Clinical trial results:
Pain relief for chest drain removal in children after cardiac surgery: Sevoflurane versus Ketamine.

Summary

EudraCT number	2011-003786-14
Trial protocol	BE
Global end of trial date	30 March 2014

Results information

Result version number	v1 (current)
This version publication date	25 September 2022
First version publication date	25 September 2022

Trial information

Trial identification

Sponsor protocol code	AGO/2011/006

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ghent University Hospital
Sponsor organisation address	C. Heymanslaan 10, Gent, Belgium, 9000
Public contact	HIRUZ CTU, Ghent University Hospital, 32 93320500, hiruz.ctu@uzgent.be
Scientific contact	HIRUZ CTU, Ghent University Hospital, 32 93320500, hiruz.ctu@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	28 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 March 2014
Global end of trial reached?	Yes
Global end of trial date	30 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Investigate whether the administration of ketamine or sevoflurane in extubated children, in addition to the standard analgesics, can provide greater comfort during the removal of surgical thoracic drains.

Protection of trial subjects:

Ethics review and approval, informed consent, supportive care and routine monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2011
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: 51
Worldwide total number of subjects	51
EEA total number of subjects	51

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)	51
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

51 patients were recruited between 28-02-2012 and 17-03-2014. End of trial notification was dated 17-03-2014 (last patient last visit) and submitted to EC and CA on 01-02-2017. There were no dropouts.

Pre-assignment

Screening details:

Age < 14 years, post cardiac surgery, presence of surgical thoracic drains, written informed consent of the legal representative (+ oral consent of the patient if older than 12 years), sober (> eight hours ago solid food, > four hours ago milk, > two hours ago clear fluid).

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	Standard of Care

Arm description:

Standard analgesia (paracetamol ± ibuprofen and possibly an infusion of morphine).

Arm type	Active comparator
Investigational medicinal product name	Paracetamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg paracetamol per administration. The administration is repeated every six hours.

Investigational medicinal product name	Nurofen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Enteral use

Dosage and administration details:

The dosage is 7.5 mg/kg per os. The administration is repeated every six hours.

Investigational medicinal product name	Morphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Morphine is administered via continuous infusion at doses ranging from 10 to 40 µg/kg/hour depending on the pain score measured by the Comfort-B scale.

Arm title	Sevoflurane

Arm description:

Standard analgesia + Sevoflurane

Arm type	Experimental

Investigational medicinal product name	Paracetamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg paracetamol per administration. The administration is repeated every six hours.

Investigational medicinal product name	Nurofen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Enteral use

Dosage and administration details:

The dosage is 7.5 mg/kg per os. The administration is repeated every six hours.

Investigational medicinal product name	Morphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Morphine is administered via continuous infusion at doses ranging from 10 to 40 µg/kg/hour depending on the pain score measured by the Comfort-B scale.

Investigational medicinal product name	Sevoflurane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Sevoflurane is administered in the form of an inhalation gas. A combination of x L oxygen/minute (x = 2 times the normal minute volume by weight) and 6% sevoflurane is started.

Arm title	Ketamine

Arm description:

Standard analgesia + Ketamine

Arm type	Experimental
Investigational medicinal product name	Paracetamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg paracetamol per administration. The administration is repeated every six hours.

Investigational medicinal product name	Nurofen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Enteral use

Dosage and administration details:

The dosage is 7.5 mg/kg per os. The administration is repeated every six hours.

Investigational medicinal product name	Morphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use

Dosage and administration details:

Morphine is administered via continuous infusion at doses ranging from 10 to 40 µg/kg/hour depending on the pain score measured by the Comfort-B scale.

Investigational medicinal product name	Ketamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The dose of ketamine is a single intravenous administration of 1mg/kg body weight over a time span of at least one minute.

