Final Study Report

Study Title: Influence of continuous administration of phenylephrine versus dobutamine on spinal oxygen saturation, measured with near-infrared spectroscopy (NIRS).

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Eudamed number: *not applicable*

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Sponsor: *UZ Ghent*

Coordinating Investigator: *Dr. Caroline Vanpeteghem*

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1. Introduction

Paraplegia and/or paraparesis is a feared and devastating complication following surgical repair of thoracic and thoraco-abdominal aortic aneurysms and dissections. The cause is thought to be a compromised perfusion of the spinal cord, and this might occur either during or after the surgical procedure.

According to the literature, the incidence of paraplegia and/or paraparesis following open surgical repair varies between 8% and 28%.[1,2] Following endovascular repair, the incidence varies between 0% to 14.5%.[3,4]

In patients with a risk of perioperative compromised spinal cord perfusion, a lumbar cerebrospinal fluid drainage is placed in order to measure and regulate the pressure into the spinal canal. It enhances the spinal cord perfusion and decreases the ischemic injury of the spinal cord.[5] In addition, higher systemic blood pressures are often aimed for in order to increase and optimize spinal cord perfusion.

Motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) have been proven to be efficient to detect spinal ischemia and might guide therapeutic actions. Unfortunately, MEPs and SSEPs are time consuming, expensive, and they require trained and experienced personnel as well as a modification of the standard anaesthetic approach (e.g. avoidance of neuromuscular blocking agents, …).

Near-infrared spectroscopy (NIRS) is gaining popularity as a non-invasive monitor of spinal cord oxygenation.[6] Therefore, NIRS is increasingly used in daily practice to measure spinal saturation and to monitor spinal ischemia.

There is ample literature describing the effect of hemodynamic supportive medication on NIRS measured cerebral saturation, [7], however their effect on spinal vasculature is still unknown.

Phenylephrine and dobutamine act completely different. Phenylephrine causes vasoconstriction, thereby increasing blood pressure, whereas the increase in blood pressure with dobutamine is related to an increase in cardiac output.

To assess the effect of hemodynamic supportive medication on spinal vasculature, patients scheduled for arterial dilation of the lower limb were chosen as our study population. The spinal cord perfusion is not compromised in these patients, however, most patients suffer from hypotension during this kind of surgery, due to the non-invasive type of surgery and the vasodilating effects of the anaesthetics. Therefore, continuous administration of vasoactive medication (phenylephrine or dobutamine) is often required in order to increase blood pressure.

The aim of our study is to evaluate the effect of a continuous administration of phenylephrine or dobutamine on the spinal oxygenation, assessed by NIRS.

2. Objectives of the study

2.1 Primary objectives

Evaluation of the effect of continuous administration of phenylephrine or dobutamine on the spinal vasculature, by measuring spinal oxygen saturation with NIRS.

2.2 Secondary objectives

Relationship between cerebral oxygen saturation, muscle saturation and the type of hemodynamic support provided.

Relationship between NIRS and MAP and CO.

Influence of sympathetic stimulation (during intubation) on cerebral, spinal and muscle oxygen saturation.

3. Investigational Medicinal Product

Phenylephrine 1% (10mg/ml)

Dobutamine Hydrochloride EG (250 mg/20ml)

3.1 Producer

Phenylephrine 1%: Beacon Pharmaceutical, Kent (UK)

Dobutamine Hydrochloride: Eurogenerics NV, Brussel (Belgium)

3.2 Distributor

Phenylephrine 1%: Beacon Pharmaceutical, Kent (UK)

Dobutamine Hydrochloride: Ecopharma supply

3.3 Packaging

Phenylephrine: glass vial (10mg/ml); diluted in syringe (10mg/ml in 100 ml NaCl 0,9%) => 0,1mg/ml, for continuous use

Dobutamine: glass vial (250mg/20ml); diluted in syringe (30mg in 50ml NaCl 0.9%) => 0,6 mg/ml, for continuous use

3.4 Administration way

Continuous Intravenous use

3.5 Labelling

Phenylephrine: date, hour of preparation, ldap code of person who prepared the syringe, ldap of person who controlled the preparation of the syringe, concentration 0,1mg/ml, following particulars will be added: sponsor, study reference code, investigator, study participant, for clinical trial use only, direction for use.

