Clinical trial results:
Does perineural dexamethasone increase the duration of an ulnar nerve block when controlling for systemic effects? A randomised, blinded, placebo-controlled, paired, non-inferiority trial in healthy volunteers

Summary

EudraCT number	2020-004242-10
Trial protocol	DK
Global end of trial date	15 May 2021

Results information

Result version number	v1 (current)
This version publication date	15 May 2022
First version publication date	15 May 2022

Trial information

Trial identification

Sponsor protocol code	MM1-2020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04817982
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zealand University Hospital
Sponsor organisation address	Lykkebækvej 1, Køge, Denmark, 4600
Public contact	Department of Anaesthesiology, Zealand University Hospital, Køge, Denmark, mmaag@regionsjaelland.dk
Scientific contact	Department of Anaesthesiology, Zealand University Hospital, Køge, Denmark, mmaag@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	02 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2021
Global end of trial reached?	Yes
Global end of trial date	15 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate if perineural dexamethasone increases the duration of an ulnar nerve block when controlling for the systemic effects of dexamethasone. We will primarily assess the duration of the ulnar nerve block by temperature discrimination.

Protection of trial subjects:

Healthy volunteers had one peripheral venous cathether placed in their forearm prior to block performence. Healthy volunteers were monitored for 30 minutes after block performance using 5-lead electrocardiography, continuous peripheral saturation measurement, and non-invasive blood pressure measurement every 5 minutes. The follow-up related to duration of the ulnar nerve blocks were conducted by health care professionals in a hospital setting. All participants were followed-up until complete block cessation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 January 2021
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: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	16
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in the Capital and Zealand Regions of Denmark between 7 April 2021 and 15 May 2021.

Pre-assignment

Screening details:

Important exclusion criteria were allergy to study medication, use of corticosteroids or prescription analgesics, alcohol or drug abuse, cardiovascular disease, and diabetes. Eighteen healthy volunteers aged 18 to 65 were screened for inclusion. One refused to participate and one were excluded due to concomitant corticosteroid therapy.

Pre-assignment period milestones

Number of subjects started	16
Number of subjects completed	16

Period 1

Period 1 title	Trial day one/two (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Research nurses, not otherwise involved in the trial, prepared trial medication in identical syringes with identical appearing medicine and identical volume. There were no incidences of unblinding. Participants were randomly allocated to receive perineural/systemic dexamethasone on either day 1 or 2 and on the other day to receive lidocaine/placebo.

Arms

Are arms mutually exclusive?	No
Arm title	Perineural dexamethasone

Arm description:

In this arm, ulnar nerve blocks were performed with 3ml of 5mg/ml bupivacaine + 1ml of 4mg/ml perineural dexamethasone + 1ml saline.

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

Dosage and administration details:

3ml of 5mg/ml bupivacaine

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Perineural use

Dosage and administration details:

1ml of 4mg/ml dexamethasone

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Perineural use

Dosage and administration details:

1ml of isotonic saline.

Arm title	Systemic dexamethasone

Arm description:

Perineural dexamethasone is added on the opposite site of this arm. Some of the perineurally administered dexamethasone would be absorbed and exert systemic effects on the 'systemic dexamethasone' arm.

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

Dosage and administration details:

3ml of 5mg/ml bupivacaine

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Perineural use

Dosage and administration details:

2ml of isotonic saline.

Arm title	Lidocaine

Arm description:

Lidocaine 20 mg/ml was added to bupivacaine 5mg/ml

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

Dosage and administration details:

3ml of 5mg/ml bupivacaine

Investigational medicinal product name	Lidocaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Perineural use

Dosage and administration details:

2ml of 20mg/ml lidocaine

Arm title	Placebo

Arm description:

Saline was added to bupivacaine.

Arm type	Placebo

Investigational medicinal product name	Bupivacaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Perineural use

Dosage and administration details:
3ml of 5mg/ml bupivacaine

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Perineural use

Dosage and administration details:
2ml of isotonic saline.

Number of subjects in period 1	Perineural dexamethasone	Systemic dexamethasone	Lidocaine
Started	16	16	16
Completed	16	16	16

Number of subjects in period 1	Placebo
Started	16
Completed	16

Baseline characteristics

Reporting groups	
Reporting group title	Trial day one/two

Reporting group description: -

Reporting group values	Trial day one/two	Total	
Number of subjects	16	16	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	16	16	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	24.6		
standard deviation	± 3.7	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	7	7	
Height Units: cm			
arithmetic mean	178		
standard deviation	± 9	-	
Weight Units: kg			
arithmetic mean	75		
standard deviation	± 15	-	
BMI Units: kg/m2			
arithmetic mean	24		
standard deviation	± 4	-	

End points

End points reporting groups

Reporting group title	Perineural dexamethasone
Reporting group description:	
In this arm, ulnar nerve blocks were performed with 3ml of 5mg/ml bupivacaine + 1ml of 4mg/ml perineural dexamethasone + 1ml saline.	
Reporting group title	Systemic dexamethasone
Reporting group description:	
Perineural dexamethasone is added on the opposite site of this arm. Some of the perineurally administered dexamethasone would be absorbed and exert systemic effects on the 'systemic dexamethasone' arm.	
Reporting group title	Lidocaine
Reporting group description:	
Lidocaine 20 mg/ml was added to bupivacaine 5mg/ml	
Reporting group title	Placebo
Reporting group description:	
Saline was added to bupivacaine.	

