Clinical trial results:
The use of intraoperative methadone in children undergoing minor open urological surgery

Summary

EudraCT number	2020-002945-41
Trial protocol	DK
Global end of trial date	22 January 2024

Results information

Result version number	v1 (current)
This version publication date	31 October 2024
First version publication date	31 October 2024

Trial information

Trial identification

Sponsor protocol code	78464317

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04680286
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Blvd. 99, Aarhus, Denmark, 8200
Public contact	Camilla Gaarsdal Uhrbrand , Aarhus University Hospital , 0045 23956082, camgaa@rm.dk
Scientific contact	Lone Nikolajsen, Aarhus University Hospital , lone.nikolajsen@clin.au.dk

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	14 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2024
Global end of trial reached?	Yes
Global end of trial date	22 January 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of a single dose of intraoperative methadone on postoperative opioid requirements and pain intensity among children with undescended testes undergoing outpatient orchiopexy.

1) Administration of opioids in the PACU(yes/no)
2) The number of children with a pain intensity of 5 or higher on the FLACC scale within the first 3 h after laryngeal mask airway removal (yes/no).

Protection of trial subjects:

Children were treated with our standard of care and the intervention was an addition to this. In this way children were not put in an increased risk of pain.
Intervention was during anesthesia and did not distress the children.

Background therapy:

Anesthesia, surgery and postoperative pain management were aligned in both groups:
Anesthesia was induced with either propofol (3–5 mg/kg) or sevoflurane (5%–8%). Before or immediately following induction, a peripheral venous catheter was inserted, and fentanyl (1–2 μg/kg) and dexamethasone (0.2 mg/kg) were administered. In relation to induction of anesthesia, children received
intravenous acetaminophen (50 mg/kg/day) and naproxen suppository (5 mg/kg/day). All children had a laryngeal mask airway. Anesthesia was maintained with remifentanil (20–50 μg/kg/h) and propofol (5–10 mg/kg/h) and no additional fentanyl was administered during anesthesia. Standard monitoring included electrocardiography, capnography, and pulse oximetry. Upon closure of the skin, local infiltration analgesia with bupivacaine 2.5 mg/mL (0.5–1 mL/kg) was administered by the surgeon. In brief, surgery was carried out through inguinal access, where
the undescended testicle was moved from the inguinal region to the scrotum and fixed there.
In the PACU, fentanyl (0.5–1 μ g/kg) was always the first choice for pain treatment. If several doses of fentanyl were inadequate, intravenous morphine (0.05 mg/kg) could be used. Before discharge, parents received oral and written information along with a written plan for at-home pain management. This plan consisted of
acetaminophen (50 mg/kg/day three to four daily doses), naproxen (5 mg/kg/day twice daily) around the clock for the first 2 days and rescue morphine (0.2 mg/kg) reserved for breakthrough pain.

Evidence for comparator:

The comparator was placebo (saline).

Actual start date of recruitment	28 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 68

Worldwide total number of subjects	68
EEA total number of subjects	68

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)	35
Children (2-11 years)	33
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:

Children recruited were all planned for surgery at Aarhus University Hospital from December 2020 until January 2024.

Parents were informed at a preoperative anesthesia assesment, and both parents had to consent.

Pre-assignment

Screening details:

147 children were screened for inclusion. 9 declined to participate. 43 met exclusion criterias (i.e.: multiple procedures planned, born premature, parents not speaking danish). In 27 cases the hospital pharmacy could not deliver/the surgery was cancelled. After inclusion of 68 children: 4 had a fever on operation day, and 4 for other reasons.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The medicine was prepared by the hospital pharmacy.
Children, parents, hospital personnel (anesthetist, surgeon, post anesthesia care unit (PACU) nurses), and investigators were blinded to the randomization. The manuscript, along with its conclusion, was written before the data were unblinded
through retrieval of an A- and B- list.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

0.1 mg/kg methadone intraoperatively.

Arm type	Experimental
Investigational medicinal product name	Methadone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.1 mg/kg administered after insertion of laryngeal mask airway.

Arm title	Placebo

Arm description:

Saline

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	NatriumChlorid
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Volume corresponding to that of the experimental. Administered after insertion og laryngeal mask airway.

Number of subjects in period 1	Intervention	Placebo
Started	34	34
Completed	29	31
Not completed	5	3
subsequent discovery of inclusion violation	-	1
surgery not needed	1	-
study drug not able to be produced	2	-
fever	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Intervention
Reporting group description: 0.1 mg/kg methadone intraoperatively.	
Reporting group title	Placebo
Reporting group description: Saline	

Reporting group values	Intervention	Placebo	Total
Number of subjects	34	34	68
Age categorical Units: Subjects			
Age continuous Units: months			
least squares mean	27	25.4	
standard deviation	± 2.8	± 2.4	-
Gender categorical			
gender			
Units: Subjects			
Female	0	0	0
Male	34	34	68
weight Units: kilogram(s)			
least squares mean	13.7	13.1	
standard deviation	± 3.3	± 2.8	-

End points

End points reporting groups	
Reporting group title	Intervention
Reporting group description: 0.1 mg/kg methadone intraoperatively.	
Reporting group title	Placebo
Reporting group description: Saline	

Primary: Opioid administration in the PACU	
End point title	Opioid administration in the PACU
End point description: Did patients receive opioids during their PACU stay (yes/no).	
End point type	Primary
End point timeframe: PACU	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: number	5	13		

Statistical analyses

Statistical analysis title	primary
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.037
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.49

Primary: FLACC ≥ 5 in the PACU	
End point title	FLACC ≥ 5 in the PACU
End point description:	
End point type	Primary
End point timeframe:	
PACU	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: Number	5	10		

Statistical analyses

Statistical analysis title	primary
Comparison groups	Placebo v Intervention
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.179
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.06

Secondary: Time from surgery end to removal of the laryngeal mask airway	
End point title	Time from surgery end to removal of the laryngeal mask airway
End point description:	
End point type	Secondary
End point timeframe:	
Surgery date	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: minute				
least squares mean (standard deviation)				
perioperative data	14.2 (± 4.9)	14.1 (± 5.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to readiness to discharge from PACU

End point title	Time to readiness to discharge from PACU

End point description:

End point type	Secondary

End point timeframe:

PACU

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: minute				
least squares mean (standard deviation)	145.4 (± 65.5)	114.6 (± 34.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Episodes of desaturation

End point title	Episodes of desaturation

End point description:

Defined as a saturation below 90% not overcome by simple actions.

End point type	Secondary

End point timeframe:

PACU

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: numbers	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Awakenings on the first night

End point title	Awakenings on the first night

End point description:

End point type	Secondary

End point timeframe:

The night between the day of operation and the first day following.

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: numbers	13	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Awake due to pain

End point title	Awake due to pain

End point description:

Assesed by parents, how many children woke up due to pain

End point type	Secondary

End point timeframe:

At home

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: numbers	1	7		

Statistical analyses

No statistical analyses for this end point

Secondary: At-home pain intensities

End point title	At-home pain intensities

End point description:

End point type	Secondary

End point timeframe:

At home (36 hours).

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: FLACC	29	31		

Attachments (see zip file)	Figure2..png

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Anesthesia duration

End point title	Anesthesia duration

End point description:

End point type	Other pre-specified

End point timeframe:

Surgery date

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: minute				
median (inter-quartile range (Q1-Q3))				
perioperative data	69 (62 to 79)	74 (61 to 86)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Surgery duration

End point title	Surgery duration

End point description:

End point type	Other pre-specified

End point timeframe:

Surgery date

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: minute				
median (inter-quartile range (Q1-Q3))				
perioperative data	33 (25 to 43)	29 (26 to 46)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From start of anesthesia and 4 days following.	
Assessment type	Systematic
Dictionary used	
Dictionary name	LMST
Dictionary version	1
Reporting groups	
Reporting group title	Intervention
Reporting group description: 0.1 mg/kg methadone intraoperatively.	
Reporting group title	Placebo
Reporting group description: Saline	

Serious adverse events	Intervention	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	0 / 31 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Intervention	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	2 / 31 (6.45%)	
Gastrointestinal disorders			
Constipation	Additional description: Short period where parents assesed constipated. Concurred the following day.		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Hypoxia	Additional description: Short hypoxia (85%) in the PACU. Patient was sick the week prior to surgery and was believed to have some residual secrete/mucus following anesthesia.		
subjects affected / exposed	0 / 29 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	

Infections and infestations			
fever	Additional description: Patient had fever the night following surgery. The family contacted the emergency department. However, no treatment was started. No relation to intervention.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 31 (0.00%)	
occurrences (all)	1	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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The inclusion of children was challenged by the COVID-19 pandemic, which extended the trial period and introduced the risk of change in clinical practice over time. However, the study protocol was strictly followed throughout the trial period.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/39306760