Phenylephrine versus EPhedrine on cerebral Perfusion during Carotid EndarteRectomy

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Primary Objective: Our primary objective is to study the influence of two routinely used drugs to increase systemic blood pressure (phenylephrine and ephedrine) on cerebral oxygenation and perfusion, estimated by changes in cerebral oxygenation (...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON38169

Source
ToetsingOnline

Brief title
PEPPER trial

Condition

- Vascular therapeutic procedures
- Decreased and nonspecific blood pressure disorders and shock

Synonym
intraoperative hypotension, low blood pressure during surgery

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Carotidendarterectomy, Cerebral oxygenation, Vasopressor

Outcome measures

Primary outcome

Change in cerebral oxygenation (rSO2) measured using Near Infrared

Spectroscopy (NIRS).

Secondary outcome

Change in velocity measured in the a. cerebri media (Vmca) measured using

transcranial Doppler (TCD).

The cerebral autoregulation will be quantified as being adequate or

non-adequate.

Study description

Background summary

Carotid endarterectomy (CEA) is the recommended treatment for patients with a symptomatic high degree stenosis of the internal carotid artery (ICA). Besides these symptoms, stenosis of the ICA jeopardizes the cerebral perfusion and may affect cerebral autoregulation (CA), implicating that cerebral perfusion becomes dependent of changes in blood pressure (BP).1 Therefore, to preserve cerebral perfusion during surgery and to prevent *watershed* stroke, intraoperative hypotension needs to be avoided and the suggested BP that should be maintained intraoperatively is a systolic arterial pressure between normal and 20% above baseline.2
To do so, different short-acting vasopressor agents can be used, such as phenylephrine or ephedrine. If existing at all, preference for either of these agents is purely based on a personal basis. Furthermore, both agents are internationally accepted and, when heart rate is in the normal range, randomly applied in cardiovascular surgery. Despite that the effect on blood pressure is more or less identical, both agents have a different mechanism of action. Phenylephrine (an *-agonist) increases BP by vasoconstriction, whereas ephedrine (a combined *- and *-agonist) increases BP with a combination of vasoconstriction and an increase in heart rate and therefore cardiac output.3

Besides this difference in systemic hemodynamics also the perfusion of the brain react different. In healthy subjects, with intact CA, cerebral tissue oxygenation decreases during phenylephrine administration while it is preserved with ephedrine use.3, 4 It is suggested that the increase in cardiac output observed during ephedrine use can explain this difference in cerebral oxygenation.5 It is unknown how in status of impaired CA, as often observed in patients undergoing a CEA, the cerebral vessels react on phenylephrine or ephedrine. The optimal agent to maintain cerebral perfusion in CEA patients, with an impaired CA is unknown. If during the use of one of the two agents cerebral perfusion would be better maintained or even increase this would clearly influence the choice for the optimal agent.

In our center during CEA, we routinely monitor rSO2 using near infrared spectroscopy (NIRS) and middle cerebral artery blood velocity (VMCA). To study the effect of both vasopressors on these parameters we have retrospectively analysed the effect of phenylephrine and ephedrine induced changes in BP on rSO2 and Vmca in 19 patients. We noticed that phenylephrine and ephedrine both increased blood pressure and VMCA in patients undergoing carotid endarterectomy. However, an increase in blood pressure induced by phenylephrine has lowering effect on the cerebral perfusion, while ephedrine had an increasing effect on the cerebral perfusion.
This pilot study indicated that the use of ephedrine should be preferred above the use of phenylephrine for correction of hypotension during CEA. However, the numbers of patients were small and the dose of agent applied not standardized. Therefore a prospective study to analyze the effect of both ephedrine and phenylephrine on cerebral perfusion during CEA is needed to make a recommendation.

(1) Ederle J et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010 20;375(9719):985-97.
(2) Stoneham MD et al. Arterial pressure management and carotid endarterectomy. Br J Anaesth 2009 April;102(4):442-52.
(3) Dyer RA et al. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. Anesthesiology 2009 ;111(4):753-65.
(4) Nissen P. et al. Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. Neurocrit Care 2010 February;12(1):17-23.

