

**Clinical trial results:****Postoperative pain treatment after elective cardiac surgery using patient-controlled target-controlled infusion (TCI-PCA) with hydromorphone vs. patient-controlled analgesia (PCA) with morphine****Summary**

| | |
|--------------------------|------------------|
| EudraCT number | 2014-004088-19 |
| Trial protocol | DE |
| Global end of trial date | 01 December 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 23 April 2020 |
| First version publication date | 23 April 2020 |

Trial information**Trial identification**

| | |
|-----------------------|-------------|
| Sponsor protocol code | TCI-PCA-002 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02483221 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Universitätsklinikum Erlangen |
| Sponsor organisation address | Maximiliansplatz 2, Erlangen, Germany, 91054 |
| Public contact | Anästhesiologische Klinik, Universitätsklinikum Erlangen, +49 91318542363, christian.jeleazcov@kfa.imed.uni-erlangen.de |
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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 December 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 December 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 December 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Comparison of analgesic efficiency of hydromorphone TCI-PCA vs. conventional morphine PCA in the early postoperative period.

Protection of trial subjects:

Assessment of pain (Numerical Rating Scale, NRS 0-10)

Assessment of sedation (Modified Observer's Assessment of Alertness/Sedation Scale, MOAAS)

Monitoring of arterial blood pressure, peripheral arterial oxygen saturation (SpO₂), heart rate and respiratory rate

Laboratory data were determined regularly by blood gas analysis

Background therapy:

Throughout the study, patients were treated and monitored according to standard protocols of the ICU. Propofol infusion until weaning from mechanical ventilation.

Vasoactive drugs were infused depending on clinical demand to maintain the mean arterial pressure in a range of 70-90 mmHg. Dobutamine, noradrenaline and glycerylnitrate infusions were routinely used. If vasoactive control was insufficient, adrenalin was administered instead of dobutamine.

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 27 April 2015 |
| 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 | Germany: 50 |
| Worldwide total number of subjects | 50 |
| EEA total number of subjects | 50 |

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) | 23 |
| From 65 to 84 years | 27 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment start: 27.04.2015

Recruitment end: 29.11.2016

Total number of screened subjects: 728

Total number of enrolled subjects: 50

Pre-assignment

Screening details:

Inclusion criteria:

Male and female

Elective cardiac surgery with thoracotomy

Age 40-85 y.

ASA<4

EF>40%

BMI<35 kg/m²

Exclusion criteria:

Allergy to opioids, diabetes mellitus, renal, neurological, psychiatric, chronic inflammatory disease

Drug abuse

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-----------------------|
| Arm title | TCI-PCA-Hydromorphone |
|------------------|-----------------------|

Arm description:

Intravenous Patient-Controlled Analgesia with Target-Controlled Infusion of hydromorphone

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Hydromorphone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Target controlled infusion with target plasma and effect site concentrations between 0.8 and 10 ng/ml in predefined increasing steps with a lock-out time of 15 min on patient request and in predefined decreasing steps on lack of patient request.

| | |
|------------------|--------------|
| Arm title | PCA-Morphine |
|------------------|--------------|

Arm description:

Patient Controlled Analgesia with morphine

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Morphine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Patient Controlled Analgesia: bolus doses of 2 mg morphine hydrochloride in one minute on patient's request with a lockout time of 10 min

| Number of subjects in period 1 | TCI-PCA- Hydromorphone | PCA-Morphine |
|--|---------------------------|--------------|
| Started | 25 | 25 |
| Completed | 23 | 21 |
| Not completed | 2 | 4 |
| Did not receive treatment, delayed operation | - | 4 |
| Adverse event, non-fatal | 1 | - |
| delayed extubation | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | TCI-PCA-Hydromorphone |
|-----------------------|-----------------------|

Reporting group description:

Intravenous Patient-Controlled Analgesia with Target-Controlled Infusion of hydromorphone

| | |
|-----------------------|--------------|
| Reporting group title | PCA-Morphine |
|-----------------------|--------------|

Reporting group description:

