Clinical trial results:
Catheter-based peripheral regional anaesthesia after orthopaedic surgery:
Comparison of low dose, automated periodic infusions with conventional high dose, continuous infusion, and patient-initiated infusions only. A non-inferiority, randomised, controlled trial.

Summary

EudraCT number	2017-002280-18
Trial protocol	DK
Global end of trial date	21 January 2019

Results information

Result version number	v1 (current)
This version publication date	27 March 2021
First version publication date	27 March 2021

Trial information

Trial identification

Sponsor protocol code	FIPRA#3

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Department of Anaesthesia and Intensive Care
Sponsor organisation address	Dyrehavevej 29, Hillerød, Denmark, 3400
Public contact	The Department of Anesthesiology, Nordsjællands Hospital Hillerød, +45 48296680, mhmadsen@gmail.com
Scientific contact	The Department of Anesthesiology, Nordsjællands Hospital Hillerød, +45 48296680, mhmadsen@gmail.com

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 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 January 2019
Global end of trial reached?	Yes
Global end of trial date	21 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial is to investigate whether a low-dose automated, periodic infusion can produce a similar analgesic effect compared to a conventional, high dose, continuous infusion in catheter-based nerve block treatment for patients undergoing orthopaedic surgery. This is exemplified in three sub-trials on different populations:
1: Patients undergoing major shoulder surgery
2: Patients undergoing foot or ankle surgery
3: Patients undergoing major knee surgery

Protection of trial subjects:

Post-trial care: Approximately two weeks after surgery an investigator called patients to explore adverse events. Furthermore, 90 days after surgery an investigator did a journal survey to investigate readmissions and potential adverse events.

All data presented in future published papers will be anonymized.

Background therapy:

Postoperative pain management
Patients were discharged on the day of surgery and instructed to use paracetamol 1 g and ibuprofen 400 mg four times daily. Patients were instructed to release a bolus if they experienced severe pain. LA overdosing was impossible due to the built-in lock-out time. In case of repeated ineffective boluses, patients were instructed to take one tablet of oxycodone 5 mg which could be repeated.

Evidence for comparator:

The comparator, being conventional continuous infusions of local anaesthestic through peripheral nerve catheters, are the standard treatment in current postoperative pain management. There is solid evidence of pain relief when used.

Actual start date of recruitment	01 September 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: 197
Worldwide total number of subjects	197
EEA total number of subjects	197

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)	119
From 65 to 84 years	78
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from September 2017 to January 2019 at Nordsjællands and Bispebjerg University Hospitals.

Pre-assignment

Screening details:

All patients who were planned to have elective surgery of the fore- and mid-foot or to undergo total knee arthroplasty.

Period 1

Period 1 title	Postoperative days 1-4 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Blinding implementation details:

Opaque envelopes ensured allocation concealment. Programming and the display of the infusion pumps were blinded to investigators as well as to participants. Also, the delivery methods of the interventions not delivering programmed intermittent boluses (i.e. continuous infusion and boluses on-demand only) were programmed with a sham bolus of 0.1ml every 8th hour to further mask the intervention.

Arms

Are arms mutually exclusive?	Yes
Arm title	Continuous infusion - FOOT

Arm description:

A basal infusion of ropivacaine of 6 mL/h with the possibility of patient controlled catheter based bolus of local anaesthesia

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

Dosage and administration details:

6 ml / h of ropivacaine 0.2% with patient controlled bolus 10 ml (foot) or 15 ml (knee) at most every 4th hour.

Arm title	Intermittent bolus - FOOT

Arm description:

A programmed intermittent bolus of ropivacaine 10 mL every 8 hour

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

Dosage and administration details:

A programmed intermittent bolus of 10 ml every 8 hour (foot) or 15 ml every 10 hour (knee) with a optional patient controlled bolus of 10 of 15 ml (foot or knee) at most every 4th hour.

Arm title	Bolus on-demand only - FOOT

Arm description:

No planned treatment but an optional patient-controlled bolus of ropivacaine 10 mL every 4th hour

(lockout period) if needed.

Arm type	Active control

No investigational medicinal product assigned in this arm

Arm title	Continuous infusion - KNEE

Arm description:

Continuous infusion of ropivacaine, 6 mL/hour and optional patient-controlled bolus of 15 mL every 6th hour if needed.

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

Dosage and administration details:

6 ml / h of ropivacaine 0.2% with patient controlled bolus 10 ml (foot) or 15 ml (knee) at most every 4th hour.

Arm title	Intermittent bolus - KNEE

Arm description:

Programmed intermittent bolus of ropivacaine 15 mL every 12th hour and optional bolus on demand every 6th hour if needed.

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

Dosage and administration details:

6 ml / h of ropivacaine 0.2% with patient controlled bolus 10 ml (foot) or 15 ml (knee) at most every 4th hour.

Arm title	Bolus on-demand only - KNEE

Arm description:

No basal treatment but optional bolus on-demand of 15 mL of ropivacaine every 6th hour if needed.

