



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 remifentanyl, 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.

Nimodipine: 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 (\pm 1.4) | 5.1 (\pm 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 | \leq 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 | 10 / 10 (100.00%) | | |
| occurrences (all) | 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>