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
Scientific contact	Anästhesiologische Klinik, Universitätsklinikum Erlangen, +49 91318542363, christian.jeleazcov@kfa.imed.uni-erlangen.de

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