Dobutamine: date, hour of preparation, ldap code of person who prepared the syringe, ldap of person who controlled the preparation of the syringe concentration 0,6mg/ml, following particulars will be added: sponsor, study reference code, investigator, study participant, for clinical trial use only, direction for use.

3.6 Storage conditions

Phenylephrine and dobutamine will be delivered by the pharmacy and stored in a locked closet in the OR under standard room temperature and pressure.

4. Investigational Medical Device

not applicable

5. Study Protocol Summary

5.1 Inclusion criteria

Subject eligibility is determined according to the following criteria at enrolment:

- Patients ≥ 18y
- Patient is scheduled for dilation of arterial blood vessels of the lower limb.

5.2 Exclusion criteria

- Age < 18y
- BMI > 30
- severe valvular disease
- previous aortic surgery
- paraplegia/ paraparesis
- kidney replacement therapy
- pacemaker
- pregnancy
- lactating participants
- preoperative use of ACE inhibitors.
- No sinus rhythm on preoperative ECG or at induction of anaesthesia (patients with a history of atrial fibrillation can be included if they have a sinus rhythm on their preoperative ECG)

5.3 Primary endpoint

Spinal oxygen saturation measured by NIRS

5.4 Secondary endpoints

Cerebral oxygen saturation

Deltoid muscle oxygen saturation

5.5 Procedures

All patients receive standard anaesthesia care during the surgical procedure.

Before induction of anaesthesia, baseline MAP will be defined and 6 additional sensors (stickers) will be applied to the back of the patient at three levels: 1 at the upper thoracic level(T_3-T_4), 2 at the lower thoracic level (T_9-T_{10}) and 2 at the lumbar region (L_1-L_2) and 1 on the deltoid muscle of the upper arm. Two sensors are routinely applied to the forehead to measure cerebral oxygenation and a BIS sensor is applied to measure depth of anaesthesia. In all patients a non-invasive cardiac output monitor (Clearsight; Edwards^{TM} LifeScience, Irvine, CA, USA) is routinely used. This monitor provides a continuous arterial pressure waveform in a non-invasive way and facilitates continuous evaluation of blood pressure. Hereby, efficient adaptation of the administration of vasopressors is feasible. Through an intravenous line, anaesthetics will be administered. Vasopressor agents will be administered through a dedicated second intravenous line. After induction of anesthesia, an endotracheal tube is placed.

A vasopressor agent will be administered continuously after intubation in order to maintain blood pressure in a range from $MAP_{baseline}$ -20% to normal (preoperative) values ($MAP_{baseline}$). If MAP decreases to a value lower than $MAP_{baseline}$ -20%, a higher dose of vasopressor will be administered. If MAP increases to a value above $MAP_{baseline}$, the dosing rate will be decreased. According to the group to which the patient has been randomized, phenylephrine or dobutamine will be administered and the dose will be adjusted to MAP during a 30-minute study period.

The total drug amount for phenylephrine and dobutamine will not exceed 5 mg, resp. 30 mg.

The study will be completed after 30 minutes of continuous medicamentous hemodynamic support administration (i.e. 30 minutes after intubation) or if administration of phenylephrine or dobutamine exceeds 1 μg/kg/min or 10 μg/kg/min, respectively.

If the administration of the study medication does not achieve the desired result, management of the haemodynamics will be left to the discretion of the attending anaesthesiologist and the patient will be excluded from further data analysis.

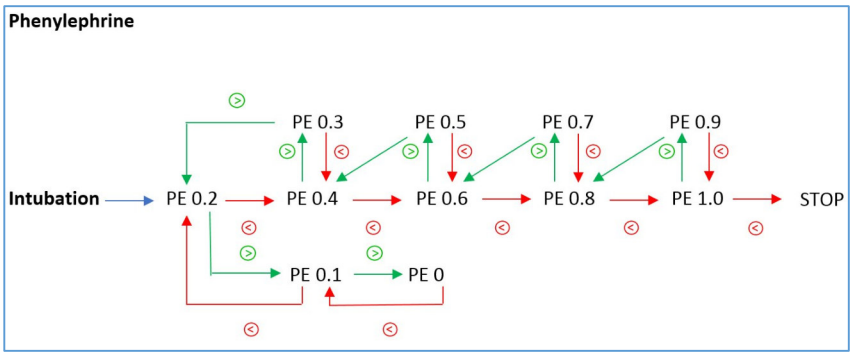
The endovascular surgical procedure can start without delay and the duration of surgery will not be prolonged because of the measurements and blood pressure management.

Flowchart

- Preoperative evaluation
    - Baseline blood pressure measurement
- Randomization in 2 groups:
    - Group 1: Phenylephrine continuous infusion (30 minutes)
    - Group 2: Dobutamine continuous infusion (30 minutes)
- Application of 5 NIRS sensors on the back and 1 on the upper arm
- Application of routine monitoring (ECG, pulse oximetry, cerebral oximetry, NIBP, BIS, respiratory monitoring, non-invasive cardiac output monitor (ClearSight™).
- Induction of anaesthesia
- Continuous administration of phenylephrine or dobutamine will be started immediately after intubation.

Phenylephrine: 10 mg/100ml

Start 0,2 μg/kg/min; to be adjusted according to the patient's hemodynamic status (Fig. 1)

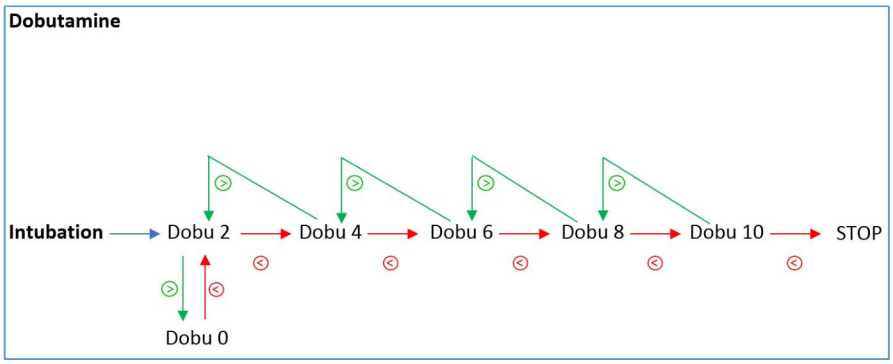


Phenylephrine represented in µg/kg/min.

⊳: MAP > $MAP_{baseline}$

⊲: MAP < $MAP_{baseline}$- 20%

- Dobutamine: 30 mg/50ml
  Start 2 µg/kg/min; to be adjusted according to the patient's hemodynamic status (Fig. 1)



Dobutamine represented in µg/kg/min.

⊳: MAP > $MAP_{baseline}$

⊲: MAP < $MAP_{baseline}$- 20%

- End of study:

  - after 30 minutes of continuous vasopressor administration.
  - if MAP does not exceed $MAP_{baseline}$ – 20% despite administration of 1 µg/kg/min phenylephrine or 10 µg/kg/min dobutamine (according to the randomization) during 4 minutes.

  Routine hemodynamic management will be continued.

  The total amount of administered medication will be registered.

5.6 Randomisation and blinding

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into one of the two observational arms.

Eligible participants will be randomized in 2 groups using sealed envelopes:

- Group 1: Phenylephrine continuous infusion (max 30 minutes)
- Group 2: Dobutamine continuous infusion (max 30 minutes)

The sealed envelopes will be stored in a locked closet in the locked office of our study nurse. The study nurse will be responsible for the randomization and the randomization list.
The persons responsible for the preparation of the syringes with the study medication will be Dr. Caroline Vanpeteghem, Dr. Vincent Bafort, Dr. Milan Besard and Dr. Martha Wolfskeil. The syringes will be prepared in the operating room at the beginning of the procedure, before the induction of anaesthesia.
Since this is an open label study, participants will be informed before the start of the procedure about the observation arm they are in.

6. Study analysis

Sample size calculation was based on previous data from our study group. We observed a statistically significant difference in response between Phenylephrine and Ephedrine of 2%. To obtain the same difference in response between phenylephrine and dobutamine with standard deviation of 2% for a power of 0.8 and an p of 0.05, 17 patients in each observation arm were calculated to be necessary to address the experimental question. Drop outs will be replaced.

Data will be analyzed using a two-way analysis of variance for repeated measurements. Statistical significance will be accepted at $p < 0.05$.

7. Independent Ethics Committee and Competent Authority

Initial FAGG approval has been obtained on 07-JAN-2019 and approval of the Ethical Committee on 31-JAN-2019

OVERVIEW APPROVED DOCUMENTS		

Initial submission:
- Protocol v 1.0 dd. 07-Nov-2018
- Protocol summary v 8.0 dd. 19-Sep-2018
- SmPC (Summary of Product Characteristics)
  o Phenylephrine 1% Dobutamine dd. Dec/2014
  o NaCl dd. Apr/2013
- Secondary label v 2 dd, 09-nov-2018
- Informed consent form v 2.0 dd. 29-Jan-2019
- CRF v 1.0 dd. 07-Nov-2018
	Approval Central EC:
	31-Jan-2019
		Approval FAGG:
		07-Jan-2019

Amendment 1 (Substantial): - Protocol v 2.0 dd. 06-Feb-2019 - Protocol summary v 2 dd.06-Feb-2019 - Informed consent form v 3.0 dd. 06-Feb-2019 - CRF v 2.0 dd. 06-Feb-2019	**Approval Central EC:** **04-Mar-2019**	**Approval FAGG :** **26-Feb-2019**
Amendment 2 (Substantial): - Protocol v 3.0 dd. 09-Jul-2020 - Protocol summary v 3 dd.09-Jul-2020 - SmPC (Summary of Product Characteristics) o Phenylephrine Unimedic 10mg/ml -	**Approval Central EC:** **29-Jul-2020**	**Approval FAGG :** **22-Jul-2020**
Amendment 2 (Non-Substantial): - Prolongation recruitment until 01-Jan-2022 - Protocol v 4.0 dd. 27-Nov-2020 - Protocol summary v 4 dd.27-Nov-2020	**Approval Central EC:** **23-Dec-2020**	**Approval FAGG :** **N.A.**

8. Results

8.1 Subject enrollment and demographics

From July 4th 2019 until May 20th 2021 36 patients were included. Last visit of the last patient was performed at May 22nd 2021

In total, 36 patients signed an informed consent (replacement of 2 drop-outs).

Demographics of patients included in group 1 (phenylephrine administration) and group 2 (dobutamine administration).

	Group 1		**Group 2**		**Total**	
	N	%	N	%	N	%
sex (male/female)	10/7	58.8/41.2	12/5	70.6/29.4	22	64.7
Smoker	13	76.5	13	76.5	26	76.5
Beta-lytics	9	52.9	9	52.9	18	52.9
CCB	9	52.9	5	29.4	14	41.2
ACE-I	12	70.6	6	35.3	18	52.9

	Group 1					Group 2				
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
Age (y)	17	67.5	10.58	52	87	17	71.7	5.76	64	81
Weight (kg)	17	71.1	10.34	54	92	17	74.9	10.03	59	90
Lenght (cm)	17	170.1	8.59	154	189	17	166.9	8.97	150	178
BMI ($kg.m^{-2}$)	17	24.5	2.40	21	28	17	26.8	2.12	22	30
MAP awake (mmHg)	17	104.0	11.34	83	119	17	103.8	13.42	79	125
MAP baseline (mmHg)	17	87.2	19.11	57	123	17	78.0	13.55	54	99

8.2 Study specific results

Baseline NIRS values in both groups at cerebral, deltoid T3-T4, T9-T10 and L1-L2 level.

The values are expressed as mean +/- sd.

rS_tO_2	Group 1	Group 2
rS_cO_2 (%)	74 ± 11	74 ± 9
rS_dO_2 (%)	84 ± 8	81 ± 5
$rS_{T3-T4}O_2$ (%)	85 ± 9	81 ± 6
$rS_{T9-T10}O_2$ (%)	76 ± 8	75 ± 9
$rS_{L1-L2}O_2$ (%)	83 ± 7	81 ± 6

Relative changes in rS_tO_2 from baseline for different dose categories.