Arm type	Active control

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Continuous infusion - FOOT	Intermittent bolus - FOOT	Bolus on-demand only - FOOT
Started	29	30	27
Completed	27	27	27
Not completed	2	3	0
Consent withdrawn by subject	1	1	-
Adverse event, non-fatal	-	-	-
Catheter failure	1	-	-
Lost to follow-up	-	2	-

Number of subjects in period 1	Continuous infusion - KNEE	Intermittent bolus - KNEE	Bolus on-demand only - KNEE
Started	39	35	37

Completed	27	27	27
Not completed	12	8	10
Consent withdrawn by subject	5	4	5
Adverse event, non-fatal	2	1	1
Catheter failure	-	-	-
Lost to follow-up	5	3	4

Baseline characteristics

Reporting groups

Reporting group title	Postoperative days 1-4

Reporting group description: -

Reporting group values	Postoperative days 1-4	Total	
Number of subjects	197	197	
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)	84	84	
From 65-84 years	111	111	
85 years and over	2	2	
Age continuous Units: years			
median	69		
standard deviation	± 8	-	
Gender categorical Units: Subjects			
Female	138	138	
Male	59	59	

Subject analysis sets

Subject analysis set title	KNEE
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients undergoing elective total knee arthroplasty

Subject analysis set title	FOOT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients undergoing elective fore- and midfoot surgery.

Reporting group values	KNEE	FOOT	
Number of subjects	111	86	
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)	23	61	
From 65-84 years	86	25	
85 years and over	2	0	
Age continuous			
Units: years			
median	70	57	
standard deviation	± 8	± 14	
Gender categorical			
Units: Subjects			
Female	69	66	
Male	42	15	

End points

End points reporting groups

Reporting group title	Continuous infusion - FOOT
Reporting group description:	
A basal infusion of ropivacaine of 6 mL/h with the possibility of patient controlled catheter based bolus of local anaesthesia	
Reporting group title	Intermittent bolus - FOOT
Reporting group description:	
A programmed intermittent bolus of ropivacaine 10 mL every 8 hour	
Reporting group title	Bolus on-demand only - FOOT
Reporting group description:	
No planned treatment but an optional patient-controlled bolus of ropivacaine 10 mL every 4th hour (lockout period) if needed.	
Reporting group title	Continuous infusion - KNEE
Reporting group description:	
Continuous infusion of ropivacaine, 6 mL/hour and optional patient-controlled bolus of 15 mL every 6th hour if needed.	
Reporting group title	Intermittent bolus - KNEE
Reporting group description:	
Programmed intermittent bolus of ropivacaine 15 mL every 12th hour and optional bolus on demand every 6th hour if needed.	
Reporting group title	Bolus on-demand only - KNEE
Reporting group description:	
No basal treatment but optional bolus on-demand of 15 mL of ropivacaine every 6th hour if needed.	
Subject analysis set title	KNEE
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients undergoing elective total knee arthroplasty	
Subject analysis set title	FOOT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients undergoing elective fore- and midfoot surgery.	

Primary: Pain

End point title	Pain
End point description:	
Pain self-reported on the Visual Analogue Scale, 0-100mm, on 18 specified time points. Measured as Area Under the Curve.	
End point type	Primary
End point timeframe:	
Postoperative days 1-4	

End point values	Continuous infusion - FOOT	Intermittent bolus - FOOT	Bolus on-demand only - FOOT	Continuous infusion - KNEE
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	27	27	27
Units: millimeter(s)				
arithmetic mean (confidence interval 95%)	1206 (749 to 1663)	1621 (1143 to 2099)	1583 (1120 to 2046)	1974 (1350 to 2482)

End point values	Intermittent bolus - KNEE	Bolus on-demand only - KNEE	KNEE	FOOT
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	27	27	81	54
Units: millimeter(s)				
arithmetic mean (confidence interval 95%)	1833 (1020 to 2670)	2621 (1450 to 3100)	141 (-692 to 874)	-416 (-1076 to 244)

Statistical analyses

Statistical analysis title	Analysis of primary endpoint

Statistical analysis description:

Intergroup comparison of the two primary intervention groups (intervention vs. comparator) was done by student's t test.

Comparison groups	Intermittent bolus - FOOT v Continuous infusion - FOOT
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	t-test, 1-sided
Parameter estimate	Mean difference (net)
Point estimate	1440
Confidence interval	
level	95 %
sides	2-sided
lower limit	1050
upper limit	1830
Variability estimate	Standard deviation
Dispersion value	1800

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately two weeks after surgery an investigator called patients to explore adverse events. Furthermore, 90 days after surgery an investigator did a journal survey to investigate readmissions and potential adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	CONSORT
Dictionary version	2010

Reporting groups

Reporting group title	Overall trial cohort

Reporting group description: -

Serious adverse events	Overall trial cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 197 (0.51%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Infections and infestations			
Infection at catheter site			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 197 (2.03%)		
Product issues			
Perineural catheter dysfunction or leak			
subjects affected / exposed	4 / 197 (2.03%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2018	Because of loss to follow-up we did not meet the expected inclusion rate and asked the appropriate authorities for trial period extension.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported