Clinical trial results:
Optimal cerebral perfusion after an extracranial-intracranial bypass: should we increase blood pressure or cardiac output?

Summary

EudraCT number	2018-002008-15
Trial protocol	NL
Global end of trial date	22 July 2019

Results information

Result version number	v1 (current)
This version publication date	06 August 2020
First version publication date	06 August 2020
Summary attachment (see zip file)	Summary of results (SummaryResults_NL6509504118EudraCT2018-002008-15.pdf)

Trial information

Trial identification

Sponsor protocol code	NL65095.041.18

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Netherlands Trial Register: NL7077

Notes:

Sponsors

Sponsor organisation name	University Medical Center Utrecht
Sponsor organisation address	Heidelberglaan , Utrecht, Netherlands, 3584 CX
Public contact	Research office DVF, University Medical Center Utrecht, 0031 0887577081,
Scientific contact	Research office DVF, University Medical Center Utrecht, 0031 0887577081, a.akkermans@umcutrecht.nl

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	01 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2019
Global end of trial reached?	Yes
Global end of trial date	22 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In this pilot study, we aim to determine the mean change in graft perfusion when increasing the cardiac output and the mean change in graft perfusion when increasing the blood pressure, to enable further research to establish We aim to study whether an increase in cardiac output results in a higher graft perfusion than an increase in blood pressure in patients undergoing cerebral revascularization surgery with a bypass.

Protection of trial subjects:

Patients were informed prior to participation in the trial. Strict in- and exclusion criteria were defined. Exclusion criteria were an emergency procedure, pregnancy, a contra-indication for either dobutamine or phenylephrine, and a mean arterial pressure (MAP) <60 mmHg or SBP >180 mmHg under general anaesthesia before start of the interventions.

Background therapy:

General anesthesia with phenylephrine to reach appropriate intra-operative blood pressure levels. The intervention (dobutamine to increase cardiac output and phenylephrine to increase blood pressure) was used on top of this.

Evidence for comparator:

We hypothesized that inotropes – to increase cardiac output - rather than vasopressors – to increase blood pressure – are a key element for adequate graft flow and cerebral perfusion, based on the Hagen–Poiseuille equation

Actual start date of recruitment	03 September 2018
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	Netherlands: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This randomized crossover study was conducted between September 2018 and July 2019 at the University Medical Centre (UMC) Utrecht Adult patients (18 years or above) presenting for an extracranial-intracranial or intracranial-intracranial cerebral bypass were eligible for inclusion after written informed consent.

Pre-assignment

Screening details:

Inclusion: ECIC bypass. Exclusion: emergency procedure, pregnancy, a contra-indication dobutamine or phenylephrine, and a mean arterial pressure (MAP) <60 mmHg or Systolic blood pressuBP >180 mmHg under general anaesthesia. 15 patients presented for 17 procedures, 8 were included for 10 procedures (two patients presented twice). Wash out: 20 minute

Pre-assignment period milestones

Number of subjects started	10
Intermediate milestone: Number of subjects	start of study intervention: 10
Number of subjects completed	10

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Subject, Monitor, Carer

Blinding implementation details:

See period 1 (intervention 1)

Arms

Arm title	Baseline

Arm description:

Before start dobutamine or phenylephrine, patients were allowed to use phenylephrine infusion prior to start of the study.

Arm type	cross over - dobutamine first
Investigational medicinal product name	Phenylephrine
Investigational medicinal product code	SUB09788MIG
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

phenylephrine 0.15-1 µg kg-1 min-1 for 6-23 minutes (depending on effect) via central venous catheter

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: The investigator and analysis were not blind, but the patient was blinded, as well the anaesthesiologist for graft flow, whereas the neurosurgeon, who measured graft flow, was blinded for medication given and blood pressure and cardiac index data.

Number of subjects in period 1	Baseline
Started	10
Completed	10

Period 2

Period 2 title	Intervention: phenylephrine (cross over)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[2]
Roles blinded	Subject, Monitor, Carer

Blinding implementation details:

The anaesthesiologist was blinded for graft flow, whereas the neurosurgeon, who measured graft flow, was blinded for medication given and blood pressure and cardiac index data.

