Clinical trial results:
The effect of the popliteal plexus block on postoperative pain after total knee arthroplasty - a randomized, controlled, double-blinded study

Summary

EudraCT number	2017-005180-40
Trial protocol	DK
Global end of trial date	23 August 2018

Results information

Result version number	v1 (current)
This version publication date	11 November 2019
First version publication date	11 November 2019

Trial information

Trial identification

Sponsor protocol code	Protocol_PPB_TKA_31122017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03439787
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle-Juul Jensens Boulevard, Aarhus N, Denmark, 8200
Public contact	Bedøvelse og Operation Nord Thomas Fichtner Bendtsen, Aarhus University Hospital, +45 51542997, tfb@dadlnet.dk
Scientific contact	Bedøvelse og Operation Nord Thomas Fichtner Bendtsen, Aarhus University Hospital, +45 51542997, tfb@dadlnet.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	10 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 August 2018
Global end of trial reached?	Yes
Global end of trial date	23 August 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the analgesic effect of the popliteal plexus block (PPB) as a supplement to a femoral triangle block (FTB) after total knee arthroplasty (TKA)

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and approved by the Danish Medicines Agency, The Central Denmark Region Committees on Health Research Ethics and the Danish Data Protection Agency. The trial was prospectively registered in the EudraCT database and was monitored by the Good Clinical Practice Unit at Aalborg and Aarhus University Hospitals. Prior to inclusion, written informed consent was obtained from all subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2018
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	Denmark: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	4
From 65 to 84 years	11

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients recruited at Silkeborg Regional Hospital in Denmark from the outpatient clinic according to the approved recruitment plan in the protocol

Pre-assignment

Screening details:

49 patients screened from May 15 2018 to August 23 2018

Screening based on in- and exclusion criteria defined in the approved protocol

Period 1

Period 1 title	overall period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention group

Arm description:

Patients with NRS > 3 in the postoperative observation period received a PPB.

Popliteal plexus block with 10 ml of Marcaine 5 mg/ml with adrenaline 5 microgram/ml + 0.5 ml dexamethasone 4 mg/ml

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

Dosage and administration details:

Each patient randomized to this arm was administered one popliteal plexus block with 10 ml Marcain 5 mg/ml with adrenaline 5 microgram/ml + 0.5 ml dexamethasone 4 mg/ml.

Arm title	Placebo group

Arm description:

Patients with NRS > 3 in the postoperative observation period received a popliteal plexus block.

Popliteal plexus block with 10 ml sodium chloride 0.9 %

Arm type	Placebo
Investigational medicinal product name	Sodium chloride 0.9 %
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Perineural use

Dosage and administration details:

Each patient randomized to this arm received one popliteal plexus block with 10 ml sodium chloride 0.9 %

Arm title	No intervention (no PPB)

Arm description:

If the patient does not report NRS > 3 during the 3-hour observation period, the patient will not receive a PPB.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Intervention group	Placebo group	No intervention (no PPB)
Started	4	4	7
Completed	4	4	7

Baseline characteristics

Reporting groups	
Reporting group title	Intervention group

Reporting group description:

Patients with NRS > 3 in the postoperative observation period received a PPB.

Popliteal plexus block with 10 ml of Marcaine 5 mg/ml with adrenaline 5 microgram/ml + 0.5 ml dexamethasone 4 mg/ml

Reporting group title	Placebo group

Reporting group description:

Patients with NRS > 3 in the postoperative observation period received a popliteal plexus block.

Popliteal plexus block with 10 ml sodium chloride 0.9 %

Reporting group title	No intervention (no PPB)

Reporting group description:

If the patient does not report NRS > 3 during the 3-hour observation period, the patient will not receive a PPB.

Reporting group values	Intervention group	Placebo group	No intervention (no PPB)
Number of subjects	4	4	7
Age categorical Units: Subjects			
Adults (18-64 years)	1	0	3
From 65-84 years	3	4	4
Gender categorical Units: Subjects			
Female	3	3	3
Male	1	1	4

Reporting group values	Total		
Number of subjects	15		
Age categorical Units: Subjects			
Adults (18-64 years)	4		
From 65-84 years	11		
Gender categorical Units: Subjects			
Female	9		
Male	6		

End points

End points reporting groups

Reporting group title	Intervention group

Reporting group description:

Patients with NRS > 3 in the postoperative observation period received a PPB.

Popliteal plexus block with 10 ml of Marcaine 5 mg/ml with adrenaline 5 microgram/ml + 0.5 ml dexamethasone 4 mg/ml

Reporting group title	Placebo group

Reporting group description:

Patients with NRS > 3 in the postoperative observation period received a popliteal plexus block.

