Clinical trial results:
Does perineural dexmedetomidine prolong the duration of an ulnar nerve block when controlling for possible systemic effects? - a randomized, blinded, placebo controlled, paired trial in healthy volunteers

Summary

EudraCT number	2016-004883-20
Trial protocol	DK
Global end of trial date	30 September 2017
Results information	
Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification	
Sponsor protocol code	SM1-JH-16
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03222323
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	ZUH, Køge
Sponsor organisation address	Lykkebækvej 1, Koege, Denmark,
Public contact	Jakob Hessel Andersen, Zealand University Hospital, +45 60610666, Jahea@regionsjaelland.dk
Scientific contact	Jakob Hessel Andersen, Zealand University Hospital, +45 60610666, Jahea@regionsjaelland.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	01 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2017
Global end of trial reached?	Yes
Global end of trial date	30 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the trial is to investigate whether dexmedetomidine used as an adjuvant to ropivacaine prolongs block duration compared to ropivacaine alone, and whether block duration is affected by the mode of dexmedetomidine administration.

Protection of trial subjects:

Ropivacaine is a well-known local anesthetic registered for perineural use, and is given within recommended doses.

Dexmedetomidine is used systemically for sedation in the ICU and for procedures in Eu-rope. Dexmedetomidine is not approved for perineural administration, but is well de-scribed in the literature as an adjuvant for peripheral nerve blocks. No overrepresentation of nerve injury has been proven in studies using dexmedetomidine perineurally. There are no existing reports of permanent nerve damage in studies employing perineural dex-medetomidine, and several in vitro studies on rats did not find increased risk of nerve in-flammation/damage when dexmedetomidine was co-administered with ropivacaine com-pared to ropivacaine alone. It is therefore our opinion that side effects and risks associat-ed with participation in this trial are minimal.
The nerve blocks are performed using ultrasound guidance minimizing the risk of compli-cations. The nerve blocks are performed by one of two anesthesiologists trained in ultra-sound-guided nerve blocks.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	24 July 2017
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: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The participants will be recruited from the news bulletin for medical students ”MOK” in Copenhagen, Facebook groups for medical students and from Forsoegsperson.dk.

Pre-assignment

Screening details:

The volunteers will be screened in a telephone interview. A copy of the participant trial information will be send prior to the trial date. They will be informed about the possibility of bringing an external assessor. On the trial date, participants will receive oral infor-mation by the principal investigator, in a closed room without interruptions

Period 1

Period 1 title	Dexmedetomidine day
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:

Blinding procedure, packaging and labeling
The trial is conducted in a blinded, randomized fashion. The randomization is done by a computer generated randomization list, generated by the Skanderborg pharmacy, who according to the randomization manufactures two boxes for each participant. The boxes contain the trial medication, one box for each of the two trial days. The trial medicine will be packed and labelled by Skanderborg Pharmacy according to the applicable rules.

Arms

Are arms mutually exclusive?	No
Arm title	Perineural treatment

Arm description:

Ulnar nerve block with 4 ml ropivacaine 0,5 % + 1,0 mL dex-medetomidine 100 µg/ml

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

Dosage and administration details:

100ug

Arm title	Systemic treatment

Arm description:

Ulnar nerve block with 4 ml ropivacaine 0,5 % + 1,0mL isotonic saline (systemic dexmedetomidine from the opposite arm)

Arm type	Active comparator
Investigational medicinal product name	Dexmedetomidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Solution for injection/infusion
Routes of administration	Perineural use, Not mentioned

Dosage and administration details:

100ug absorbed and redistributed from opposite arm

Number of subjects in period 1	Perineural treatment	Systemic treatment
Started	22	22
Completed	22	22

Period 2

Period 2 title	Placebo day
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The trial is conducted in a blinded, randomized fashion. The randomization is done by a computer generated randomization list, generated by the Skanderborg pharmacy, who according to the randomization manufactures two boxes for each participant.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo treatment

Arm description:

Ulnar nerve block with 4 ml ropivacaine 0,5% + 1,0 mL isotonic saline

Arm type	Placebo
Investigational medicinal product name	saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Perineural use

Dosage and administration details:

1 ml coadministered perineurally

Arm title	High-dose ropivacaine

Arm description:

Ulnar nerve block with 4 ml ropivacaine 0,75 % + 1,0mL isotonic saline

Arm type	Active comparator
Investigational medicinal product name	ropivavcaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Perineural use

Dosage and administration details:

7.5mg/ml 4 ml perineurally

Number of subjects in period 2	Placebo treatment	High-dose ropivacaine
Started	22	22
Completed	22	22

Baseline characteristics

Reporting groups	
Reporting group title	Dexmedetomidine day

Reporting group description: -

Reporting group values	Dexmedetomidine day	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	24		
standard deviation	± 2	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	12	12	

End points

End points reporting groups	
Reporting group title	Perineural treatment
Reporting group description:	
Ulnar nerve block with 4 ml ropivacaine 0,5 % + 1,0 mL dex-medetomidine 100 µg/ml	
Reporting group title	Systemic treatment
Reporting group description:	
Ulnar nerve block with 4 ml ropivacaine 0,5 % + 1,0mL isotonic saline (systemic dexmedetomidine from the opposite arm)	
Reporting group title	Placebo treatment
Reporting group description:	
Ulnar nerve block with 4 ml ropivacaine 0,5% + 1,0 mL isotonic saline	
Reporting group title	High-dose ropivacaine
Reporting group description:	
Ulnar nerve block with 4 ml ropivacaine 0,75 % + 1,0mL isotonic saline	

Primary: Duration of sensory nerve block (Mechanical discrimination)	
End point title	Duration of sensory nerve block (Mechanical discrimination)
End point description:	
End point type	Primary
End point timeframe:	
0-36 h	

End point values	Perineural treatment	Systemic treatment	Placebo treatment	High-dose ropivacaine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	22	22	22
Units: hours				
arithmetic mean (confidence interval 95%)	14.4 (13.1 to 15.6)	9.2 (8.6 to 9.8)	7.1 (6.6 to 7.6)	7.8 (7.3 to 8.3)

Statistical analyses

Statistical analysis title	Paired T test
Comparison groups	Perineural treatment v Placebo treatment
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	t-test, 2-sided

Secondary: Onset of block (mechanical discrimination)

End point title	Onset of block (mechanical discrimination)

End point description:

End point type	Secondary

End point timeframe:

0-120 minutes

End point values	Perineural treatment	Systemic treatment	Placebo treatment	High-dose ropivacaine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	22	22	22
Units: Minutes				
arithmetic mean (confidence interval 95%)	13 (10 to 16)	12 (10 to 15)	13 (10 to 15)	12 (8 to 16)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of block (temperature discrimination)(h)

End point title	Duration of block (temperature discrimination)(h)

End point description:

End point type	Secondary

End point timeframe:

0-36 h

End point values	Perineural treatment	Systemic treatment	Placebo treatment	High-dose ropivacaine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	22	22	22
Units: hours				
arithmetic mean (confidence interval 95%)	14 (13.1 to 15)	9.1 (8.6 to 9.7)	7.5 (6.9 to 8.1)	8.1 (7.5 to 8.6)

Statistical analyses

Statistical analysis title	Paired T test
Comparison groups	Perineural treatment v Placebo treatment
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Statistical analysis title	Paired T-test
Comparison groups	Systemic treatment v Placebo treatment
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Statistical analysis title	Non- inferiority
Comparison groups	Perineural treatment v Systemic treatment
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.05
Method	t-test, 2-sided

Statistical analysis title	Paired T test
Comparison groups	Perineural treatment v High-dose ropivacaine
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 2-sided

Statistical analysis title	Paired T test
Comparison groups	Systemic treatment v High-dose ropivacaine
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.05
Method	t-test, 2-sided

Secondary: Duration of block-analgesia (PDTH) (h)

End point title	Duration of block-analgesia (PDTH) (h)

End point description:

End point type	Secondary

End point timeframe:

0-36 h

End point values	Perineural treatment	Systemic treatment	Placebo treatment	High-dose ropivacaine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	22	22	22
Units: hours				
arithmetic mean (confidence interval 95%)	13.6 (12.7 to 14.6)	9.3 (8.5 to 10)	7.6 (7.1 to 8.1)	8 (7.5 to 8.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of motor block (MVIC) (h)

End point title	Duration of motor block (MVIC) (h)

End point description:

End point type	Secondary

End point timeframe:

0-36 h

End point values	Perineural treatment	Systemic treatment	Placebo treatment	High-dose ropivacaine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	22	22	22
Units: hours				
arithmetic mean (confidence interval 95%)	15.4 (14.2 to 16.6)	9.8 (9.1 to 10.5)	7.4 (6.9 to 8.0)	8.1 (7.5 to 8.7)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 0-36h	
Assessment type	Systematic
Dictionary used	
Dictionary name	ICH
Dictionary version	10
Reporting groups	
Reporting group title	Bradycardia/hypotension

Reporting group description: -

Serious adverse events	Bradycardia/hypotension		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Bradycardia/hypotension		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)		
Cardiac disorders			
bradycardia/hypotension	Additional description: 1 participant experienced this event		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2017	Changed statistical plan from equality to non-inferiority trial Changed primary outcome to duration of nerve block measured by mechanical discrimination.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported