Clinical trial results:
Preanesthetic medication in pediatric patients: A comparison of midazolam, clonidine and dexmedetomidine

Summary

EudraCT number	2015-003676-70
Trial protocol	SE
Global end of trial date	30 June 2019

Results information

Result version number	v3 (current)
This version publication date	01 January 2024
First version publication date	11 October 2022
Version creation reason	• Changes to summary attachments Adding links to manuscript 2 and 3

Trial information

Trial identification

Sponsor protocol code	PedPreMed

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Region Norrbotten
Sponsor organisation address	Robertsviksgatan 7, Luleå, Sweden, 90187
Public contact	Magnus Hultin, Norrbottens läns landsting, 46 920282341, magnus.hultin@umu.se
Scientific contact	Magnus Hultin, Norrbottens läns landsting, 46 920282341, magnus.hultin@umu.se

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	30 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of this research is to compare three different preanesthetic medications (midazolam, clonidine and dexmedetomidine) in elective minor surgery under total intravenous anesthesia in pediatric patients for anxiolysis and sedation, hemodynamic stability and recovery profiles.

Protection of trial subjects:

The trial was conducted in the normal perioperative pediatric flow at the hospital to ensure a close monitoring of the child while acute effects of the IMPs were studied. One parent was present with the child until the child was anesthetized in the operation theatre. During the preanesthetic phase there was a registered nurse present in the same room until the registered anesthetic nurse (RNA) brought the child and the parent to the operation theatre. During induction of anesthesia and until being delivered to the postoperative ward, and anesthesiologist (registered specialist physician) and the RNA was present all the time. At the postoperative ward a registered nurse attended the needs of the child in addition to having the parent present.

For unexpected long-term effects after the child had left the hospital and the acute effect of the premedication (IMP) was undetectable, the parent had access to a study-telephone number in addition to being able to contact the surgeon or the emergency ward. Information about the trial was added to the patients electronic health registry (chart) and a procedure for breaking the code for the individual patient by opening a sealed envelope was in place 24/7/365 if it would have been necessary. The decision to break the code was left at the discretion of the attending at the intensive care unit of the hospital.

Background therapy:

Preoperative lidocain/prilocain local cream 20 mg/g, 2g, paracetamol 30 mg/kg, ibuprofen oral solution 10 mg/kg, betamethasone, 0.3 mg/kg.
Anesthesia with atropine 0.01 mg/kg iv, propofol and remifentanil infusion.
Postoperative iv morphine 0.1-0.2 mg/kg and ondansetron 0.1 mg/kg.

Evidence for comparator:

The comparators were three groups receiving oral midazolam, oral clonidine or intranasal dexmedetomidine as preanesthetic medication. Oral dexmedetomidine was not preferred because of poor bioavailability. Results from clinical trials in children, suggests that intranasal administration of dexmedetomidine is more effective as premedication, with adequate sedation achieved within 30 to 45 minutes (Cimen, Hanci, Sivrikaya, Kilinc, & Erol, n.d.; Zhang, Bai, Zhang, Wang, & Lu, 2013). Using oral preanesthetic, onset of sedation is significantly faster after premedication with oral midazolam (30 min) than with oral clonidine (60 min) (Almenrader, Passariello, Coccetti, Haiberger, & Pietropaoli, 2007).

The compared premedications are oral midazolam 0.5 mg/kg, oral clonidine 4 µg/kg, and intranasal dexmedetomidine 2 µg/kg. These products are used “off label” as clinical routine in hospitals in Sweden and worldwide for sedation to children undergoing procedures. Course of therapy are current regimens, tested and recommended in clinical studies and by the Medical Products Agency (Almenrader et al., 2007; Cimen, Hanci, Sivrikaya, Kilinc, & Erol, n.d.; Zhang, Bai, Zhang, Wang, & Lu, 2013).

Actual start date of recruitment	01 February 2017
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	Sweden: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	90
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:

The study took place in Region Norrbotten, Sweden. Patients were recruited between February 1, 2017 and May 6, 2017.

Pre-assignment

Screening details:

In total, 239 patients aged 2-6 years and planned for ENT surgery were assessed for eligibility. Due to shortness of research staff on the day of surgery (n=199), declined to participate (n=4), not meeting inclusion cirri (n=49) or being removed from the operation program (n=5), only 90 patients were randomized.

