Research involving

Human

Sponsors and support

Primary sponsor: University Heidelberg, University Hospital Mannheim
Source(s) of monetary or material Support: Universiteit van Heidelberg.

Intervention

Keyword: Digital Subtraction Angiography, MRA, Peripheral Artery Disease, Vasovist

Outcome measures

Primary outcome

This study will be conducted to determine the diagnostic accuracy of Vasovist* enhanced MRA in stenosis grading (<50%, >=50%) with regard to DSA as SOR for the defined segments. To have a sufficient prevalence of stenotic lesions all patients in this study have to be scheduled for therapeutic DSA of one leg.

Secondary outcome

The secondary efficacy variables are

• to determine the proportion of correct stenosis gradings (<50%, 50-99%, occlusion) of Vasovist® enhanced MRA compared to DSA

• to calculate the sensitivity and specificity (<50%, >=50%) of Vasovist enhanced MRA compared to DSA

• to correlate the determination of the length of stenosis (target) of Vasovist® enhanced MRA compared to DSA

• to correlate the description of the inflow, target, outflow of Vasovist® enhanced MRA (combined) compared to DSA [what is target lesion? , is it significant [>50%]?, is there disease in inflow segment?, determination of outflow y/n, significant disease in outflow]? Determined in a consensus reading)

• to determine the number of patients with change of therapeutic approach after reviewing Vasovist enhanced MRA compared to initial non-invasive angiography (MRA, CTA, US)

• to evaluate the diagnostic value (detection of target lesion y/n) of time-resolved first pass MRA in comparison to high-spatial resolution steady state MRA

• Additional venous pathologies: thrombus (y/n), venous aneurysm, varicosis (y/n), clinical relevance?

• to evaluate the diagnostic confidence of Vasovist enhanced MRA and DSA

Safety variables in this study will include the evaluation of physical examinations and vital signs as well as the assessment of adverse events (AEs) for Vasovist* enhanced MRA.

Study description

Background summary

Digital subtraction angiography (DSA) of the lower extremity is still the diagnostic modality of choice for the detection and grading of vascular lesions in patients with peripheral arterial occlusive disease (PAOD). It is characterized by a high inplane resolution of 0.3 mm^2 and also allows for dynamic imaging to show hemodynamic alterations. It is however also characterized by an approximately 1%-2% risk for severe side effects including stroke and even death. In addition, the administration of iodinated contrast agents in patients suffering from PAOD who are often concomitantly suffering from chronic renal failure carries the risk of contrast-induced nephropathy which leads to a substantially increased mortality in affected patients. The therapeutic DSA cannot be replaced by other modalities at this time.
In contrast, the technical advances and new MR-contrast agents have made high-spatial resolution magnetic resonance angiography (MRA) a challenger for diagnostic imaging. Conventional, extracellular contrast agents (ECCM), optimized MR-scanner and parallel imaging allow for submillimeter three-dimensional MRA of the lower extremity during the first pass of the

contrast agent. Due to the singularity of the first pass of ECCM and the fast extravasation of ECCM into the interstitium either no ultra-high spatial resolution MRAs can be acquired as the required measurement times exceed available imaging times. It is also not feasible to obtain dynamic images and high-spatial resolution images after a single injection of ECCM.
Intravascular contrast agents like gadofosveset (Vasovist®) can overcome this limitation because they allow for minute-long image acquisition. The newly developed blood pool contrast agent Vasovist* provides a prolonged imaging window of about 1 hour. Vasovist* is the designation for the drug product which has the active pharmaceutical ingredient: gadofosveset trisodium{(2(R)[(4,4iphenylcyclohexyl)-phosphonooxymethyl]-diethyl-enetriamine-pentaacetato)(aquo)gadolinium(III)}, formulated as 244 mg/mL. Due to reversible binding to albumin the relaxivity of Vasovist* is increased which allows lower doses for the same contrast effect and additionally prolongs vascular persistence. Compared to conventional ECCM, T1 relaxivity is about 4-5 times higher at 1.5T which is the field strength of most clinically used scanners.
With Vasovist® three-dimensional image data with less than 0.5x0.5x0.5 mm^3 can be acquired. Hence, MRA with intravascular contrast agents almost reaches the inplane resolution of MRA but has the added advantage of being three-dimensional. In addition, the first pass of the contrast agent can be used to acquire time-resolved MRA data. The combination of dynamic imaging during the first pass and ultra-high spatial resolution imaging during the steady state precludes typical MRA errors such as missing the contrast agent bolus and reduces the risk of non-diagnostic images due to patient motion.
The aim of this study is to evaluate the diagnostic accuracy of gadofosveset-enhanced MRA in detecting and grading vascular lesions in patients suffering from PAOD stage III° or IV° using intra-arterial digital subtraction angiography (i.a. DSA) as standard of reference (SOR).
The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Study objective

