Clinical trial results:
Influence of intra-arterial cerebral Papaverine Hydrochloride on cerebral glucose, lactate, pyruvate, glycerol, and glutamate concentrations, cerebral oxygenation, angiographic vasospasm, delayed stroke rates, and neurologic outcome in patients suffering life-threatening post-subarachnoid hemorrhage cerebral vasospasm irresponsive to hyperdynamic treatment.

Summary

EudraCT number	2010-023878-40
Trial protocol	AT
Global end of trial date	10 December 2019

Results information

Result version number	v1 (current)
This version publication date	19 February 2020
First version publication date	19 February 2020

Trial information

Trial identification

Sponsor protocol code	2.3

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria,
Public contact	Neurosurgery, AKH Wien, Medical University Vienna, 0043 1404002565,
Scientific contact	Neurosurgery, AKH Wien, Medical University Vienna, 0043 1404002565,

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	21 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2019
Global end of trial reached?	Yes
Global end of trial date	10 December 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

o demonstrate the influence of intra-arterial cerebral Papaverine Hydrochloride on cerebral glucose, lactate, pyruvate, glycerol, and glutamate concentrations and cerebral oxygenation in patients suffering severe post-SAH cerebral VSP

Protection of trial subjects:

Continuous multimodality Neuromonitoring including intracranial pressure, brain tissue oxygen tension and cerebral microdialysis monitoring
Computed tomography scans
Daily blood tests

Background therapy:

sedation: propofol and remifentanil, switched to midazolam (up to 20 mg/h) and sufentanil (up to 0.25 µg/kg/min) after 3 to 5 days. Ketamine (up to 200mg/h), and metohexital (up to 1mg/kg/h) was added in case of inadequate sedation.
Nimodpine: orally, 60 mg every 4 hours

Evidence for comparator: -

Actual start date of recruitment	14 May 2016
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	Austria: 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 months)	0
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:

Patient recruitment was performed between May 2016 and March 2019.
Patients fulfilling the inclusion criteria (multimodality monitoring and clinical indication for intra-arterial papaverine-hydrochloride administration) were recruited consecutively.

Pre-assignment

Screening details:

Screening visit included: physical and neurological examination, vital signs, laboratory tests (haematology, chemistry, serology), transcranial doppler ultrasound, medical and medication history, concomitant medication

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	intra-arterial Papaverine-Hydrochloride

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Papaverin-Hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarterial use

Dosage and administration details:

super-selective intra-arterial administration of 75 - 125 mg (concentration 5 mg/mL) in each spastic vascular territory manually via microcatheter

Number of subjects in period 1	intra-arterial Papaverine-Hydrochloride
Started	10
Completed	10

Period 2

Period 2 title	12 hours post-interventional
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms	
Arm title	intra-arterial Papaverine-Hydrochloride
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Papaverin-Hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarterial use

Dosage and administration details:

super-selective intra-arterial administration of 75 - 125 mg (concentration 5 mg/mL) in each spastic vascular territory manually via microcatheter

Number of subjects in period 2	intra-arterial Papaverine-Hydrochloride
Started	10
Completed	10

Period 3	
Period 3 title	7 days post intervention
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms	
Arm title	intra-arterial Papaverine-Hydrochloride
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Papaverin-Hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarterial use

Dosage and administration details:

super-selective intra-arterial administration of 75 - 125 mg (concentration 5 mg/mL) in each spastic vascular territory manually via microcatheter

Number of subjects in period 3	intra-arterial Papaverine-Hydrochloride
Started	10
Completed	10

Period 4	
Period 4 title	3 month functional outcome
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	intra-arterial Papaverine-Hydrochloride
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Papaverin-Hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarterial use

Dosage and administration details:

super-selective intra-arterial administration of 75 - 125 mg (concentration 5 mg/mL) in each spastic vascular territory manually via microcatheter

Number of subjects in period 4	intra-arterial Papaverine-Hydrochloride
Started	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			
Adults (18-64 years)	10	10	
Age continuous Units: years			
median	51		
inter-quartile range (Q1-Q3)	44 to 55	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	2	2	

Subject analysis sets

Subject analysis set title	All patients
Subject analysis set type	Full analysis

Subject analysis set description:
All included patients

Reporting group values	All patients		
Number of subjects	10		
Age categorical Units: Subjects			
Adults (18-64 years)	10		
Age continuous Units: years			
median	51		
inter-quartile range (Q1-Q3)	44 to 55		
Gender categorical Units: Subjects			
Female	8		
Male	2		

End points

End points reporting groups

Reporting group title	intra-arterial Papaverine-Hydrochloride
Reporting group description: -	
Reporting group title	intra-arterial Papaverine-Hydrochloride
Reporting group description: -	
Reporting group title	intra-arterial Papaverine-Hydrochloride
Reporting group description: -	
Reporting group title	intra-arterial Papaverine-Hydrochloride
Reporting group description: -	
Subject analysis set title	All patients
Subject analysis set type	Full analysis
Subject analysis set description: All included patients	

Primary: Cerebral lactate concentration following intra-arterial Papaverine-Hydrochloride administration

End point title	Cerebral lactate concentration following intra-arterial Papaverine-Hydrochloride administration
End point description:	
End point type	Primary
End point timeframe: within 12 hours after intervention	

