Study protocol: The Effect of Blood Pressure on Cerebral Blood Flow During Propofol Anesthesia

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Ethics

The study protocol (H-17021598-61256) was approved by the Regional Ethical Committee of the Copenhagen Region (De Videnskabsetiske Komiteer Region Hovedstaden, 004538666395, Email: vek@regionh.dk, Adress: Kongens Vænge 2, DK-3400 Hillerød, Denmark

The study is monitored by the Danish Dataprotection Agency.

Study is planned to be conducted from December 2017-April 2018

FDA Regulated: No

FDA Regulated Intervention: No

Sponsor: Rigshospitalet, Denmark

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Short Description

General anesthesia often reduces blood pressure whereby blood flow to the brain and other vital organs may become insufficient. Thus, medicine is often administered to maintain blood pressure but it is unclear at what level blood pressure should be aimed at during anesthesia.

Thirty patients undergoing major abdominal surgery will be included. The study will start one hour after the start of surgery and lasts for approximately half an hour. The purpose of the study is to evaluate whether blood flow to the brain can be increased by maintaining blood pressure at a higher level than that used in clinical practice. In the study, MAP is adjusted to a high, moderate, and low level for a short time. The low level of blood pressure used in the study, corresponds to the level aimed at in clinical practice. The drug noradrenaline will be used to control blood pressure. Blood flow to the brain will be evaluated on the neck using ultrasound.

Background

Propofol anesthesia reduces cerebral blood flow (CBF) and mean arterial pressure (MAP) but it is unclear whether the decrease in CBF is accentuated by hypotension. Cerebral autoregulation is

generally considered to maintain CBF when MAP is between 60-150 mmHg. Hence, vasoactive medication is administered if MAP decreases to below approximately 60 mmHg.

It is controversial whether there is a plateau for cerebral autoregulation. Thus, middle cerebral artery blood velocity (MCA Vmean), as an index of CBF, is associated to MAP during pharmacological changes in MAP between approximately 40-125 mmHg. Similarly, CBF is affected by pharmacological changes in MAP between 40-80 mmHg during hypothermic cardiopulmonary bypass surgery in propofol anesthesia. Arterial hypertension may increase the lower limit of cerebral autoregulation which can be mitigated by antihypertensive treatment.

Cognitive dysfunction and delirium are common following major surgery, particularly in the elderly, and may be related to hypotension and cerebral hypoperfusion. Further, hypotensive anesthesia is associated with an increase in markers of neuronal damage, but studies have been too small to detect any difference in incidence of cognitive dysfunction following hypotensive as compared to normotensive anesthesia.

In young healthy adults, propofol anesthesia causes limited reduction in blood pressure and decreases CBF by approximately 50% by a reduction in neuronal activity. An increase in MAP from approximately 80 to 100 mmHg during propofol anesthesia does not affect CBF but it is unknown whether CBF can be increased by an increase in MAP from approximately 60 to 80 mmHg. Propofol appears to maintain cerebral autoregulation but it is unknown whether the lower level of cerebral autoregulation is affected. The internal carotid artery supplies most of CBF and dilates during moderate hypotension with maintained blood flow which indicates that the vessel contributes to cerebral autoregulation. Further, central blood volume and cardiac output may be important factors for maintaining CBF.

The study will include thirty patients planned for major abdominal surgery in propofol-remifentanil anesthesia combined with epidural analgesia. Internal carotid artery blood flow will be

evaluated on the neck using duplex ultrasound. The study will be conducted one hour after the start of surgery and lasts for approximately half an hour. In the study, MAP is set pharmacologically at 80-85, 70-75 and 60-65 mmHg for a short time in random order. The level of 60-65 mmHg corresponds to the level at which MAP is maintained in clinical practice. Control of MAP is by intravenous infusion of noradrenaline, an α - and β -adrenergic agonist.

Objective

The purpose of the study is to evaluate whether internal carotid artery blood flow is increased by maintaining MAP at a higher level than that used in clinical practice during propofol anesthesia. Further, we evaluate whether a lower limit of cerebral autoregulation can be detected by comparing the slopes of linear regression of internal carotid artery blood flow and MAP at the evaluations when MAP is 60-65 and 70-75 mmHg and when MAP is 70-75 and 80-85 mmHg.

Hypotheses

- Internal carotid artery blood flow is higher when MAP is 80-85 mmHg as compared to a MAP of 60-65 mmHg.
- Internal carotid artery blood flow is higher when MAP is 70-75 mmHg as compared to a MAP of 60-65 mmHg.
- Internal carotid artery blood flow is higher when MAP is 80-85 mmHg as compared to a MAP of 70-75 mmHg.
- The slope of linear regression between changes in MAP and internal carotid artery blood flow is higher for the evaluations at a MAP of 70-75 and 60-65 mmHg than for the evaluations at a MAP of 80-85 and 70-75 mmHg.

Methods

The study is a single-center, prospective cohort study of thirty consecutive patients planned for major abdominal surgery in propofol anesthesia. In case surgery is cancelled, or if gas anesthesia is used the patient will be excluded and excluded patients will be replaced. The number of dropouts is expected to be between zero to five patients. Patients will be recruited the day before surgery, at which time the internal carotid artery will be evaluated using ultrasound. In case the vessel cannot be visualized, e.g. due to high localization of the carotid bifurcation the patient will not be able to participate in the study.

Anesthesia and surgery are according to clinical practice. Anesthesia is induced by propofol and maintained by propofol and remifentanil. A thoracic epidural catheter is placed at Th8/9 or Th9/10 and epidural anesthesia is initiated before surgery by bupivacaine infusion 0.5%, 5 ml/hr. and bolus 15 mg bupivacaine that is repeated hourly. Stroke volume is optimized after induction of anesthesia by repeated administration of 250 ml 5% human albumin until the increase in stroke volume is less than 10%, and volume optimization is repeated in case of persistent decrease in stroke volume by more than 10%. Noradrenaline infusion (0.6 μ g/kg*ml) is started after induction of anesthesia to maintain MAP > 60 mmHg and to avoid volume optimization when the circulation is dilated.

Development of a so-called mesenteric traction syndrome can affect MAP in the first hour of major abdominal surgery. Thus, the study is conducted from 60 min after incision and lasts for approximately half an hour. Anesthesia reduces MAP, but the reduction varies between patients and is affected by administration of propofol, remifentanil, and epidural anesthesia, fluid status, and surgical stimulation etc. The start of the study is postponed until any larger bleeding, transfusion or volume optimization is treated or finished. Before the start of the study, the infusion speed of propofol and remifentanil must have been constant for at least 10 min, and at least 15 min must have elapsed since the last bolus dose bupivacaine, as any changes in anesthesia may affect both

cerebral and central hemodynamics. In case the infusion of propofol or remifentanil is changed or bolus bupivacaine is administered during the study, the experiment is halted, and the study is restarted when the anesthesia has been stable for 10 min. The experiment can only be restarted once and only data from the last trial with the highest number of evaluations are used.

In the experiment MAP is temporally set to 80-85, 70-75, and 60-65 mmHg by adjusting the infusion of noradrenaline. The order of evaluations is randomized by drawing an envelope just before the start of the experiment. Noradrenaline is short lasting and have no direct effect on CBF. The experiment lasts approximately 30 min until evaluations have been conducted at the three levels of MAP. If MAP does not drop to 60-65 mmHg by halting the infusion of noradrenaline this evaluation is not conducted but we expect that this will be the case in only few patients. In clinical practice noradrenaline is used to maintain MAP > 60 mmHg. The study is not an investigation of medicinal products as noradrenaline is used as a tool to control MAP.

Administration of noradrenaline is by a central venous or large peripheral catheter, using an electronic infusion pump, and infusion speed is adjusted slowly until the level of MAP is reached. Noradrenaline is effective within 1-2 min after administration and the effect lasts only for a few minutes. When MAP has been stable at the desired level for at least 3 min, measurements are conducted during the following 2 min. When the study is finished, control of MAP will be according to clinical practice. We consider that there is no increased risk by a short term increase in MAP to 80-85 mmHg.

Measurements

Arterial and central venous pressure are determined invasively while stroke volume, cardiac output, and total peripheral resistance are evaluated by modified pulse-contour analysis of the arterial pressure curve (Nexfin, BMEYE, Holland). Cerebral and biceps muscle oxygenation are evaluated

using near-infrared spectroscopy (INVOS 5100C, Somanetics, Troy, MI, USA). Depth of anesthesia is assessed by Bispectral Index (BIS Complete Monitoring Systems, Covidien, USA).

Internal carotid artery blood flow is evaluated unilaterally on the neck using duplex ultrasound (Logiq E, GE Medical System, Jiangsu, Kina). Evaluation is in the longitudinal section at least 1.5 cm distal to the carotid bifurcation with the head turned approximately 30^0 to the contralateral side. In order to limit the influence of ventilation, three recordings of approximately 15-20 s are conducted at each level of MAP and the mean is reported. A frequency of 8-12 MHz is used and gain is set as high as possible while vessel lumen is echo-free. Ultrasonic adjustments are not changed during the study. Diameter is assessed using automatic software to track the vessel wall (Brachial Analyser for Research v. 6, Medical Imaging Applications LLC, Coralville, IA, USA). The angle-corrected time maximum flow velocity (TAVMAX) is evaluated using pulsed-wave Doppler at an angle of insonation $\leq 60^0$. The TAVMAX corresponds to twice the mean blood velocity and blood flow is: 0.125*60*TAVMAX* π *diameter^2. Arterial and central venous blood is sampled for blood gas analysis. Internal carotid artery blood flow is corrected for changes in $PaCO_2$ using a factor of 18%/kPa and for the S_cO_2 a correction factor of 4.3%/kPa is used (unpublished results from the study "Cerebral Blood Flow During Propofol Anaesthesia" NCT02951273).

Statistics

Trial size: The minimal clinically important difference in internal carotid artery blood flow between evaluations at MAP 60-65 and 80-85 mmHg is considered to be 10% as evaluations using near-infrared spectroscopy indicate that intraoperative cerebral deoxygenation of > 10% associates to postoperative cognitive dysfunction.

A power calculation indicated that at least 18 patients were required to detect a difference in internal carotid artery blood flow of 10% corresponding to 19 ml/min assuming a standard deviation for the change of 27 ml/min (unpublished results from the study "Cerebral Blood Flow During Propofol Anaesthesia" NCT02951273) to obtain a 5% significance level and a power of 80%. We plan to include 30 patients.

Inclusion Criteria

- Patient planned for Whipple’ s surgery or total pancreatic resection
- Age > 18 years

Exclusion Criteria

- No informed consent
- Alcohol intake ≥ 420 g / week
- Beard on the neck
- Visualization of the internal carotid artery not possible, e.g. due to high
- placement of the bifurcation
- Stenosis that obstructs ≥ 16% of the internal carotid artery
- Cardiac disease, including congestive heart failure (NYHA II-IV),
- myocardial infarction, valvular heart disease or atrial fibrillation
- Neurologic disease considered to affect cerebral blood flow, including
- dementia, epilepsy, and apoplexy

- Intake of moclobemide, isocarboxazid or tricyclic antidepressantsNeurologic disease considered

Primary Outcome Measure:

1. Change in internal carotid artery blood flow when mean arterial pressure (MAP) is set to 80-85 and 60-65 mmHg

Secondary Outcome Measures:

2. Change in internal carotid artery blood flow when MAP is set to 70-75 and 60-65 mmHg

3. Change in internal carotid artery blood flow when MAP is set to 80-85 and 70-75 mmHg

4. Comparison of the slope of linear regression of MAP and internal carotid artery blood flow for the evaluations when MAP is set to 80-85 and 70-75 mmHg and that of the evaluations when MAP is set to 70-75 and 60-65 mmHg

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