Non-invasive vagus nerve stimulation in acute ischemic stroke.

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The main objective will be to investigate whether treatment with nVNS on top of best medical practice in acute ischemic stroke patients results in smaller infarct volumes compared with the infarct volumes of patients not treated with nVNS.

Ethical review	Approved WMO
Status	Completed
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON55551

Source
ToetsingOnline

Brief title
NOVIS

Condition

- Central nervous system vascular disorders

Synonym
brain ischemia, Stroke

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: VIDI,electroCore

Intervention

Keyword: Ischemic stroke, Vagus nerve stimulation

Outcome measures

Primary outcome

The primary endpoint will be the infarct volume on MRI scan after 5 days of

patients treated with nVNS compared with those of patients not treated with

VNS.

Secondary outcome

Secondary endpoints will be:

o Feasibility and tolerability of nVNS

o Proportion of patients in whom <50% of the penumbra turned into ischemic core

on day 3

o Degree of blood-brain barrier leakage on day three measured with CTP

o NIHSS at day 5 or at day of discharge

o Clinical outcome (modified Rankin Scale, mRS) on day 90

o Occurrence of seizures, depression or headache in the first 90 days

Study description

Background summary

Stroke is the third most disabling disease world-wide and the second leading cause of death. Secondary damage in the first few hours after ischemic stroke contributes substantially to poor outcome. Currently, there are no therapies to prevent secondary damage after ischemic stroke. Non-invasive vagus nerve stimulation (nVNS) has been shown to reduce the extent of tissue injury and functional deficit after ischemic stroke in rats. It is unknown whether nVNS has the same effects in humans. Our hypothesis is that nVNS will reduce tissue

injury and prevent and reverse secondary damage after ischemic stroke.

Study objective

The main objective will be to investigate whether treatment with nVNS on top of best medical practice in acute ischemic stroke patients results in smaller infarct volumes compared with the infarct volumes of patients not treated with nVNS.

Study design

The study will be a prospective randomized clinical trial with blinded outcome assessment (PROBE design).

Intervention

Patients will be randomized by computer to nVNS with the gammaCore Sapphire* on top of best medical practice versus best medical practice alone (including intravenous thrombolysis and/or thrombectomy if indicated). If patients are randomized to nVNS, two stimulations of two minutes each will be applied in the neck every 15 minutes in the first 3 hours. Thereafter two stimulations will be applied every 8 hours over the next 5 days or until discharge, whichever occurs first. The stimulation side in the neck will be the radiological side of the stroke.

Study burden and risks

Invasive VNS (iVNS) has already been approved for treatment of depression and refractory epilepsy and was safe in a small pilot study in ischemic stroke patients. Non-invasive VNS (nVNS) has not yet been investigated in acute ischemic stroke patients so the safety profile is not fully known. However, based on results in earlier trials, we don*t expect major risks to be associated with nVNS.

The following investigations will be done: all patients will undergo a CT/ CT angiography (CTA)/ CT perfusion (CTP) scan on admission as part of standard clinical care. On day 3 a CT/CTA/CTP scan will be repeated (for research purposes). The risk related to this will be the radiation exposure (approximately 13 mSv) and exposure to contrast agent. On day 5 or day of discharge a non-contrast MRI scan will be performed (for research purposes) which has minimal risks. On admission, day 5 or day of discharge, and after 90 days (by telephone) the modified Ranking Scale (mRS) will be assessed and a few short questionnaires will be taken.

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

- Ischemic stroke
- NIHSS >=1
- Perfusion deficit on the admission CTP scan; the penumbra must comprise at least 1/3 of the total ischemic area (ischemic core and penumbra)
- The infarct has to comprise the supratentorial region
- Treatment has to start <12 hours after stroke onset
- Patients or their representatives need to give their informed consent

Exclusion criteria

- Age below 18

- A life expectancy of less than three months
- mRS >2 prior to admission
- Contra-indication for contrast CT
- Contra-indications for VNS:
-> An active implantable medical device such as a pacemaker, deep brain stimulator, or any implanted electronic device
-> Symptomatic stenosis or dissection of the carotid artery (in these patients the other side will be stimulated unless a significant stenosis or dissection on the other side is present as well)
-> Structural abnormality e.g. lymphadenopathy, previous surgery or abnormal anatomy (in these patients the other side will be stimulated)
-> Metal cervical spine hardware or metallic implant near the stimulation site
-> Cervical vagotomy (in these patients the other side will be stimulated)
-> Pregnancy

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	09-10-2019
Enrollment:	150
Type:	Actual

Medical products/devices used

Generic name:	Vagus nerve stimulator
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	19-11-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	31-07-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	13-01-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
ClinicalTrials.gov	NCT04050501

Register
CCMO

ID
NL64702.058.18