Arms

Arm title	Phenylephrine

Arm description:

The interventions took place after construction of the bypass. Patients were randomized to sequentially receive dobutamine and phenylephrine via a central venous catheter. After a first reference phase to record baseline graft flow, the first intervention (administration of dobutamine or phenylephrine) was applied. After a wash-out period of twenty minutes and a second reference phase, the alternative intervention was applied. The dosages of dobutamine (2-15 µg kg-1 min-1) and phenylephrine (0.15-1 µg kg-1 min-1) varied depending on their effect on cardiac index and blood pressure, respectively. For dobutamine, the infusion rate was targeted at an increase in cardiac index of at least 10%, as compared to the mean cardiac index in the reference phase. For phenylephrine, the infusion rate was adjusted to target a 10% increase in MAP as compared to the reference phase. During the reference and the intervention phases SBP, MAP, heart rate, stroke volume, cardiac index and graft

Arm type	Active comparator
Investigational medicinal product name	Phenylephrine
Investigational medicinal product code	SUB09788MIG
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

phenylephrine 0.15-1 µg kg-1 min-1 for 6-23 minutes (depending on effect) via central venous catheter

Notes:

[2] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: The investigator and analysis were not blind, but the patient was blinded, as well the anaesthesiologist for graft flow, whereas the neurosurgeon, who measured graft flow, was blinded for medication given and blood pressure and cardiac index data.

Number of subjects in period 2	Phenylephrine
Started	10
reference stage	10
intervention stage	10
Completed	10

Period 3

Period 3 title	Intervention: dobutamine (cross over)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[3]
Roles blinded	Subject, Monitor, Carer

Blinding implementation details:

The anaesthesiologist was blinded for graft flow, whereas the neurosurgeon, who measured graft flow, was blinded for medication given and blood pressure and cardiac index data.

Arms

Arm title	Dobutamine (cross over)

Arm description:

The interventions took place after construction of the bypass. Patients were randomized to sequentially receive dobutamine and phenylephrine via a central venous catheter. After a first reference phase to record baseline graft flow, the first intervention (administration of dobutamine or phenylephrine) was applied. After a wash-out period of twenty minutes and a second reference phase, the alternative intervention was applied. The dosages of dobutamine (2-15 µg kg-1 min-1) and phenylephrine (0.15-1 µg kg-1 min-1) varied depending on their effect on cardiac index and blood pressure, respectively. For dobutamine, the infusion rate was targeted at an increase in cardiac index of at least 10%, as compared to the mean cardiac index in the reference phase. For phenylephrine, the infusion rate was adjusted to target a 10% increase in MAP as compared to the reference phase. During the reference and the intervention phases SBP, MAP, heart rate, stroke volume, cardiac index and graft

Arm type	Experimental
Investigational medicinal product name	Dobutamine hydrochloride
Investigational medicinal product code	SUB01803MIG
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Dobutamine 2-15 µg kg-1 min-1 for 8-31 minuets (depending on effect) via central venous catheter

Notes:

[3] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: The investigator and analysis were not blind, but the patient was blinded, as well the anaesthesiologist for graft flow, whereas the neurosurgeon, who measured graft flow, was blinded for medication given and blood pressure and cardiac index data.

Number of subjects in period 3	Dobutamine (cross over)
Started	10
reference	10
Intervention	10
Completed	10

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age of all ten patients			
Units: years			
median	48		
inter-quartile range (Q1-Q3)	41 to 53	-	
Gender categorical			
gender for all ten patients			
Units: Subjects			
Female	5	5	
Male	5	5	
Indication bypass			
indication: moya Mona disease or atherosclerotic disease			
Units: Subjects			
Moya Moya	7	7	
Atherosclerotic	3	3	

Subject analysis sets

Subject analysis set title	Full analysis
Subject analysis set type	Full analysis

Subject analysis set description:

All ten patients were included for analysis. Only the results from dobutamine stage in one patient were excluded from the analysis since this patient developed an arrhythmia, making cardiac output measurements no longer reliable.