Period 1

Period 1 title	Perioperative period (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:

A separate nurse, not involved in any of the other roles, performed the randomization by opening a sealed envelope, preparing and giving the three doses: two placebos and one with an active substance.

Arms

Are arms mutually exclusive?	Yes
Arm title	CLO group

Arm description:

Children who received clonidine 4 µg/kg oral solution 60 min before going to surgery

Arm type	Active comparator
Investigational medicinal product name	Clonidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Enteral use

Dosage and administration details:

Clonidine APL, oral solution 20 µg/ml, 4 µg/kg (0.2 ml/kg), given per os 60 min before going to surgery

Arm title	MID group

Arm description:

Children who received midazolam 0.5mg/kg oral solution 40 min before going to surgery

Arm type	Active comparator
Investigational medicinal product name	Midazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Enteral use

Dosage and administration details:

Clonidine APL, oral solution 1 mg/ml, 0.5 mg/kg (0.5 ml/kg), given per os 40 min before going to surgery

Arm title	DEX group

Arm description:

Children who received dexmedetomidine 2 µg/kg intranasal 40 min before going to surgery

Arm type	Active comparator

Investigational medicinal product name	Dexmedetomidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intranasal use

Dosage and administration details:

Dexmedetomidine, 100 µg/ml, 2 µg/kg, 0.2 ml/kg (0.02 ml/kg) was given intranasally with a mucosal atomizing device (https://www.teleflex.com/emea/en/product-areas/anaesthesia/atomization/mad-nasal-atomization-device/index.html) 40 min before going to surgery

Number of subjects in period 1	CLO group	MID group	DEX group
Started	30	30	30
Completed	26	27	30
Not completed	4	3	0
Refused to take IMP	3	3	-
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Perioperative period

Reporting group description: -

Reporting group values	Perioperative period	Total	
Number of subjects	90	90	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	90	90	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	36	36	
Male	54	54	

End points

End points reporting groups

Reporting group title	CLO group
Reporting group description:	
Children who received clonidine 4 µg/kg oral solution 60 min before going to surgery	
Reporting group title	MID group
Reporting group description:	
Children who received midazolam 0.5mg/kg oral solution 40 min before going to surgery	
Reporting group title	DEX group
Reporting group description:	
Children who received dexmedetomidine 2 µg/kg intranasal 40 min before going to surgery	

Primary: Preoperative anxiety

End point title	Preoperative anxiety
End point description:	

End point type	Primary
End point timeframe:	
Baselline Anesthesia preparation	

End point values	CLO group	MID group	DEX group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	30	
Units: mYPAS				
median (full range (min-max))	0 (-8 to 67)	0 (-13 to 77)	0 (-13 to 63)	

Attachments (see zip file)	mYPAS/Figure 3 mYPAS NEW.pdf

Statistical analyses

Statistical analysis title	Effect on mYPAS
Statistical analysis description:	
Comparing the change in mYPAS from baseline until the child is asleep after three different premedications. The table and comparisons are shown in Table 2 in the published paper (https://doi.dx.org/10.1111/pan.14279)	
Comparison groups	CLO group v MID group v DEX group

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.036 [1]
Method	Kruskal-wallis

Notes:

[1] - Comparing the differences in mYPAS at baseline and during anesthesia preparation.

Secondary: Behavioral distress scale

End point title	Behavioral distress scale

End point description:

End point type	Secondary

End point timeframe:

60 min

End point values	CLO group	MID group	DEX group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	30	
Units: Points				
median (full range (min-max))	1 (0 to 3)	1 (1 to 3)	1 (0 to 6)	

Statistical analyses

Statistical analysis title	Effect on distress at Peripheral cannula insertion

Statistical analysis description:

Behavioral distress scale was assessed at insertion of peripheral cannula

Comparison groups	CLO group v MID group v DEX group
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.173 [2]
Method	Kruskal-wallis

Notes:

[2] - Non significant, i.e. no differences between groups

Secondary: Induction compliance checklist

End point title	Induction compliance checklist

End point description:

The Childs compliance during induction

End point type	Secondary

End point timeframe:

During induction of anesthesia

End point values	CLO group	MID group	DEX group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	30	
Units: points				
median (full range (min-max))	0 (0 to 7)	0 (0 to 5)	0 (0 to 7)	