Dose category:

d2: 0.2 mcg/kg/min and 2 mcg/kg/min;

d4: 0.4 mcg/kg/min and 4 mcg/kg/min;

d6: 0.6 mcg/kg/min and 6 mcg/kg/min;

d8: 0.8 mcg/kg/min 8 mcg/kg/min ;

d10: 1 mcg/kg/min and 10 mcg/kg/min

for phenylephrine and dobutamine resp.).

*: significantly different from baseline; §: significantly different between group 1 and group 2.

Relative changes from baseline (expressed in %) for rS_tO_2 at cerebral level (Delta rS_cO_2) for both groups

Dose category	Delta rS_cO_2 Group 1 (%)	Delta rS_cO_2 Group 2 (%)
D2	-3±6	-4±5*
D4	-5±16§	-5±9*§
D6	-9±17§	-6±9*§
D8	-12±16*§	-5±9*§
D10	-14 ±16*§	-6±11*§

Relative changes from baseline (expressed in %) for rS_tO_2 at deltoid level (Delta rS_dO_2) for both groups

Dose category	Delta rS_dO_2 Group 1 (%)	Delta rS_dO_2 Group 2 (%)
D2	-1±4	0±3
D4	-1±5	0±3
D6	-2±5	0±3
D8	-2±5	1±4
D10	-2±5	2±5

Relative changes from baseline (expressed in %) for rS_tO_2 at T3-T4 (Delta $rS_{T3-T4}O_2$) for both groups

Dose category	Delta $rS_{T3-T4}O_2$ Group 1 (%)	Delta $rS_{T3-T4}O_2$ Group 2 (%)
D2	-1±4	0±3
D4	-1±4	1±4
D6	-1±4§	0±4§
D8	-2±4§	1±4§
D10	-2±4	2±4

Relative changes from baseline (expressed in %) for rS_tO_2 at T9-T10 (Delta $rS_{T9-T10}O_2$) for both groups

Dose category	Delta $rS_{T9-T10}O_2$ Group 1 (%)	Delta $rS_{T9-T10}O_2$ Group 2 (%)
D2	1±3	0±5
D4	1±3	-1±6
D6	1±3	-1±6
D8	2±4	0±8
D10	2±4	0±8

Relative changes from baseline (expressed in %) for rS_tO_2 at L1-L2 ($rS_{L1-L2}O_2$) for both groups

Dose category	Delta $rS_{L1-L2}O_2$ Group 1 (%)	Delta $rS_{L1-L2}O_2$ Group 2 (%)
D2	1±2	1±3
D4	0±4§	1±3§
D6	0±2§	2±3§
D8	0±2§	2±4§
D10	0±2	3±5

9. Safety

There has been 1 Serious Adverse Event.

SAE Overview				
Subject ID	Study Arm (if applicable)	SUSAR (Y/N)	SAE Description	Outcome (ongoing, resolved, death, …)
024	Dobutamine EG continuous infusion 30 minutes	No	Swelling groin at end of surgery (hematoma)	resolved

10. Device deficiencies

not applicable

11. Protocol deviations

no major protocol deviations took place fort his trial

12. Discussion and overall conclusions

Both PE and dobutamine negatively affect rS_cO_2. The PE-related negative effect on rS_cO_2 is more pronounced, compared to dobutamine.

At T_3-T_4 level, $rS_{T3-T4}O_2$ significantly differs between the 2 groups at d6 and d8.

At d4, d6 and d8, $rS_{L1-L2}O_2$ significantly differs between the 2 groups.

No significant effect on rS_dO_2 and $rS_{T9-T10}O_2$ is observed in both groups.

No correlations were observed between rS_tO_2 and MAP of cardiac index.

13. References

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7. Pennekamp et al. Differential effect of phenylephrine and ephedrine on cerebral haemodynamics before carotid cross-clamping during carotid endarterectomy. BJ Anaesth 2012 Nov: 109(5): p 831-833