



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 blood 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/m ² | | | |
| 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/m ² | | | |
| median | 24.6 | | |
| full range (min-max) | 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 | Statistical 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