Study objective

Primary Objective:
Our primary objective is to study the influence of two routinely used drugs to increase systemic blood pressure (phenylephrine and ephedrine) on cerebral oxygenation and perfusion, estimated by changes in cerebral oxygenation (NIRS)

and middle cerebral artery blood velocity, in patient undergoing carotid endarterectomy.

Secondary Objective:
To study whether the influence of phenylephrine and ephedrine on cerebral perfusion and oxygenation is different between patients with and without an adequate functioning cerebral autoregulation.

Study design

A prospective randomized trial in symptomatic patients undergoing CEA because of a hemodynamically significant stenosis of the ICA.
Currently, the preference of administering either phenylephrine or ephedrine for correction of relative intraoperative hypotension (which is required in virtually all carotid procedures) is mainly based on physician*s preferences.
For this trial randomization will be performed preoperatively between these two agents:
For this trial randomization will be performed peroperatively between 1) phenylephrine (50-100 µg), or 2) ephedrine (5-10 mg), to increase blood pressure.
If relative hypotension persists 5 minutes after administration of either phenylephrine or ephedrine, the patient will classified as a non-responder and, escape medication preferred by the anesthesiologist will be administered.
Before surgery all patients will be informed about the trial procedure and written informed consent will be obtained from all patients.
As part of the standard of care for patients undergoing CEA in our hospital, cerebral monitoring including transcranial Doppler (TCD), Near Infrared Spectroscopy (NIRS) and electroencephalography (EEG) will be provided. To quantify whether the intra-operative cerebral autoregulation is impaired or not, the breathing frequency will be decreased from the normal 12 breaths per minute to 6 breaths per minute for an episode of three minutes.

Intervention

Medication
During surgery randomization will be performed for treatment with either phenylephrine (50-100µg) or ephedrine (5-10mg) for correction of relative hypotension after tracheal intubation.
Relative hypotension requiring intervention is defined as a decrease in mean BP >20% of baseline BP (as reported on the nursing ward the day before surgery).

Measurements
As part of the standard of care a radial artery catheter is placed in each patient for continuous blood pressure measurement and cerebral monitoring including transcranial Doppler (TCD), Near Infrared Spectroscopy (NIRS) and electroencephalography (EEG) will be provided.

Intervention:
To quantify whether the intra-operative cerebral autoregulation is impaired or not, the breathing frequency is decreased from the normal 12 breaths per minute to 6 breaths per minute for an episode of three minutes.

Study burden and risks

Phenylephrine and ephedrine are two of the most commonly used short acting agents to increase blood pressure in clinical anesthesiologic practice. Monitoring of middle cerebral artery blood velocity with TCD and frontal lobe cerebral tissue oxygenation with NIRS are part of the standard of care. Furthermore, there are no reports that the three minute modification in breathing frequency described in the *intervention*-section is harmful. Therefore risks for participating patients are negligible and the burden minimal.

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

To be included in the current study all patients must meet the following criteria:
1. Undergoing CEA because of a symptomatic high degree stenosis of the ICA in the University Medical Centre Utrecht
2. Having an appropriate temporal bone window for reliable perioperative TCD monitoring
3. Have given written informed consent.
4. A decrease in MAP >20%

Exclusion criteria

Exclusion criteria
Patients will be excluded if they meet one of the following criteria:
1. Not having a temporal bone window appropriate for TCD measurement
2. Not willing to give informed consent.
3. No decrease in MAP >20%
4. A heart rate less than 50 beats per minute at the time of administration.
5. Hypersensitivity to either ephedrine of phenylephrine

Study design

Design

Study type: Interventional

Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-10-2012
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ephedrine
Generic name:	Ephedrine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Phenylephrine
Generic name:	Phenylephrine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-03-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-07-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2011-003470-88-NL
ClinicalTrials.gov	NCT01451294
CCMO	NL37658.041.11

Study results

Date completed: 01-11-2013

Results posted: 16-01-2017

Actual enrolment: 40

First publication
01-01-1900