Number of subjects in period 1	Standard of Care	Sevoflurane	Ketamine
Started	17	17	17
Completed	17	17	17

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	51	51	
Age categorical Units: Subjects			
Age continuous Units: years			
median	2.2		
inter-quartile range (Q1-Q3)	0.5 to 4.6	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	32	32	
Drains Units: Subjects			
1 drain	8	8	
2 drains	23	23	
3 drains	12	12	
4 drains	8	8	
RACHS-1 score Units: Subjects			
Score 1	12	12	
Score 2	18	18	
Score 3	20	20	
Score 4	1	1	
Length Units: cm			
median	82		
inter-quartile range (Q1-Q3)	66 to 102	-	
Weight Units: kg			
median	11		
inter-quartile range (Q1-Q3)	6 to 16	-	

Subject analysis sets

Subject analysis set title	Pain and comfort
Subject analysis set type	Full analysis

Subject analysis set description:

All groups started and ended with an average Comfort-B score between comfort limits of 12 to 16. When removing the dressing, the standard group peaked at an average value of about 21. In the ketamine group, there was a slight decrease in the average score. The sevoflurane group peaked at an average value of about eight. This trend persisted throughout the entire procedure.

Reporting group values	Pain and comfort		
Number of subjects	51		
Age categorical Units: Subjects			

Age continuous Units: years median inter-quartile range (Q1-Q3)	 2.2 0.5 to 4.6		
Gender categorical Units: Subjects			
Female Male			
Drains Units: Subjects			
1 drain 2 drains 3 drains 4 drains			
RACHS-1 score Units: Subjects			
Score 1 Score 2 Score 3 Score 4			
Length Units: cm median inter-quartile range (Q1-Q3)			
Weight Units: kg median inter-quartile range (Q1-Q3)			

End points

End points reporting groups

Reporting group title	Standard of Care
Reporting group description:	
Standard analgesia (paracetamol ± ibuprofen and possibly an infusion of morphine).	
Reporting group title	Sevoflurane
Reporting group description:	
Standard analgesia + Sevoflurane	
Reporting group title	Ketamine
Reporting group description:	
Standard analgesia + Ketamine	
Subject analysis set title	Pain and comfort
Subject analysis set type	Full analysis
Subject analysis set description:	
All groups started and ended with an average Comfort-B score between comfort limits of 12 to 16. When removing the dressing, the standard group peaked at an average value of about 21. In the ketamine group, there was a slight decrease in the average score. The sevoflurane group peaked at an average value of about eight. This trend persisted throughout the entire procedure.	

Primary: Comfort Behavior

End point title	Comfort Behavior
End point description:	
End point type	Primary
End point timeframe:	
Comfort B-score measured during all phases of the procedure: pre-measurement, removal bandage, removal drains, bandage, post-measurement.	

End point values	Standard of Care	Sevoflurane	Ketamine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17	
Units: Score				
number (not applicable)				
pre-measurement	13	13	15	
removal bandage	21	8	12	
removal drains	22	8	13	
bandage	20	8	14	
post-measurement	14	14	13	

Statistical analyses

Statistical analysis title	Pain and comfort evolution
Statistical analysis description:	
It was tested whether the visual differences are also statistically significant. Before the procedure and one hour after the procedure, the respective categorized Comfort-B scores between the three groups	

were not significantly different from each other, but during the removal of the dressing, the drains and the re-establishment of the dressing, the difference of the respective categorized Comfort-B scores between the three groups was significant.

Comparison groups	Standard of Care v Sevoflurane v Ketamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Kruskal-wallis

Secondary: Impact on arterial blood pressure - RRs0 and RRs2

End point title	Impact on arterial blood pressure - RRs0 and RRs2

End point description:

RRs0 (mmHg) = systolic blood pressure before the start of the procedure
RRs2 (mmHg) = systolic blood pressure when removing drains

Mean = RRs0 - RRs2

End point type	Secondary

End point timeframe:

Before administration of anesthesia, 3x during procedure (removal of thoracic drains) and 60 minutes after end of procedure.

End point values	Standard of Care	Sevoflurane	Ketamine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17	
Units: difference between RRs0 and RRs2 (mmHg)				
arithmetic mean (standard deviation)	-27.250 (± 19.443)	16.182 (± 9.998)	-12.167 (± 17.440)	

Statistical analyses

Statistical analysis title	Standard Care
Comparison groups	Standard of Care v Sevoflurane v Ketamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [1]
Method	t-test, 2-sided

Notes:

[1] - A paired t-test (P < 0.05) was used to determine statistically significance. When p < 0.05, it can be concluded that the blood pressure (systolic/mean) before the start significantly differ from that during the removal of the drains.