End point values	intra-arterial Papaverine-Hydrochloride	intra-arterial Papaverine-Hydrochloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: mmol/L				
arithmetic mean (standard deviation)	3.8 (± 1.4)	5.1 (± 2.1)		

Statistical analyses

Statistical analysis title	comparison to baseline
Comparison groups	intra-arterial Papaverine-Hydrochloride v intra-arterial Papaverine-Hydrochloride
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:
[1] - single-arm: comparison of baseline with post-interventional values

Primary: Cerebral lactate-pyruvate ratio concentration following intra-arterial Papaverine-Hydrochloride administration

End point title	Cerebral lactate-pyruvate ratio concentration following intra-arterial Papaverine-Hydrochloride administration

End point description:

End point type	Primary

End point timeframe:
within 12 hours after intervention

End point values	intra-arterial Papaverine-Hydrochloride	intra-arterial Papaverine-Hydrochloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: no units (ratio)				
arithmetic mean (standard deviation)	39.3 (± 15.3)	30.5 (± 6.7)		

Statistical analyses

Statistical analysis title	comparison to baseline
Comparison groups	intra-arterial Papaverine-Hydrochloride v intra-arterial Papaverine-Hydrochloride
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:
[2] - single-arm: comparison of baseline with post-interventional values

Primary: Cerebral glycerol concentration following intra-arterial Papaverine-Hydrochloride administration

End point title	Cerebral glycerol concentration following intra-arterial Papaverine-Hydrochloride administration

End point description:

End point type	Primary

End point timeframe:
within 12 hours after intervention

End point values	intra-arterial Papaverine-Hydrochloride	intra-arterial Papaverine-Hydrochloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: µmol/L				
arithmetic mean (standard deviation)	92.8 (± 86.7)	104.4 (± 89.8)		

Statistical analyses

Statistical analysis title	comparison to baseline
Comparison groups	intra-arterial Papaverine-Hydrochloride v intra-arterial Papaverine-Hydrochloride
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - single-arm: comparison of baseline with post-interventional values

Primary: Cerebral glutamate concentration following intra-arterial Papaverine-Hydrochloride administration

End point title	Cerebral glutamate concentration following intra-arterial Papaverine-Hydrochloride administration

End point description:

End point type	Primary

End point timeframe:

within 12 hours after intervention

End point values	intra-arterial Papaverine-Hydrochloride	intra-arterial Papaverine-Hydrochloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: µmol/L				
arithmetic mean (standard deviation)	10.7 (± 16.3)	6.6 (± 8.9)		

Statistical analyses

Statistical analysis title	comparison to baseline
Comparison groups	intra-arterial Papaverine-Hydrochloride v intra-arterial Papaverine-Hydrochloride

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - single-arm: comparison of baseline with post-interventional values

Primary: Cerebral oxygenation concentration following intra-arterial Papaverine-Hydrochloride administration

End point title	Cerebral oxygenation concentration following intra-arterial Papaverine-Hydrochloride administration

End point description:

End point type	Primary

End point timeframe:

within 12 hours after intervention

End point values	intra-arterial Papaverine-Hydrochloride	intra-arterial Papaverine-Hydrochloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: mmHg				
arithmetic mean (standard deviation)	20.8 (± 12.4)	23.7 (± 12.5)		

Statistical analyses

Statistical analysis title	comparison to baseline
Comparison groups	intra-arterial Papaverine-Hydrochloride v intra-arterial Papaverine-Hydrochloride
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - single-arm: comparison of baseline with post-interventional values

Secondary: Improvement of angiographic vasospasm

End point title	Improvement of angiographic vasospasm

End point description:

End point type	Secondary

End point timeframe:

during angiography directly after intervention

End point values	intra-arterial Papaverine-Hydrochloride	intra-arterial Papaverine-Hydrochloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: number	0	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of delayed ischemic strokes

End point title	Incidence of delayed ischemic strokes

End point description:

End point type	Secondary

End point timeframe:

within 7 days following the endovascular intervention

End point values	intra-arterial Papaverine-Hydrochloride	intra-arterial Papaverine-Hydrochloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: numbers	0	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Outcome after 3 month

End point title	Functional Outcome after 3 month

End point description:

modified Rankin scale

End point type	Secondary

End point timeframe:

3 month after intervention

End point values	intra-arterial Papaverine-Hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Points				
median (inter-quartile range (Q1-Q3))	4 (1 to 5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 month after intra-arterial Papaverine-Hydrochloride administration

Adverse event reporting additional description:

regular investigator assessment and laboratories testing

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	intra-arterial Papaverine-Hydrochloride

Reporting group description: -

Serious adverse events	intra-arterial Papaverine-Hydrochloride		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Nervous system disorders			
Death	Additional description: Death due to multiple cerebral infarction with brain herniation		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebral infarction	Additional description: new cerebral infarction due to underlying disease (severe post-subarachnoid haemorrhage vasospasm)		
subjects affected / exposed	5 / 10 (50.00%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	intra-arterial Papaverine-Hydrochloride		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		

Nervous system disorders Intracranial pressure increased subjects affected / exposed occurrences (all)	 10 / 10 (100.00%) 10		

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.

early termination leading to a small number of subjects analysed

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31792510