Reporting group values	Full analysis		
Number of subjects	10		

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age of all ten patients			
Units: years			
median	48		
inter-quartile range (Q1-Q3)	41 to 53		
Gender categorical			
gender for all ten patients			
Units: Subjects			
Female Male			
Indication bypass			
indication: moya Mona disease or atherosclerotic disease			
Units: Subjects			
Moya Moya	7		
Atherosclerotic	3		

End points

End points reporting groups

Reporting group title	Baseline

Reporting group description:

Before start dobutamine or phenylephrine, patients were allowed to use phenylephrine infusion prior to start of the study.

Reporting group title	Phenylephrine

Reporting group description:

The interventions took place after construction of the bypass. Patients were randomized to sequentially receive dobutamine and phenylephrine via a central venous catheter. After a first reference phase to record baseline graft flow, the first intervention (administration of dobutamine or phenylephrine) was applied. After a wash-out period of twenty minutes and a second reference phase, the alternative intervention was applied. The dosages of dobutamine (2-15 µg kg-1 min-1) and phenylephrine (0.15-1 µg kg-1 min-1) varied depending on their effect on cardiac index and blood pressure, respectively. For dobutamine, the infusion rate was targeted at an increase in cardiac index of at least 10%, as compared to the mean cardiac index in the reference phase. For phenylephrine, the infusion rate was adjusted to target a 10% increase in MAP as compared to the reference phase. During the reference and the intervention phases SBP, MAP, heart rate, stroke volume, cardiac index and graft

Reporting group title	Dobutamine (cross over)

Reporting group description:

The interventions took place after construction of the bypass. Patients were randomized to sequentially receive dobutamine and phenylephrine via a central venous catheter. After a first reference phase to record baseline graft flow, the first intervention (administration of dobutamine or phenylephrine) was applied. After a wash-out period of twenty minutes and a second reference phase, the alternative intervention was applied. The dosages of dobutamine (2-15 µg kg-1 min-1) and phenylephrine (0.15-1 µg kg-1 min-1) varied depending on their effect on cardiac index and blood pressure, respectively. For dobutamine, the infusion rate was targeted at an increase in cardiac index of at least 10%, as compared to the mean cardiac index in the reference phase. For phenylephrine, the infusion rate was adjusted to target a 10% increase in MAP as compared to the reference phase. During the reference and the intervention phases SBP, MAP, heart rate, stroke volume, cardiac index and graft

Subject analysis set title	Full analysis
Subject analysis set type	Full analysis

Subject analysis set description:

All ten patients were included for analysis. Only the results from dobutamine stage in one patient were excluded from the analysis since this patient developed an arrhythmia, making cardiac output measurements no longer reliable.

Primary: Graft flow

End point title	Graft flow

End point description:

Graft flow was measured with an ultrasonographic flow meter (Transonic Systems Inc., Ithaca, New York, USA), with a probe encircling the bypass in close proximity to the anastomosis with the intracranial artery. The mean graft flow was estimated for each reference and intervention phase and was plotted over time for each patient. The change in graft flow between intervention phase I and the corresponding reference phase I, and between intervention phase II and reference phase II was calculated. Afterwards, a two-sided Wilcoxon signed rank test was used to assess the difference in flow, after confirmation that the data was not normally distributed

End point type	Primary

End point timeframe:

Difference between first and second intervention

End point values	Phenylephrine	Dobutamine (cross over)	Full analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	9	9	
Units: ml min -1				
median (inter-quartile range (Q1-Q3))	3.6 (1.3 to 7.8)	4.1 (1.7 to 12.0)	-0.6 (-14.5 to 5.3)	

Statistical analyses

Statistical analysis title	Analysis

Statistical analysis description:

The mean graft flow was estimated for each reference and intervention phase and was plotted over time for each patient. The change in graft flow between intervention phase I and the corresponding reference phase I, and between intervention phase II and reference phase II was calculated. Afterwards, a two-sided Wilcoxon signed rank test was used to assess the difference in flow, after confirmation that the data was not normally distributed. A pseudo median was reported.