Patient Controlled Analgesia with morphine

| Reporting group values | TCI-PCA-Hydromorphone | PCA-Morphine | Total |
|---------------------------------------|-----------------------|--------------|-------|
| Number of subjects | 25 | 25 | 50 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 13 | 10 | 23 |
| From 65-84 years | 12 | 15 | 27 |
| Age continuous Units: years | | | |
| median | 64 | 66 | |
| full range (min-max) | 46 to 84 | 44 to 79 | - |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 3 | 7 |
| Male | 21 | 22 | 43 |
| Body weight Units: kg | | | |
| median | 86 | 82 | |
| full range (min-max) | 45 to 107 | 63 to 115 | - |

End points

End points reporting groups

| | |
|------------------------------|---|
| Reporting group title | TCI-PCA-Hydromorphone |
| Reporting group description: | Intravenous Patient-Controlled Analgesia with Target-Controlled Infusion of hydromorphone |
| Reporting group title | PCA-Morphine |
| Reporting group description: | Patient Controlled Analgesia with morphine |

Primary: Pain in rest

| | |
|------------------------|---|
| End point title | Pain in rest |
| End point description: | Pain in rest (assessed using the Numerical Rating Scale, NRS 0-10) |
| End point type | Primary |
| End point timeframe: | from extubation until end of observation period (8:00 in the morning of the next day) |

| End point values | TCI-PCA-Hydromorphone | PCA-Morphine | | |
|-------------------------------|-----------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 ^[1] | 21 ^[2] | | |
| Units: Points | | | | |
| median (full range (min-max)) | 2 (0 to 4) | 1 (0 to 5) | | |

Notes:

[1] - 2 subjects were excluded due to:
Incomplete data (n=2)

[2] - 4 subjects were excluded due to:
Did not receive intervention, delayed operation(n=4)

Statistical analyses

| | |
|---|--|
| Statistical analysis title | TCI-PCA versus PCA |
| Statistical analysis description: | NRS scores in rest were tested for significant difference between the two groups |
| Comparison groups | TCI-PCA-Hydromorphone v PCA-Morphine |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.33 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.29 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.65 |
| upper limit | 1.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.46 |

Primary: Pain under inspiration

| | |
|---|------------------------|
| End point title | Pain under inspiration |
| End point description: Pain under deep inspiration (assessed using the Numerical Rating Scale, NRS 0-10) | |
| End point type | Primary |
| End point timeframe: from extubation until end of observation period (8:00 in the morning of the next day) | |

| End point values | TCI-PCA-Hydromorphone | PCA-Morphine | | |
|-------------------------------|-----------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 ^[3] | 21 ^[4] | | |
| Units: Points | | | | |
| median (full range (min-max)) | 4 (0 to 7) | 3.5 (0 to 7) | | |

Notes:

[3] - 2 subjects were excluded due to:
Incomplete data (n=2)

[4] - 4 subjects were excluded due to:
Did not receive intervention, delayed operation (n=4)

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | TCI-PCA versus PCA |
| Statistical analysis description: NRS scores under inspiration were tested for significant difference between the two groups | |
| Comparison groups | TCI-PCA-Hydromorphone v PCA-Morphine |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.69 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.85 |
| upper limit | 1.41 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.56 |

Secondary: Sedation score

| | |
|---|----------------|
| End point title | Sedation score |
| End point description: Depth of sedation, assessed by the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S, 0-5) | |
| End point type | Secondary |
| End point timeframe: from extubation until end of observation period (8:00 in the morning of the next day) | |

| End point values | TCI-PCA-Hydromorphone | PCA-Morphine | | |
|-------------------------------|-----------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 ^[5] | 21 ^[6] | | |
| Units: Points | | | | |
| median (full range (min-max)) | 5 (5 to 5) | 5 (4 to 5) | | |

Notes:

[5] - 2 subjects were excluded due to:
Incomplete data (n=2)

[6] - 4 subjects were excluded due to:
Did not receive intervention, delayed operation (n=4)

