Clinical trial results:
Influence of a bolus administration of ephedrine and phenylephrine on spinal oxygen saturation, measured with NIRS.

Summary

EudraCT number	2016-001839-13
Trial protocol	BE
Global end of trial date	09 September 2017

Results information

Result version number	v1 (current)
This version publication date	15 February 2020
First version publication date	15 February 2020

Trial information

Trial identification

Sponsor protocol code	AGO/2016/006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03767296
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ghent University Hospital
Sponsor organisation address	Corneel Heymanslaan 10, Ghent, Belgium,
Public contact	Bimetra Clinics, Ghent University Hospital, +32 93320500, bimetra.clinics@uzgent.be
Scientific contact	Bimetra Clinics, Ghent University Hospital, +32 93320500, bimetra.clinics@uzgent.be

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2017
Global end of trial reached?	Yes
Global end of trial date	09 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the effect of vasoactive agents (ephedrine and phenylephrine) on the spinal vasculature by measuring spinal oxygenation, using near infrared spectroscopy in peripheral vascular surgery.

Protection of trial subjects:

Ethics review and approval, informed consent and routine monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	11
From 65 to 84 years	15
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

33 patients were included in the period 06-Feb-2017 until 09-Sep-2017. 5 drop-outs been replaced. End of trial notification was dated 09-Sep-2017 (last patient last visit) and submitted to EC and CA 06-Dec-2018.

Pre-assignment

Screening details:

Patients who are 18 years or older and who are scheduled for dilatation of arterial bloos vessels of the lower limb.
Patients were screened as per inclusion and exclusion criteria per protocol.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Ephedrine- Phenylephrine - Ephedrine

Arm type	Experimental
Investigational medicinal product name	Ephedrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Intravenous bolus use

Dosage and administration details:

MAP decrease > 20%:
6 mg, 6mg, 9 mg, 9 mg, 12 mg, …..(max 24mg/bolus) (until x mg)
A total amount of 140 mg Ephedrine will not be exceeded.

Investigational medicinal product name	Phenylephrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

MAP decrease >20%:
50µg, 50µg, 100µg, 100µg, 150µg, 150µg,…(max 500µg/bolus)
A total amount of 1500 µg will not be exceeded.

Investigational medicinal product name	Ephedrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravenous bolus use

Dosage and administration details:

Decrease MAP > 20%:
6 mg, 6mg, 9 mg, 9 mg, 12 mg, …..(max 24mg/bolus) (starting from x mg)
A total amount of 140 mg Ephedrine will not be exceeded.

Arm title	Group 2

Arm description:

Phenylephrine- Ephedrine - Phenylephrine

Arm type	Experimental
Investigational medicinal product name	Phenylephrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

MAP decrease > 20%:
50µg, 50µg, 100µg, 100µg, 150µg, 150µg,…(max 500µg/bolus) (until x mg)
A total amount of 1500 µg will not be exceeded.

Investigational medicinal product name	Ephedrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravenous bolus use

Dosage and administration details:

Decrease MAP > 20%:
6 mg, 6mg, 9 mg, 9 mg, 12 mg, …..(max 24mg/bolus) (starting from x mg)
A total amount of 140 mg Ephedrine will not be exceeded.

Investigational medicinal product name	Phenylephrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

MAP decrease > 20%:
50µg, 50µg, 100µg, 100µg, 150µg, 150µg,…(max 500µg/bolus) (starting from x mg)
A total amount of 1500 µg will not be exceeded.

Arm title	Group 3

Arm description:

Ephedrine- Ephedrine - Ephedrine

Arm type	Experimental
Investigational medicinal product name	Ephedrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Intravenous bolus use

Dosage and administration details:

MAP decrease > 20%:
6 mg, 6mg, 9 mg, 9 mg, 12 mg, …..(max 24mg/bolus) (until x mg)
A total amount of 140 mg Ephedrine will not be exceeded.

Investigational medicinal product name	Ephedrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Intravenous bolus use

Dosage and administration details:

MAP decrease > 20%:
6 mg, 6mg, 9 mg, 9 mg, 12 mg, …..(max 24mg/bolus) (from x mg until y mg)
A total amount of 140 mg Ephedrine will not be exceeded.

Investigational medicinal product name	Ephedrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Intravenous bolus use

Dosage and administration details:

MAP decrease > 20%:
6 mg, 6mg, 9 mg, 9 mg, 12 mg, …..(max 24mg/bolus) (from y mg)
A total amount of 140 mg Ephedrine will not be exceeded.

Arm title	Group 4

Arm description:

Phenylephrine- Phenylephrine - Phenylephrine

Arm type	Experimental
Investigational medicinal product name	Phenylephrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

MAP decrease >20%:
50µg, 50µg, 100µg, 100µg, 150µg, 150µg,…(max 500µg/bolus) (until x mg)
A total amount of 1500 µg will not be exceeded.

Investigational medicinal product name	Phenylephrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

MAP decrease >20%:
50µg, 50µg, 100µg, 100µg, 150µg, 150µg,…(max 500µg/bolus) (starting from x until y mg)
A total amount of 1500 µg will not be exceeded.

Investigational medicinal product name	Phenylephrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

MAP decrease >20%:
50µg, 50µg, 100µg, 100µg, 150µg, 150µg,…(max 500µg/bolus) (starting from y mg)
A total amount of 1500 µg will not be exceeded.

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	7	7	7
Completed	7	7	7

Number of subjects in period 1	Group 4
Started	7
Completed	7

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description: Ephedrine- Phenylephrine - Ephedrine	
Reporting group title	Group 2
Reporting group description: Phenylephrine- Ephedrine - Phenylephrine	
Reporting group title	Group 3
Reporting group description: Ephedrine- Ephedrine - Ephedrine	
Reporting group title	Group 4
Reporting group description: Phenylephrine- Phenylephrine - Phenylephrine	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	7	7	7
Age categorical Units: Subjects			
Age continuous Units: years			
median	70	61	66
full range (min-max)	56 to 81	48 to 84	54 to 83
Gender categorical Units: Subjects			
Female	3	1	6
Male	4	6	1
BMI Units: kg/m²			
median	23.5	27.4	27.6
full range (min-max)	17.5 to 25.8	19.3 to 29.9	18.4 to 30.0

Reporting group values	Group 4	Total	
Number of subjects	7	28	
Age categorical Units: Subjects			
Age continuous Units: years			
median	67		
full range (min-max)	52 to 87	-	
Gender categorical Units: Subjects			
Female	4	14	
Male	3	14	

BMI Units: kg/m² median full range (min-max)	 24.6 19.6 to 27.3	 -	

End points

End points reporting groups

Reporting group title	Group 1
Reporting group description: Ephedrine- Phenylephrine - Ephedrine	
Reporting group title	Group 2
Reporting group description: Phenylephrine- Ephedrine - Phenylephrine	
Reporting group title	Group 3
Reporting group description: Ephedrine- Ephedrine - Ephedrine	
Reporting group title	Group 4
Reporting group description: Phenylephrine- Phenylephrine - Phenylephrine	
Subject analysis set title	Ephedrine
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients treated with ephedrine for MAP decrease > 20%	
Subject analysis set title	Phenylephedrine
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients treated with phenylephedrine for MAP decrease > 20%	

Primary: Spinal oxygen saturation measured by NIRS (T3-T4)

End point title	Spinal oxygen saturation measured by NIRS (T3-T4)
End point description:	
End point type	Primary
End point timeframe: From start induction until end of procedure	

End point values	Ephedrine	Phenylephedrine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: percentage				
arithmetic mean (standard deviation)				
Pre	78.4 (± 7.4)	79.5 (± 8.3)		
Post	77.1 (± 8.6)	79.9 (± 7.7)		
Pre-Post difference	-1.3 (± 3.4)	0.4 (± 2.5)		

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Ephedrine v Phenylephedrine
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	-1.1
Variability estimate	Standard deviation

Primary: Spinal oxygen saturation measured by NIRS (T9-T10)	
End point title	Spinal oxygen saturation measured by NIRS (T9-T10)
End point description:	
End point type	Primary
End point timeframe:	
From start induction until end of procedure	

End point values	Ephedrine	Phenylephedrine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: percentage				
arithmetic mean (standard deviation)				
Pre	73.4 (± 10.9)	74.7 (± 8.9)		
Post	72.6 (± 11.4)	75.4 (± 8.8)		
Pre-Post difference	-0.7 (± 2.6)	0.7 (± 2.0)		

Statistical analyses

Statistical analysis title	Statystical analysis
Comparison groups	Phenylephedrine v Ephedrine

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.006
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	-0.4
Variability estimate	Standard deviation

Primary: Spinal oxygen saturation measured by NIRS (L1-L2)

End point title	Spinal oxygen saturation measured by NIRS (L1-L2)

End point description:

End point type	Primary

End point timeframe:

From start induction until end of procedure

End point values	Ephedrine	Phenylephedrine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: percentage				
arithmetic mean (standard deviation)				
Pre	76.0 (± 11.8)	76.0 (± 10.5)		
Post	74.7 (± 12.3)	75.9 (± 10.2)		
Pre-Post difference	-1.3 (± 2.7)	-0.1 (± 1.4)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Ephedrine v Phenylephedrine
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-0.8
Variability estimate	Standard deviation

Secondary: Cerebral oxygenation (NIRS)

End point title	Cerebral oxygenation (NIRS)

End point description:

End point type	Secondary

End point timeframe:

From start induction until end procedure

End point values	Ephedrine	Phenylephedrine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: percentage				
arithmetic mean (standard deviation)				
Pre	65.3 (± 8.3)	66.4 (± 8.9)		
Post	64.7 (± 7.7)	63.7 (± 9.1)		
Pre-post difference	-0.6 (± 3.9)	-2.7 (± 3.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Heartrate

End point title	Heartrate

End point description:

End point type	Secondary

End point timeframe:

From start induction until end procedure

End point values	Ephedrine	Phenylephedrine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: bpm				
arithmetic mean (standard deviation)				
Pre	58 (± 11)	60 (± 12)		
Post	61 (± 11)	57 (± 12)		
Pre-Post difference	3 (± 6)	-3 (± 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood pressure

End point title	Blood pressure

End point description:

End point type	Secondary

End point timeframe:

From start induction until end procedure

End point values	Ephedrine	Phenylephedrine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: mmHg				
arithmetic mean (standard deviation)				
Pre	68 (± 10)	73 (± 11)		
Post	80 (± 12)	86 (± 12)		
Pre-Post difference	12 (± 9)	13 (± 8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total amount of vasoactive medication used

End point title	Total amount of vasoactive medication used

End point description:

End point type	Secondary

End point timeframe:

From start induction until end of procedure

End point values	Ephedrine	Phenylephedrine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: µg				
median (full range (min-max))	18000 (6000 to 144000)	100 (50 to 500)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events will be reported between the first dose administration of trial medication and the last trial related activity.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Group 4

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No other adverse events occurred during the study

Serious adverse events	Group 4		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Myocardial rupture	Additional description: Pseudo aneurysme : surgical complication		
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group 4		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2016	Protocol update to version 6

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported