Clinical trial results:
METATONS -
Intraoperative methadone for postoperative pain in patients undergoing tonsillectomy -
a randomized controlled trial

Summary

EudraCT number	2022-002496-11
Trial protocol	DK
Global end of trial date	30 November 2023
Results information	
Result version number	v1 (current)
This version publication date	28 May 2025
First version publication date	28 May 2025

Trial information

Trial identification	
Sponsor protocol code	07072022v1.0
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05445856
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juels Jensens Boulevard, Aarhus, Denmark, 8200
Public contact	Kristian Dahl Friesgaard, Aarhus University Hospital, 0045 25113204,
Scientific contact	Kristian Dahl Friesgaard, Aarhus University Hospital, 0045 25113204,

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	15 April 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2023
Global end of trial reached?	Yes
Global end of trial date	30 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to investigate the effect of a single dose of intravenous intraoperative methadone on postoperative opioid consumption, pain and side effects in patients scheduled for tonsillectomy. A single dose of intravenous intraoperative fentanyl will be used as an active comparator.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice (GCP) and monitored by the GCP unit at Aarhus University Hospital, Aarhus, Denmark. The study protocol was approved by the Danish Protection Agency, the Central Denmark Region Committees on Health Research Ethics , and the Danish Health and Medicines Authority

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2022
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: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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)	120
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were screened for inclusion at the first ambulatory contact at Randers Regional Hospital, Randers, Denmark, and informed oral and written consent was obtained before surgery. Adults scheduled for elective tonsillectomy were enrolled.

Pre-assignment

Screening details:

Patients were screened for inclusion at the first ambulatory contact at Randers Regional Hospital, Randers, Denmark, and informed oral and written consent was obtained before surgery. Adults scheduled for elective tonsillectomy were enrolled.

Period 1

Period 1 title	Intervention (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

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

The study drug was given as an intravenous dose (methadone: 0.2 mg/kg) according to ideal body weight (definition: Height (cm) – 105 for females and height (cm) – 100 for males)).

Arm type	Experimental
Investigational medicinal product name	methadone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

The study drug was given as an intravenous dose (methadone: 0.2 mg/kg) according to ideal body weight (definition: Height (cm) – 105 for females and height (cm) – 100 for males)).

Arm title	Control

Arm description:

The study drug was given as an intravenous dose (fentanyl: 3 µg/kg) according to ideal body weight (definition: Height (cm) – 105 for females and height (cm) – 100 for males)).

Arm type	Active comparator
Investigational medicinal product name	fentanyl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

The study drug was given as an intravenous dose (fentanyl: 3 microgram/kg) according to ideal body weight (definition: Height (cm) – 105 for females and height (cm) – 100 for males)).

Number of subjects in period 1	Intervention	Control
Started	62	58
Completed	62	58

Baseline characteristics

Reporting groups	
Reporting group title	Intervention
Reporting group description:	
The study drug was given as an intravenous dose (methadone: 0.2 mg/kg) according to ideal body weight (definition: Height (cm) – 105 for females and height (cm) – 100 for males)).	
Reporting group title	Control
Reporting group description:	
The study drug was given as an intravenous dose (fentanyl: 3 µg/kg) according to ideal body weight (definition: Height (cm) – 105 for females and height (cm) – 100 for males)).	

Reporting group values	Intervention	Control	Total
Number of subjects	62	58	120
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	62	58	120
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	24	25.5	
inter-quartile range (Q1-Q3)	20 to 30	22 to 30	-
Gender categorical Units: Subjects			
Female	45	41	86
Male	17	17	34

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description:	
The study drug was given as an intravenous dose (methadone: 0.2 mg/kg) according to ideal body weight (definition: Height (cm) – 105 for females and height (cm) – 100 for males)).	
Reporting group title	Control
Reporting group description:	
The study drug was given as an intravenous dose (fentanyl: 3 µg/kg) according to ideal body weight (definition: Height (cm) – 105 for females and height (cm) – 100 for males)).	

Primary: Pain intensity (NRS, 0-10)

End point title	Pain intensity (NRS, 0-10)
End point description:	
End point type	Primary
End point timeframe:	
on arrival at the post-anesthesia care unit	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: 0-10				
median (inter-quartile range (Q1-Q3))	3 (2 to 5)	4.5 (3 to 7)		

Statistical analyses

Statistical analysis title	Mann-Whitney test
Statistical analysis description:	
Medians with interquartile ranges (IQR) are given for skewed data and compared with Mann-Whitney test.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Primary: Total postoperative opioid consumption from extubation to 5 days after surgery

End point title	Total postoperative opioid consumption from extubation to 5 days after surgery

End point description:

End point type	Primary

End point timeframe:

from extubation to 5 days after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: mg				
median (inter-quartile range (Q1-Q3))	30 (10 to 50)	49 (29 to 80)		

Statistical analyses

Statistical analysis title	Mann-Whitney test

Statistical analysis description:

Medians with interquartile ranges (IQR) are given for skewed data and compared with Mann-Whitney test.