Statistical analyses

| | |
|--|--------------------------------------|
| Statistical analysis title | TCI-PCA versus PCA |
| Statistical analysis description: MOAA/S scores were tested for significant difference between the two groups | |
| Comparison groups | TCI-PCA-Hydromorphone v PCA-Morphine |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.13 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.04 |
| upper limit | 0.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.07 |

Secondary: PONV

| | |
|---|-----------|
| End point title | PONV |
| End point description: Incidence of postoperative nausea and vomiting | |
| End point type | Secondary |
| End point timeframe: from extubation until end of observation period (8:00 in the morning of the next day) | |

| End point values | TCI-PCA-Hydromorphone | PCA-Morphine | | |
|-----------------------------|-----------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 ^[7] | 21 ^[8] | | |
| Units: number | 8 | 7 | | |

Notes:

[7] - 2 subjects were excluded due to:
Incomplete data (n=2)[8] - 4 subjects were excluded due to:
Did not receive intervention, delayed operation (n=4)**Statistical analyses**

| | |
|--|--------------------------------------|
| Statistical analysis title | TCI-PCA versus PCA |
| Statistical analysis description: Incidence of postoperative nausea and vomiting was tested for significant difference between the two groups | |
| Comparison groups | TCI-PCA-Hydromorphone v PCA-Morphine |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Fisher exact |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 2.38 |

Secondary: Respiration rate

| | |
|---|------------------|
| End point title | Respiration rate |
| End point description: | |
| End point type | Secondary |
| End point timeframe: from extubation until end of observation period (8:00 in the morning of the next day) | |

| End point values | TCI-PCA-Hydromorphone | PCA-Morphine | | |
|--------------------------------------|-----------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 ^[9] | 21 ^[10] | | |
| Units: breaths per min | | | | |
| arithmetic mean (standard deviation) | 15 (± 2) | 16 (± 4) | | |

Notes:

[9] - 2 subjects were excluded due to:
Incomplete data (n=2)

[10] - 4 subjects were excluded due to:
Did not receive intervention, delayed operation (n=4)

Statistical analyses

| Statistical analysis title | TCI-PCA versus PCA |
|---|--------------------------------------|
| Statistical analysis description: | |
| Respiration rates were tested for significant difference between the two groups | |
| Comparison groups | TCI-PCA-Hydromorphone v PCA-Morphine |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.35 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3 |
| upper limit | 1.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of treatment with hydromorphone or morphine on the first study day (day of surgery) until 8:00 AM of the second study day (1st postoperative day)

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | TCI-PCA-Hydromorphone |
|-----------------------|-----------------------|

Reporting group description:

Intravenous Patient-Controlled Analgesia with Target-Controlled Infusion of hydromorphone

| | |
|-----------------------|--------------|
| Reporting group title | PCA-Morphine |
|-----------------------|--------------|

Reporting group description:

Patient Controlled Analgesia with morphine

| Serious adverse events | TCI-PCA-Hydromorphone | PCA-Morphine | |
|---|-----------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | TCI-PCA- Hydromorphone | PCA-Morphine | |
|---|---------------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 25 (76.00%) | 15 / 21 (71.43%) | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 1 | 1 | |
| Hypertonia | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiopulmonary bypass occlusion | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 2 | |
| General disorders and administration site conditions | | | |
| Nausea | | | |
| subjects affected / exposed | 7 / 25 (28.00%) | 7 / 21 (33.33%) | |
| occurrences (all) | 9 | 7 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 1 | 1 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 1 | 1 | |
| Shivering | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | 4 / 21 (19.05%) | |
| occurrences (all) | 4 | 4 | |
| Delayed recovery from anaesthesia | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Restlessness | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | 4 / 21 (19.05%) | |
| occurrences (all) | 4 | 4 | |

| | | | |
|---|---------------------|----------------------|--|
| Hypothermia subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 21 (0.00%) 0 | |
| Pain subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 2 / 21 (9.52%) 2 | |
| Respiratory, thoracic and mediastinal disorders Respiratory depression subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 3 / 21 (14.29%) 3 | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 21 (0.00%) 0 | |

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

None reported