Statistical analyses

Statistical analysis title	ICC
Comparison groups	CLO group v MID group v DEX group
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.871
Method	Kruskal-wallis

Secondary: Sedation level Anesthesia preparation

End point title	Sedation level Anesthesia preparation

End point description:

End point type	Secondary

End point timeframe:
at Anesthesia preparation

End point values	CLO group	MID group	DEX group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	30	
Units: RSS				
median (full range (min-max))	3 (2 to 5)	2 (2 to 3)	4 (2 to 5)	

Statistical analyses

Statistical analysis title	RSS at anesthesia preparation
Comparison groups	CLO group v DEX group v MID group

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Kruskal-wallis

Secondary: Time to recover from anesthesia and surgery

End point title	Time to recover from anesthesia and surgery

End point description:

Time to recover from anaesthesia and surgery defined as the time from arrival at the PACU until the criteria of discharge from PACU was reached using the Post Anesthesia Scoring System (PADSS)

End point type	Secondary

End point timeframe:

First few hours after anesthesia

End point values	CLO group	MID group	DEX group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	30	
Units: minutes				
median (full range (min-max))	90 (38 to 162)	76 (45 to 150)	105 (60 to 325)	

Statistical analyses

Statistical analysis title	Time until discharge criteria fulfilled

Statistical analysis description:

Kruskal-Wallis for the time until the discharge criteria were fulfilled, comparing the three arms.

Comparison groups	CLO group v MID group v DEX group
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.211 [3]
Method	Kruskal-wallis

Notes:

[3] - No difference detected in time to full recovery from anesthesia between the groups

Secondary: Emergence delirium

End point title	Emergence delirium

End point description:

PAED score ≥10p

End point type	Secondary

End point timeframe:

The time period at the postoperative ward until being discharged

End point values	CLO group	MID group	DEX group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	30	
Units: PAED > 10p	3	8	1	

Statistical analyses

Statistical analysis title	Emergence delirium

Statistical analysis description:

Emergence delirium at any timepoint, defined as PAES score >10p

Comparison groups	CLO group v MID group v DEX group
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.013 [4]
Method	Chi-squared

Notes:

[4] - The three premedications are likely to cause different proportions of children with emergence delirium after premedication + anesthesia with total intravenous anesthesia (propofol + remifentanil)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: The full trial period	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25
Reporting groups	
Reporting group title	CLO group
Reporting group description: Children who received clonidine 4 µg/kg oral solution 60 min before surgery	
Reporting group title	MID group
Reporting group description: Children who received midazolam 0.5mg/kg oral solution 40 min before surgery	
Reporting group title	DEX group
Reporting group description: Children who received dexmedetomidine 2 µg/kg intranasal 40 min before surgery	

Serious adverse events	CLO group	MID group	DEX group
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Surgical failure	Additional description: During adenectomy unexpected liquor leak. The patient was referred to a university hospital for investigation and further treatment. It was considered a congenital malformation and completely unrelated to IMP or the surgeon.		
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	CLO group	MID group	DEX group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 27 (11.11%)	9 / 27 (33.33%)	6 / 30 (20.00%)
Cardiac disorders			

Bradycardia	Additional description: Heart frequency		
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Delirium	Additional description: Postoperative emergence delirium		
subjects affected / exposed	0 / 27 (0.00%)	3 / 27 (11.11%)	0 / 30 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Nausea	Additional description: Postoperative nausea and/or vomiting		
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	3 / 30 (10.00%)
occurrences (all)	0	1	3
Respiratory, thoracic and mediastinal disorders			
Laryngospasm			
subjects affected / exposed	1 / 27 (3.70%)	4 / 27 (14.81%)	2 / 30 (6.67%)
occurrences (all)	1	4	2
Postoperative wound complication	Additional description: small venous bleeding from the site of surgery		
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Postoperative wound infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus	Additional description: General pruritus for two weeks after surgery		
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	0 / 30 (0.00%)
occurrences (all)	0	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.

An interim analysis was performed after 90 included participants without breaking the code. The variance within the groups in the primary objective was smaller than expected, and the intended power had been reached. Thus the study was closed.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34403548

http://www.ncbi.nlm.nih.gov/pubmed/36604221

http://www.ncbi.nlm.nih.gov/pubmed/37528645