To determine the accuracy of Vasovist® enhanced MRA of the leg with regard to quantitative grading of stenosis (<50%, >=50%) compared to digital subtraction angiography (DSA, standard of reference (SOR))

Study design

Multicenter, multinational, intra-individual, open label study with an independent blinded off-site evaluation for MRA by two radiologists and for i.a. DSA by one radiologist. In case the assessments of the two MRA readers are contradictory a third independent reader will be involved for clarification

Study burden and risks

MRA is a very safe examination method. So far, neither risk to health nor side effects have been observed in the used magnetic field strengths. The examination is completely painless, however, it is accompanied by a loud knocking sound. For this reason ear protectors will be at the patients* disposal. Due to the strong magnetic fields required for this examination, which amount to a thousandfold of the earth*s magnetic field, patients with metal implants (e.g. shell splinters) may only be examined within certain limits. Dependent on their metallic characteristics and dimension, metals in the body can cause problems. Aside from being moved by the magnetic field, metal objects can get too warm during the examination. Fixed dental implants, however, usually do not lead to problems in MRA examinations. In case of other metal implants (artificial joints, metal splinters to support broken bones, etc.), it has to be decided individually whether or not they may cause problems during MRA. In the course of the studies carried out so far the most frequent complaints (i.e. occurrence in 1% or more of the patients receiving Vasovist*) were: Pruritus, Paresthesia, Headaches, Nausea, Vasodilatation, Burning Sensation and Dysgeusia. These complaints were usually only of short duration.

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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 who have Fontaine-stage III and IV and an indication for therapeutic i.a. DSA
2. PAOD has to be confirmed by ECCM MRA, CTA, non-selective DSA, Doppler ultrasound (DUS) prior to the study.
3. Patients who are willing to undergo the study MRA procedure with Vasovist*.
4. Patients who are willing to comply with the study procedures (e.g. being followed-up for 12 hours after the Vasovist* injection).
5. Patients who have given their fully informed and written consent voluntarily.

Exclusion criteria

1. Being less than 18 years of age.
2. Women who are pregnant, lactating or who are of childbearing potential and have not had a negative urine pregnancy test the same day as administration of Vasovist*. The manufacturer*s instructions for performing the urinary pregnancy test are to be followed.
3. Patients who are scheduled for any therapy between any of the two procedures (MRA and DSA) that interferes with the comparability of the two angiographic procedures.
4. Having an underlying disease or concomitant medication which may interfere with efficacy or safety evaluations as planned in this study.
5. Having any physical or mental status that interferes with the informed consent procedure including self-signed consent.
6. GFR < 30ml/m²/1.73m² (MDRD), values <= 1 week or patients on hemodialysis
7. Renal or liver transplant patients, including patients with scheduled liver transplant are excluded due to the potential risk for nephrogenic systemic fibrosis (NSF).
8. MR contraindications (pacemaker, magnetic clips, severe claustrophobia)
9. Known allergy to Gadofosveset
10. Presenting with history of anaphylactoid or anaphylactic reaction to any allergen including drugs and contrast agents.
11. Untreated significant stenosis in pelvis
12. Known severe coagulopathy (PTT >25s, Quick < 60%)
13. Having received any investigational drug within 7 days prior to entering this study or who are planned to receive any investigational drug during the safety follow-up period.
14. Not being able to remain lying down for at least 30-45min (e.g. patients with unstable angina, dyspnea at rest, severe pain at rest, severe back pain).
15. Being clinically unstable and whose clinical course during the 12 hours observation period is unpredictable.
16. Being scheduled for, or likely to require, any surgical intervention within 12 hours before

or within the follow-up period.
17. Patients in whom i.a. DSA is contra-indicated preventing him/her from undergoing standard of reference (SOR) procedure.
18. Close affiliation with the investigational site; e.g. a close relative of the investigator.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-08-2008
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Contrast liquid, Vasovist

Ethics review

Approved WMO Date:	28-07-2008
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-12-2008

Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2007-006014-41-NL
ClinicalTrials.gov	NCT00717639
CCMO	NL22483.068.08