Statistical analysis title	Sevoflurane
Comparison groups	Sevoflurane v Standard of Care v Ketamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [2]
Method	t-test, 2-sided

Notes:

[2] - A paired t-test (P < 0.05) was used to determine statistically significance. When p < 0.05, it can be concluded that the blood pressure (systolic/mean) before the start significantly differ from that during the removal of the drains.

Statistical analysis title	Ketamine
Comparison groups	Ketamine v Standard of Care v Sevoflurane
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034 [3]
Method	t-test, 2-sided

Notes:

[3] - A paired t-test (P < 0.05) was used to determine statistically significance. When p < 0.05, it can be concluded that the blood pressure (systolic/mean) before the start significantly differ from that during the removal of the drains.

Secondary: Impact on arterial blood pressure - RRm0 and RRm2

End point title	Impact on arterial blood pressure - RRm0 and RRm2

End point description:

RRm0 (mmHg) = meanblood pressure before the start of the procedure
RRm2 (mmHg) = mean blood pressure when removing drains

Mean = RRm0 - RRm2

End point type	Secondary

End point timeframe:

Before administration of anesthesia, 3x during procedure (removal of thoracic drains) and 60 minutes after end of procedure.

End point values	Standard of Care	Sevoflurane	Ketamine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17	
Units: difference between RRm0 and RRm2 (mmHg)				
arithmetic mean (standard deviation)	-21.000 (± 14.924)	13.364 (± 8.441)	-9.750 (± 12.913)	

Statistical analyses

Statistical analysis title	Standard Care
Comparison groups	Standard of Care v Sevoflurane v Ketamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [4]
Method	t-test, 2-sided

Notes:

[4] - A paired t-test (P < 0.05) was used to determine statistically significance. When p < 0.05, it can be concluded that the blood pressure (systolic/mean) before the start significantly differ from that during the removal of the drains.

Statistical analysis title	Sevoflurane
Comparison groups	Sevoflurane v Standard of Care v Ketamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [5]
Method	t-test, 2-sided

Notes:

[5] - A paired t-test (P < 0.05) was used to determine statistically significance. When p < 0.05, it can be concluded that the blood pressure (systolic/mean) before the start significantly differ from that during the removal of the drains.

Statistical analysis title	Ketamine
Comparison groups	Ketamine v Standard of Care v Sevoflurane
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024 [6]
Method	t-test, 2-sided

Notes:

[6] - A paired t-test (P < 0.05) was used to determine statistically significance. When p < 0.05, it can be concluded that the blood pressure (systolic/mean) before the start significantly differ from that during the removal of the drains.

Secondary: Impact on hartrate

End point title	Impact on hartrate

End point description:

HF0-HF2)

End point type	Secondary

End point timeframe:

Start of procedure (O) until drain removal (2)

End point values	Standard of Care	Sevoflurane	Ketamine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17	
Units: BPM				
number (not applicable)	-3.061	-1.734	-2.228	

Statistical analyses

No statistical analyses for this end point

Secondary: impact on arterial oxygen saturation

End point title	impact on arterial oxygen saturation

End point description:

Sat0 (start of procedure)-Sat2 (drain removal

End point type	Secondary

End point timeframe:

From start of procedure until drain removal

End point values	Standard of Care	Sevoflurane	Ketamine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17	
Units: SpO2%				
number (not applicable)	-1.409	-1.577	-0.216	

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	14.1

Frequency threshold for reporting non-serious adverse events: 0 %

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: All Serious Adverse Events and Serious Adverse Reactions were reported according to the applicable regulatory requirements. None of them occurred.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2012	Adjustment of the dose of paracetamol according to the latest scientific guidelines. Adjustment of the amount of oxygen in the sevoflurane group: adjustment of the amount of oxygen administered for a particular patient group because in this patient group the administration of extra oxygen is also done according to these proportions in other circumstances (e.g. giving aerosol). Supplementing the exclusion criteria in order to avoid the creation of further subgroups.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported