Clinical trial results:
The effect of intraoperative low dose adrenaline on bleeding in total hip arthroplasty - a randomized placebo-controlled trial

Summary

EudraCT number	2012-002889-12
Trial protocol	DK
Global end of trial date	10 October 2013

Results information

Result version number	v1 (current)
This version publication date	04 February 2022
First version publication date	04 February 2022

Trial information

Trial identification

Sponsor protocol code	RH-4074-OJ2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01708642
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, DK-2100
Public contact	Oeivind Jans, Rigshospitalet, Section of surgical Pathophysiology, 4074, 45 35451631, oeivind.jans@rh.regionh.dk
Scientific contact	Pär I. Johansson, Rigshospitalet, Section 2034, Capital Blood Bank, 45 35452030, per.johansson@regionh.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	15 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 October 2013
Global end of trial reached?	Yes
Global end of trial date	10 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The evaluate the effect of intraoperative administration of low-dose adrenaline on intraoperative blood loss.

Protection of trial subjects:

All patients were admitted to the hospital and were closely monitored during the intervention

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2012
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: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	30
From 65 to 84 years	60
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Patients who need hip replacement will be recruited from Gentofte hospital and Vejle Hospital

Pre-assignment

Screening details:

Patients who were eligable for total hip arthroplasty and above 18 years old were screened for inclusion

Period 1

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

Blinding implementation details:

Acomputer generated randomization list (www.randomization.org) was generated by a researcher outside the author group using permuted blocks (block size 10, allocation ratio 1:1). Subjectswere enrolled in the trial by a dedicated study nurse and assigned a unique randomization number based on sequentially numbered,sealed, opaque envelopes in which allocation was concealed. Just before surgery the envelope was opened by the anaesthesia
nurse, who also prepared the study drug (epinephrine

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention arm

Arm description:

Before surgery subjects were randomly allocated to receive an infusion of either epinephrine (Adrenalin "DAK", Nycomed Denmark ApS) at a weight-adjusted rate of 0.05 µg kg−1 min−1 from placement of spinal anaesthesia to end of surgery (last suture).

Arm type	Experimental
Investigational medicinal product name	Adrenaline DAK
Investigational medicinal product code	
Other name	epinephrine
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A weight-adjusted rate of 0.05 µg kg−1 min−1 will be given from placement of spinal anaesthesia to end of surgery

Arm title	Placebo

Arm description:

Before surgery subjects were randomly allocated to receive an infusion of placebo (0.9% saline) from placement of spinal anaesthesia to end of surgery (last suture).

Arm type	Placebo
Investigational medicinal product name	Saline 0.9%
Investigational medicinal product code	
Other name	sodium chloride
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A weight-adjusted rate corresponding the the intervention arm will be given from placement of spinal anaesthesia to end of surgery (last suture).

Number of subjects in period 1	Intervention arm	Placebo
Started	50	50
Completed	50	50

Baseline characteristics

Reporting groups	
Reporting group title	Intervention arm
Reporting group description:	
Before surgery subjects were randomly allocated to receive an infusion of either epinephrine (Adrenalin "DAK", Nycomed Denmark ApS) at a weight-adjusted rate of 0.05 µg kg−1 min−1 from placement of spinal anaesthesia to end of surgery (last suture).	
Reporting group title	Placebo
Reporting group description:	
Before surgery subjects were randomly allocated to receive an infusion of placebo (0.9% saline) from placement of spinal anaesthesia to end of surgery (last suture).	

Reporting group values	Intervention arm	Placebo	Total
Number of subjects	50	50	100
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			
median	67	69	
standard deviation	± 10	± 8	-
Gender categorical			
Units: Subjects			
Female	23	24	47
Male	27	26	53

End points

End points reporting groups

Reporting group title	Intervention arm
Reporting group description:	
Before surgery subjects were randomly allocated to receive an infusion of either epinephrine (Adrenalin "DAK", Nycomed Denmark ApS) at a weight-adjusted rate of 0.05 µg kg−1 min−1 from placement of spinal anaesthesia to end of surgery (last suture).	
Reporting group title	Placebo
Reporting group description:	
Before surgery subjects were randomly allocated to receive an infusion of placebo (0.9% saline) from placement of spinal anaesthesia to end of surgery (last suture).	

Primary: Blood loss

End point title	Blood loss
End point description:	
Interaoperative blood loos in ml during the operation	
End point type	Primary
End point timeframe:	
From start of operation for HIP arthroplasty to end op operation	

End point values	Intervention arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: ml				
arithmetic mean (standard deviation)				
Blood loss	343 (± 156)	383 (± 177)		

Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	Intervention arm v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.23
Method	t-test, 2-sided

Notes:

[1] - Before analyses, all data were evaluated for normal distribution by histograms and Q-Q plots and by the Kolmogrov-Schmirnof test. The primary and secondary outcomes were analysed by modified intention to treat by group comparison using a twosided independent samples t-test for continuous outcomes.

Secondary: Blood loss at 24 hours

End point title	Blood loss at 24 hours

End point description:

The secondary outcome
measure was blood loss at 24 h after surgery

End point type	Secondary

End point timeframe:

From start of operation to 24 hours

End point values	Intervention arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: ml				
arithmetic mean (standard deviation)				
Blood loss	902 (± 368)	1082 (± 481)		

Statistical analyses

Statistical analysis title	Secondaty endpoint - Blood loss 24 h
Comparison groups	Intervention arm v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	t-test, 2-sided

Secondary: Hb concentration 24 hours

End point title	Hb concentration 24 hours

End point description:

Hb measurements were by venous sampling at 24 h after end of surgery (last suture).

End point type	Secondary

End point timeframe:

Changes from start op operation to 24 hours post surgery

End point values	Intervention arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: g dl(-1)				
arithmetic mean (standard deviation)				
Haemaglobin	11.5 (± 1.3)	11.3 (± 1.4)		

Statistical analyses

Statistical analysis title	Hb secondary endpoint
Comparison groups	Placebo v Intervention arm
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From start of operation to post 24 hours.	
Assessment type	Systematic

Dictionary used	
Dictionary name	none
Dictionary version	0

Reporting groups	
Reporting group title	Intervention group
Reporting group description: -	
Reporting group title	Placebo group
Reporting group description: -	

Serious adverse events	Intervention group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Intervention group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 50 (12.00%)	5 / 50 (10.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 50 (2.00%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Haematoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Bradycardia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			

Sedation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Dizziness			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Elevated temperature			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Elevated kidney parameters			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26821696