Comparison groups	Intervention v Control
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Pain intensity (NRS 0-10) 1 day after surgery

End point title	Pain intensity (NRS 0-10) 1 day after surgery

End point description:

End point type	Secondary

End point timeframe:

From extubation to 1 day after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: 0-10				
median (inter-quartile range (Q1-Q3))	4 (2.5 to 5)	5 (3 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain intensity (NRS 0-10) 2 days after surgery

End point title	Pain intensity (NRS 0-10) 2 days after surgery

End point description:

End point type	Secondary

End point timeframe:

From extubation to 2 days after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: 0-10				
median (inter-quartile range (Q1-Q3))	4 (3 to 6)	5 (4 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain intensity (NRS 0-10) 3 days after surgery

End point title	Pain intensity (NRS 0-10) 3 days after surgery

End point description:

End point type	Secondary

End point timeframe:

From extubation to 3 days after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: 0-10				
median (inter-quartile range (Q1-Q3))	4.5 (3 to 6)	5 (3 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain intensity (NRS 0-10) 5 days after surgery

End point title	Pain intensity (NRS 0-10) 5 days after surgery

End point description:

End point type	Secondary

End point timeframe:

From extubation to 5 days after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: 0-10				
median (inter-quartile range (Q1-Q3))	5 (4 to 7)	6 (4 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain intensity (NRS 0-10) 7 days after surgery

End point title	Pain intensity (NRS 0-10) 7 days after surgery

End point description:

End point type	Secondary

End point timeframe:

From extubation to 7 days after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: 0-10				
median (inter-quartile range (Q1-Q3))	4 (3 to 6)	4 (3 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total postoperative opioid consumption 24 hours after surgery

End point title	Total postoperative opioid consumption 24 hours after surgery

End point description:

End point type	Secondary

End point timeframe:

From extubation to 24 hours after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: mg				
median (inter-quartile range (Q1-Q3))	20 (10 to 35)	35 (20 to 52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total postoperative opioid consumption 7 days after surgery

End point title	Total postoperative opioid consumption 7 days after surgery

End point description:

End point type	Secondary

End point timeframe:

From extubation to 7 days after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: mg				
median (inter-quartile range (Q1-Q3))	36.5 (10 to 60)	50 (30 to 92.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient satisfaction 24 hours after extubation

End point title	Patient satisfaction 24 hours after extubation

End point description:

End point type	Secondary

End point timeframe:

From extubation to 24 hours after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: 0-10				
median (inter-quartile range (Q1-Q3))	9 (8 to 10)	9 (8 to 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient satisfaction 7 days after extubation

End point title	Patient satisfaction 7 days after extubation

End point description:

End point type	Secondary

End point timeframe:

From extubation to 7 days after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: 0-10				
median (inter-quartile range (Q1-Q3))	8 (6 to 9)	8 (5 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: PONV (moderate to severe) 1 day after extubation

End point title	PONV (moderate to severe) 1 day after extubation

End point description:

End point type	Secondary

End point timeframe:
from extubation to 1 day after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: n				
number (not applicable)	27	8		

Statistical analyses

No statistical analyses for this end point

Secondary: PONV (moderate to severe) 2 days after extubation

End point title	PONV (moderate to severe) 2 days after extubation

End point description:

End point type	Secondary

End point timeframe:
From extubation to 2 days after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: n				
number (not applicable)	26	10		

Statistical analyses

No statistical analyses for this end point

Secondary: PONV (moderate to severe) 3 days after extubation

End point title	PONV (moderate to severe) 3 days after extubation

End point description:

End point type	Secondary

End point timeframe:

From extubation to 3 days after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: n				
number (not applicable)	21	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from arrival to discharge from PACU

End point title	Time from arrival to discharge from PACU

End point description:

End point type	Secondary

End point timeframe:

Time from arrival to discharge from PACU

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: Hours				
median (inter-quartile range (Q1-Q3))	2.1 (1.7 to 2.4)	2.1 (1.8 to 2.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from arrival to discharge from hospital

End point title	Time from arrival to discharge from hospital

End point description:

End point type	Secondary

End point timeframe:

Time from arrival to discharge from hospital

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: Hours				
median (inter-quartile range (Q1-Q3))	5.7 (3.8 to 6.9)	4.7 (3.8 to 5.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Level of sedation at the PACU 4 hours after extubation (normal level of consciousness according to Ramsay Sedation Scale)

End point title	Level of sedation at the PACU 4 hours after extubation (normal level of consciousness according to Ramsay Sedation Scale)

End point description:

End point type	Secondary

End point timeframe:

From extubation to 4 hours after surgery

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: n				
number (not applicable)	47	47		

Statistical analyses

No statistical analyses for this end point

Secondary: Any adverse events (hypoventilation/hypoxemia) at the PACU

End point title	Any adverse events (hypoventilation/hypoxemia) at the PACU

End point description:

End point type	Secondary

End point timeframe:

From extubation to discharge from PACU

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: n				
number (not applicable)	4	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From administration of study drug to 7 days after surgery

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Intervention
Reporting group description: -	
Reporting group title	Control
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: We have no non-serious adverse events reported.

Serious adverse events	Intervention	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 62 (8.06%)	10 / 58 (17.24%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Bleeding after surgery			
subjects affected / exposed	2 / 62 (3.23%)	5 / 58 (8.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain after surgery	Additional description: Pain requiring hospital admission		
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling after surgery			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nausea and/or vomiting	Additional description: Nausea and/or vomiting requiring hospital admission		

subjects affected / exposed	3 / 62 (4.84%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Intervention	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (0.00%)	

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