Popliteal plexus block with 10 ml sodium chloride 0.9 %

Reporting group title	No intervention (no PPB)

Reporting group description:

If the patient does not report NRS > 3 during the 3-hour observation period, the patient will not receive a PPB.

Primary: Success of the PPB

End point title	Success of the PPB[1][2]

End point description:

Success of the PPB is defined as the proportion of patients with significant postoperative pain (NRS > 3) after FTB, who drop in pain score to NRS ≤ 3 after PPB and maintain NRS ≤ 3 without any opioids until 60 minutes after PPB.

No data available as this trial was terminated early and no statistical analyses have been performed.

End point type	Primary

End point timeframe:

Up until 60 minutes after PPB

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been performed as the trial was terminated early due to problems in the study design. The Danish Medicines Agency and the Central Denmark Region Committees on Health Research Ethics were notified after this early termination. The termination was only due to problems in the study design and not related to any safety concerns regarding the patients.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point can only be assessed in patients receiving a popliteal plexus block - and not for the non intervention group where the patients did not receive a popliteal plexus block.

End point values	Intervention group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: yes/no				

Notes:

[3] - No statistical analysis performed at the trial was terminated early.

[4] - No statistical analysis performed at the trial was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Onset time of the PPB

End point title	Onset time of the PPB[5]

End point description:

The onset time is defined as the time from withdrawal of the block needle and until the patient reports NRS ≤ 3. The maximal onset time is defined as 60 minutes. The pain scores after PPB are evaluated every 5 minutes until 15 minutes after PPB and hereafter every 15 minutes until 60 minutes after PPB.

End point type	Secondary

End point timeframe:

The pain scores after PPB are evaluated every 5 minutes until 15 minutes after PPB and hereafter every 15 minutes until 60 minutes after PPB.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point can only be assessed in patients receiving a popliteal plexus block - and not for the non intervention group where the patients did not receive a popliteal plexus block.

End point values	Intervention group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: NRS scale 0-10				

Notes:

[6] - No statistical analysis performed at the trial was terminated early.

[7] - No statistical analysis performed at the trial was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: The effect of the PPB on cutaneous sensation on the lateral aspect of the lower leg

End point title	The effect of the PPB on cutaneous sensation on the lateral aspect of the lower leg[8]

End point description:

Sensation is graded on a 3-point scale: 0 = no sensation, 1 = reduced sensation and 2 = normal sensation to pinprick compared to the contralateral side

End point type	Secondary

End point timeframe:

Cutaneous sensation is evaluated with a pinprick test. The pinprick test is performed at baseline and 2 hours after the placement of the PPB, t,PPB = 2 hours

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point can only be assessed in patients receiving a popliteal plexus block - and not for the non intervention group where the patients did not receive a popliteal plexus block.

End point values	Intervention group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: 0-3				

Notes:

[9] - No statistical analysis performed at the trial was terminated early.

[10] - No statistical analysis performed at the trial was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: The effect of PPB on isometric muscle strength of the dorso- and plantar flexors of the ankle joint

End point title	The effect of PPB on isometric muscle strength of the dorso- and plantar flexors of the ankle joint[11]

End point description:

Dorsal and plantar flexion of the foot is measured with a handheld dynamometer as the maximum isometric contraction (MVIC). The test is performed at baseline and 2 hours after the placement of the PPB. The highest value of three consecutive MVIC measurements, separated by a minimum of 30 seconds, is registered.

End point type	Secondary

End point timeframe:

Measured at baseline and 3 hours after popliteal plexus block

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point can only be assessed in patients receiving a popliteal plexus block - and not for the non intervention group where the patients did not receive a popliteal plexus block.

End point values	Intervention group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Newton				
number (not applicable)				

Notes:

[12] - No statistical analysis performed at the trial was terminated early.

[13] - No statistical analysis performed at the trial was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulated opioid consumption from 0-4 hours

End point title	Cumulated opioid consumption from 0-4 hours[14]

End point description:

Opioid consumption is registered from the electronic patient record (EPJ) and entered into REDCap.

End point type	Secondary

End point timeframe:

0-4 hours

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point can only be assessed in patients receiving a popliteal plexus block - and not for the non intervention group where the patients did not receive a popliteal plexus block.

End point values	Intervention group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: mg				
number (not applicable)				

Notes:

[15] - No statistical analysis performed at the trial was terminated early.

[16] - No statistical analysis performed at the trial was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulated opioid consumption from 4-24 hours

End point title	Cumulated opioid consumption from 4-24 hours[17]

End point description:

End point type	Secondary

End point timeframe:

4-24 hours

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point can only be assessed in patients receiving a popliteal plexus block - and not for the non intervention group where the patients did not receive a popliteal plexus block.

End point values	Intervention group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[18]	0[19]		
Units: mg				
number (not applicable)				

Notes:

[18] - No statistical analysis performed at the trial was terminated early.

[19] - No statistical analysis performed at the trial was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain scores

End point title	Pain scores[20]

End point description:

For subjects receiving a PPB, pain scores will be performed at 2, 4 and 24 hours after PPB. The patient is asked about the worst pain since last test time. For subjects not receiving a PPB, final pain scores will be made at the follow-up visit after 24 hours.

End point type	Secondary

End point timeframe:

2, 4 and 24 hours after PPB

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point can only be assessed in patients receiving a popliteal plexus block - and not for the non intervention group where the patients did not receive a popliteal plexus block.

End point values	Intervention group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[21]	0[22]		
Units: NRS 0-10				

Notes:

[21] - No statistical analysis performed at the trial was terminated early.

[22] - No statistical analysis performed at the trial was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: The number of patients experiencing significant pain (NRS > 3) as a proportion of all patients with FTB

End point title	The number of patients experiencing significant pain (NRS > 3) as a proportion of all patients with FTB

End point description:

All patients receive a FTB and are observed postoperatively for the development of significant pain (NRS > 3) during an observation period defined as: A 3-hour observation period starting at the return of normal cutaneous sensation after spinal anaesthesia. Normal cutaneous sensation is defined as a pinprick score of 2 on both the lateral thigh and the lateral aspect of the lower leg.

End point type	Secondary

End point timeframe:

A 3-hour observation period starting at the return of normal cutaneous sensation after spinal anaesthesia.

End point values	Intervention group	Placebo group	No intervention (no PPB)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[23]	0[24]	0[25]	
Units: Frequency				

Notes:

[23] - No statistical analysis performed at the trial was terminated early.

[24] - No statistical analysis performed at the trial was terminated early.

[25] - No statistical analysis was done because the trial was terminated early

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From time of block placement (popliteal plexus block) to 24 hours after block placement	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0
Reporting groups	
Reporting group title	Intervention group
Reporting group description: Popliteal plexus block with 10 ml of Marcaine 5 mg/ml with adrenaline 5 microgram/ml + 0.5 ml dexamethasone 4 mg/ml	
Reporting group title	Placebo group
Reporting group description: Popliteal plexus block with 10 ml sodium chloride 0.9 %	
Reporting group title	No intervention group
Reporting group description: -	

Serious adverse events	Intervention group	Placebo group	No intervention group
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Intervention group	Placebo group	No intervention group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	2 / 4 (50.00%)	0 / 7 (0.00%)
General disorders and administration site conditions			
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	0 / 7 (0.00%)
occurrences (all)	1	3	0
Dizziness	Additional description: Mild dizziness when the patient stands up, resolves immediately when the patients lies down.		
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Leg cramp	Additional description: Mild leg cramp		
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Shivering	Additional description: Mild shivering in the early postoperative period		
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2018	Amendment approved March 26 2018 by the Ethics Committee and March 21 2018 by the Danish Medicines Agency Amendment: Aarhus University Hospital is added as a center. The randomization is made with envelopes instead of electronic randomization i REDCap. All patients are allowed to receive 8 mg dexamethasone IV at the end of the operation to prevent nausea.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 August 2018	At the time of trial termination, 15 patients have been included, and 8 of these patients have received the active PPB and 7 the placebo PPB according to the protocol and randomization. We have become aware of two major issues in the study design, which compromise the validity of the data: 1) Competing pain. Several patients have complained of competing pain from the incision site at the front of the knee. The PPB will only anesthetize pain from the posterior aspect of the knee, but according to the protocol the PPB is given at any pain score above 3. 2) Placebo effect. Performance of the PPB when the patient complains of pain introduces a risk of a placebo effect, where the block procedure itself generates a feeling of pain relief. We did take this into account when designing the study, but we did not expect the placebo effect to continue beyond the first 60 minutes after PPB performance. Data from the 8 patients with active PPB suggest that we have underestimated the placebo effect, which invalidates our primary end point as defined in the protocol. At the time of termination all 15 patients have completed the study according to the protocol. There have been no serious adverse events during the trial period, and we have not experienced any problems regarding the safety of the patients. The decision to terminate the trial is solely based on the problems in the study design, which compromise the validity of the data. Therefore, the most ethical decision is to terminate the trial in its current from instead of using resources on a trial that will not provide valid or relevant data. This trial was terminated and will not be restarted.	-

Notes:

Limitations and caveats

None reported