Primary: Duration of the sensory block as measured by temperature discrimination

End point title	Duration of the sensory block as measured by temperature discrimination
End point description:	
Participants were stimulated with an alcohol swab in the hypothenar area. When the alcohol swab was identified as cold, the block was defined as having cessated.	
End point type	Primary
End point timeframe:	
Every 30 minutes from block onset until a cold swab feels cold again.	

End point values	Perineural dexamethasone	Systemic dexamethasone	Lidocaine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	16
Units: Minutes				
arithmetic mean (confidence interval 95%)	706 (656 to 756)	677 (617 to 736)	452 (373 to 530)	640 (576 to 705)

Statistical analyses

Statistical analysis title	Paired t-test arm 1 versus arm 4
Statistical analysis description:	
We performed paired t-test for the comparisons of perineural dexamethasone versus placebo, systemic dexamethasone versus placebo, and lidocaine versus placebo.	
Comparison groups	Perineural dexamethasone v Placebo

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.005
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	66
Confidence interval	
level	95 %
sides	2-sided
lower limit	23
upper limit	108
Variability estimate	Standard deviation

Notes:

[1] - Paired t-test

Statistical analysis title	Paired t-test arm 2 versus arm 4
Comparison groups	Systemic dexamethasone v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.26
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30
upper limit	103
Variability estimate	Standard deviation

Notes:

[2] - Paired t-test

Statistical analysis title	Paired t-test arm 3 versus arm 4
Comparison groups	Placebo v Lidocaine
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-189
Confidence interval	
level	95 %
sides	2-sided
lower limit	-243
upper limit	-135
Variability estimate	Standard deviation

Notes:

[3] - Paired t-test

Secondary: Duration of the sensory block measured by mechanical discrimination

End point title	Duration of the sensory block measured by mechanical discrimination

End point description:

The participants were stimulated in the hypothenar area with a needle. The block was defined as having cessated when a needle felt sharp again.

End point type	Secondary

End point timeframe:

Measured every 30 minutes from block onset until a needle felt sharp again.

End point values	Perineural dexamethasone	Systemic dexamethasone	Lidocaine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	16
Units: minutes				
arithmetic mean (confidence interval 95%)	612 (548 to 677)	624 (559 to 689)	374 (321 to 427)	604 (523 to 685)

Statistical analyses

Statistical analysis title	Paired t-test arm 1 versus arm 4
Comparison groups	Perineural dexamethasone v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.79
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57
upper limit	73
Variability estimate	Standard deviation

Notes:

[4] - Paired t-test

Statistical analysis title	Paired t-test arm 1 versus arm 4
Comparison groups	Perineural dexamethasone v Placebo

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.79
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57
upper limit	73
Variability estimate	Standard deviation

Notes:

[5] - Paired t-test

Statistical analysis title	Paired t-test arm 2 versus arm 4
Comparison groups	Placebo v Systemic dexamethasone
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.56
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51
upper limit	91
Variability estimate	Standard deviation

Notes:

[6] - Paired t-test

Statistical analysis title	Paired t-test arm 3 versus arm 4
Comparison groups	Placebo v Lidocaine
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-230
Confidence interval	
level	95 %
sides	2-sided
lower limit	-290
upper limit	-170
Variability estimate	Standard deviation

Notes:

[7] - Paired t-test

Secondary: Duration of the sensory block measured by pain during tonic heat stimulatiom

End point title	Duration of the sensory block measured by pain during tonic heat stimulatiom

End point description:

Participants were stimulated every 30 minutes with a probe heated to 45 degrees Celcius for 30 seconds. The block was defined as having cessated when stimulation elicited a painful response again.

End point type	Secondary

End point timeframe:

Every 30 minutes from block onset until stimulation with a 45 degrees Celcius probe in the hypothenar area elicited pain again.

End point values	Perineural dexamethasone	Systemic dexamethasone	Lidocaine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	16
Units: minutes				
arithmetic mean (confidence interval 95%)	651 (586 to 715)	661 (606 to 717)	398 (335 to 462)	578 (493 to 664)

Statistical analyses

Statistical analysis title	Paired t-test arm 1 versus arm 4
Comparison groups	Perineural dexamethasone v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	72
Confidence interval	
level	95 %
sides	2-sided
lower limit	14
upper limit	130
Variability estimate	Standard deviation

Statistical analysis title	Paired t-test arm 2 versus arm 4
Comparison groups	Placebo v Systemic dexamethasone

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	82
Confidence interval	
level	95 %
sides	2-sided
lower limit	11
upper limit	154
Variability estimate	Standard deviation

Statistical analysis title	Paired t-test arm 3 versus arm 4
Comparison groups	Placebo v Lidocaine
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-180
Confidence interval	
level	95 %
sides	2-sided
lower limit	-237
upper limit	-124
Variability estimate	Standard deviation

Secondary: Duration of the motor block measured by fifth finger abduction

End point title	Duration of the motor block measured by fifth finger abduction

End point description:

Participants' hands were immobilised allowing only for fifth finger abduction. The strength during abduction was assessed using the modified Bromage scale. The motor block was defined as cessated when fifth finger abduction reached a Bromage score of 4 or the participant indicated normal strength.

End point type	Secondary

End point timeframe:

Measured every 30 minutes from block onset until fifth finger abduction reached a Bromage score of 4 or the participant indicated normal strength in the fifth finger.

End point values	Perineural dexamethasone	Systemic dexamethasone	Lidocaine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	16
Units: minutes				
arithmetic mean (confidence interval 95%)	613 (564 to 662)	652 (587 to 716)	391 (337 to 445)	603 (537 to 669)

Statistical analyses

Statistical analysis title	Paired t-test arm 1 versus arm 4
Comparison groups	Perineural dexamethasone v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37
upper limit	57
Variability estimate	Standard deviation

Statistical analysis title	Paired t-test arm 2 versus arm 4
Comparison groups	Placebo v Systemic dexamethasone
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20
upper limit	118
Variability estimate	Standard deviation

Statistical analysis title	Copy of Paired t-test arm 3 versus arm 4
Comparison groups	Placebo v Lidocaine

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-212
Confidence interval	
level	95 %
sides	2-sided
lower limit	-265
upper limit	-159
Variability estimate	Standard deviation

Secondary: Onset of the sensory block measured by temperature discrimination

End point title	Onset of the sensory block measured by temperature discrimination

End point description:

The participants were stimulated in their hypothenar area using an alcohol swab. Block onset was defined as when an alcohol swab no longer felt cold.

End point type	Secondary

End point timeframe:

Measured every minute until an alcohol swab no longer felt cold.

End point values	Perineural dexamethasone	Systemic dexamethasone	Lidocaine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	16
Units: minutes				
arithmetic mean (confidence interval 95%)	2.8 (2.1 to 3.6)	2.7 (1.6 to 3.8)	2.3 (1.6 to 3.0)	3.1 (2.1 to 4.1)

Statistical analyses

Statistical analysis title	Paired t-test arm 1 versus arm 4
Comparison groups	Perineural dexamethasone v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.8
Variability estimate	Standard deviation

Statistical analysis title	Paired t-test arm 2 versus arm 4
Comparison groups	Placebo v Systemic dexamethasone
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	0.9
Variability estimate	Standard deviation

Statistical analysis title	Paired t-test arm 3 versus arm 4
Comparison groups	Placebo v Lidocaine
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	0.1
Variability estimate	Standard deviation

Secondary: Onset of the motor block measured by fifth finger abduction

End point title	Onset of the motor block measured by fifth finger abduction

End point description:

The participants' hands were immobilised allowing only for fifth finger abduction. The motor block onset was assessed every 1 minute until the fifth finger abduction reached a Bromage score of 0.

End point type	Secondary

End point timeframe:

Measured every minute until fifth finger abduction reached a Bromage score of 0.

End point values	Perineural dexamethasone	Systemic dexamethasone	Lidocaine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	16
Units: minutes				
arithmetic mean (confidence interval 95%)	5.5 (3.4 to 7.6)	4.5 (3.0 to 6.0)	4.2 (2.9 to 5.5)	5.9 (4.0 to 7.7)

Statistical analyses

Statistical analysis title	Paired t-test arm 1 versus arm 4
Comparison groups	Perineural dexamethasone v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	2.6
Variability estimate	Standard deviation

Statistical analysis title	Paired t-test arm 2 versus arm 4
Comparison groups	Placebo v Systemic dexamethasone
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	1

Variability estimate	Standard deviation

Statistical analysis title	Paired t-test arm 3 versus arm 4
Comparison groups	Placebo v Lidocaine
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	-0.4
Variability estimate	Standard deviation

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From block performance until 24 hours after completion of each of the two trial days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	All participants

Reporting group description: -

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)		

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: None of the healthy volunteers experienced non-serious adverse events during follow-up.

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