Comparison groups	Dobutamine (cross over) v Phenylephrine
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %

Notes:

[1] - Mean graft flow was estimated for each reference and intervention phase and was plotted over time. Change in flow between intervention phase I and reference phase I, and between intervention II and reference II was calculated. A two-sided Wilcoxon signed rank test was used to assess the difference in flow. A pseudomedian was reported. The same was done for secondary endpoints. A random multivariable linear effect model was constructed to assess treatment and carry over effect.

Secondary: Secondary endpoint mean arterial blood pressure

End point title	Secondary endpoint mean arterial blood pressure

End point description:

The change in blood pressure between intervention phase I and the corresponding reference phase I, and between intervention phase II and reference phase II was calculated. Afterwards, a two-sided Wilcoxon signed rank test was used to assess the difference in blood pressure, after confirmation that the data was not normally distributed

End point type	Secondary

End point timeframe:

Difference between two interventions

End point values	Phenylephrine	Dobutamine (cross over)	Full analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	9	9	
Units: mmHg				
median (inter-quartile range (Q1-Q3))	16 (14 to 19)	-7 (-7 to 0)	21 (12 to 31)	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint systolic blood pressure

End point title	Secondary endpoint systolic blood pressure

End point description:

The change in blood pressure between intervention phase I and the corresponding reference phase I, and between intervention phase II and reference phase II was calculated. Afterwards, a two-sided Wilcoxon signed rank test was used to assess the difference in blood pressure, after confirmation that the data was not normally distributed

End point type	Secondary

End point timeframe:

Difference between two interventions

End point values	Phenylephrine	Dobutamine (cross over)	Full analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	9	9	
Units: mmHg				
median (inter-quartile range (Q1-Q3))	32 (26 to 33)	5 (-1 to 20)	24 (7 to 35)	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint Cardiac output

End point title	Secondary endpoint Cardiac output

End point description:

The change in cardiac output between intervention phase I and the corresponding reference phase I, and between intervention phase II and reference phase II was calculated. Afterwards, a two-sided Wilcoxon signed rank test was used to assess the difference in cardiac output after confirmation that the data was not normally distributed

End point type	Secondary

End point timeframe:

Difference between two interventions

End point values	Phenylephrine	Dobutamine (cross over)	Full analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	9	9	
Units: ml min-1				
median (inter-quartile range (Q1-Q3))	0.1 (-0.2 to 0.3)	1.1 (0.8 to 1.5)	-1 (-1.4 to -0.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint heart rate

End point title	Secondary endpoint heart rate

End point description:

The change in heart rate between intervention phase I and the corresponding reference phase I, and between intervention phase II and reference phase II was calculated. Afterwards, a two-sided Wilcoxon signed rank test was used to assess the difference in heart rate , after confirmation that the data was not normally distributed

End point type	Secondary

End point timeframe:

Difference between two interventions

End point values	Phenylephrine	Dobutamine (cross over)	Full analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	9	9	
Units: min-1				
median (inter-quartile range (Q1-Q3))	-1 (-2 to -1)	5 (2 to 6)	-7 (-12 to -4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint stroke volume

End point title	Secondary endpoint stroke volume

End point description:

The change in stroke volume between intervention phase I and the corresponding reference phase I, and between intervention phase II and reference phase II was calculated. Afterwards, a two-sided Wilcoxon signed rank test was used to assess the difference in stroke volume, after confirmation that the data was not normally distributed

End point type	Secondary

End point timeframe:

Difference between two interventions

End point values	Phenylephrine	Dobutamine (cross over)	Full analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	9	9	
Units: ml				
median (inter-quartile range (Q1-Q3))	4 (-0.5 to 7)	13 (11 to 22)	-10 (-19 to -4)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Until end of bypass procedure	
Adverse event reporting additional description:	
Short follow-up due to fast washout of both dobutamine and phenylephrine	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
Before start dobutamine or phenylephrine	

Serious adverse events	Baseline		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Baseline		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)		
Cardiac disorders			
Arrhytmia	Additional description: Short arrhythmia after dobutamine administration, stopped when infusion of dobutamine was stopped. No hemodynamic consequences (e.a. no effect on blood pressure)		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Data for one patient receiving dobutamine were not included in analysis due to unreliable cardiac output values caused by arrhythmia, results during phenylephrine phase were used for this patients.

Notes: