Clinical trial results:
Highdose steroids in High Pain Responders undergoing total knee-arthroplasty - A randomized doubleblindet controlled trial.

Summary

EudraCT number	2018-002635-23
Trial protocol	DK
Global end of trial date	01 March 2021

Results information

Result version number	v1 (current)
This version publication date	23 September 2022
First version publication date	23 September 2022
Summary attachment (see zip file)	Journal article, BJA 2021 (1-s2.0-S0007091221006255-main (2).pdf)

Trial information

Trial identification

Sponsor protocol code	NBF_HK_02_2018.

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03763734
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Anesthesia-research group of Prof. Nicolai Bang Foss
Sponsor organisation address	Kettegård alle 30, Hvidovre , Denmark, 2650
Public contact	Niklas Ingemann Nielsen, Anesthesia-Research group., Anaesthesia Department, Hvidovre Hospital, Capital Region of Denmark, +45 38623862, Niklas.Ingemann.Nielsen@regionh.dk
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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	11 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 January 2021
Global end of trial reached?	Yes
Global end of trial date	01 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of high dose steroids on the amount of patients with VAS >30 in a 5-meter walktest, 24 hours postoperatively efter total kneearthroplasty in a High Pain responder cohort.

Protection of trial subjects:

All patients had standardized care, surgery and treatments as part of a Fast-track surgery regimen in Total Knee Arthroplasty surgery, and both study-treatment-groups had active treatment (standard-dose vs. higher dose).

Background therapy:

Multimodal opioid-sparring analgesia including Cox-2 inhibitors, acetaminophen(paracetamol) and rescue opioids (morphine or oxycodone).
All patients had pre- and postoperative tranexamic acid, Local Infiltration Analgesia applied by the surgeon perioperatively, postoperative compression bandage.
Perioperative antibiotic regimen of i.v. dicloxacillin 2 g at start of surgery and repeated if body weight >80 kg or if length of surgery >2 h. Dicloxacillin was repeated as 1 g tablet 8 h after end of surgery. Cefuroxim in case of allergy.
Thromboprophylaxis was used in-hospital only (xarelto or eliquis).
All patients had neuraxial anesthesia with bupivacaine.

Evidence for comparator:

The use of steroids as a perioperative mean of reducing postoperative stress and hence reducing postoperative pain is well-known, and several articles exist on the topic.

T.H. Lunn, B.B. Kristensen, L. Andersen, et al.
Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial
Br J Anaesth, 106 (2011), pp. 230-238

De Oliveira GS, Almeida MD, Benzon HT, McCarthy RJ.
Perioperative single dose systemic dexamethasone for postoperative pain: A meta-analysis of randomized controlled trials.
Anesthesiology 2011; 115: 575–88

C.C. Jørgensen, F.T. Pitter, H. Kehlet
Safety aspects of preoperative high-dose glucocorticoid in primary total knee replacement
Br J Anaesth, 119 (2017), pp. 267-275

A. Toner, V. Ganeshanathan, M. Chan, K. Ho, T. Corcoran
Safety of perioperative glucocorticoids in elective noncardiac surgery, a systematic review and meta-analysis
Anesthesiology, 126 (2017), pp. 234-248

Actual start date of recruitment	03 December 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: 88
Worldwide total number of subjects	88
EEA total number of subjects	88

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)	25
From 65 to 84 years	62
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were recruited before surgery at their information meeting. All participants had had oral and written project information in accordance with guidelines and had at least 24 hours of consideration. All participants gave informed consent. Patients were screened at Hvidovre Hospital and Vejle sygehus from January 2019 to August 2020.

Pre-assignment

Screening details:

From February 13, 2019 to August 26, 2020, a total of 1037 patients planned for knee arthroplasty were assessed for inclusion in accordance to inclusion and exclusioncriteria. 25% of screened patients were eligible and 88 patients were included and randomised.

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, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Randomisation sequence were made by unblinded physicians not otherwise connected to the study or the participants with double-control.
Study-specific trained unblinded nurses at each site, not having any contact with the participants were responsible for preparing the study-drug and blinding this for all other personnel.
Study-drug was mixed into a blinded 100 ml. container, and intervention and control were alike in both volume and appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention (High dose, HD)

Arm description:

Intervention arm, High dose Dexamethasone 1mg/kg of patient's actual bodyweight.

Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Dexamethasone 10mg/ml, added to a 100 ml. NaCl container in accordance to the patient's actual weight, thus the intervention dose was 1mg/kg.
Infusion initiated after application of neuraxial anesthesia and administered within 10-15 minutes.

Arm title	Control (standard/intermediate dose (ID)

Arm description:

Intermediate dose dexamethasone 0.3mg/kg of actual bodyweight

Arm type	Active comparator

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Dexamethasone 10mg/ml, added to a 100 ml. NaCl container in accordance to the patient's actual weight, thus the intervention dose was 0.3mg/kg.
Infusion initiated after application of neuraxial anesthesia and administered within 10-15 minutes.

Number of subjects in period 1	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)
Started	44	44
Completed	42	42
Not completed	2	2
excluded due to change of surgery/anesthesia	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Intervention (High dose, HD)
Reporting group description:	
Intervention arm, High dose Dexamethasone 1mg/kg of patient's actual bodyweight.	
Reporting group title	Control (standard/intermediate dose (ID)
Reporting group description:	
Intermediate dose dexamethasone 0.3mg/kg of actual bodyweight	

Reporting group values	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)	Total
Number of subjects	44	44	88
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			
Age			
Units: years			
median	70	70	
full range (min-max)	50 to 86	50 to 82	-
Gender categorical			
Sex (n/n)			
Units: Subjects			
Female	16	16	32
Male	28	28	56
ASA-score			
ASA-score American Society of Anesthesiologist score of morbidity and physical status. Range I-VI (1-6) ranging from I: Healthy patient to VI: Brain-dead patient awaiting organ-donation.			
Units: Subjects			
Score I	7	7	14
Score II	20	31	51
Score III	17	6	23

End points

End points reporting groups

Reporting group title	Intervention (High dose, HD)
Reporting group description:	
Intervention arm, High dose Dexamethasone 1mg/kg of patient's actual bodyweight.	
Reporting group title	Control (standard/intermediate dose (ID)
Reporting group description:	
Intermediate dose dexamethasone 0.3mg/kg of actual bodyweight	

Primary: Primary Outcome: Percentage of patients experiencing VAS>30mm on a 0-100 mm. VAS scale 24 hours after surgery upon ambulation

End point title	Primary Outcome: Percentage of patients experiencing VAS>30mm on a 0-100 mm. VAS scale 24 hours after surgery upon ambulation
End point description:	
Percentage of patients experiencing VAS>30mm on a 0-100 mm VAS scale 24 hours after surgery upon ambulation in a 5 meter walk test.	
End point type	Primary
End point timeframe:	
24 hours after knee replacement surgery (a timeframe of 1 hour before and after precise timepoint of end of surgery).	

End point values	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[1]	42[2]		
Units: Percentage				
VAS>30	21	33		
VAS<31	21	9		

Notes:

[1] - 2 patients excluded before intervention

[2] - 2 patients excluded before intervention

Statistical analyses

Statistical analysis title	Chi-squared test.
Statistical analysis description:	
Chi-squared test of significance	
Comparison groups	Control (standard/intermediate dose (ID) v Intervention (High dose, HD)

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	Chi-squared

Secondary: PAIN (VAS-score) 24hours after surgery upon ambulation

End point title	PAIN (VAS-score) 24hours after surgery upon ambulation

End point description:

VAS-score upon ambulation in a 0-100mm. VAS scale upon a 5 meter walk test 24 hours after surgery.

End point type	Secondary

End point timeframe:

24 hours after surgery (prespecified timeframe of 1 hour before and after actual end of surgery timepoint).

End point values	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[3]	42[4]		
Units: mm				
median (inter-quartile range (Q1-Q3))				
VAS score	30 (18 to 58)	45 (32 to 58)		

Notes:

[3] - 2 patients excluded before intervention

[4] - 2 patients excluded before intervention

Attachments (see zip file)	Distribution of VAS at 24h (median(IQR))/Figure 3 VAS T24

Statistical analyses

Statistical analysis title	Mann-whitney U test

Statistical analysis description:

Mann-whitney

Comparison groups	Intervention (High dose, HD) v Control (standard/intermediate dose (ID)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: VAS>30mm 24hours after surgery upon rest

End point title	VAS>30mm 24hours after surgery upon rest

End point description:

Percentage of patients experiencing VAS>30mm upon rest in a 0-100mm. VAS scale 24 hours after surgery.

End point type	Secondary

End point timeframe:

24 hours after surgery (prespecified timeframe of 1 hour before and after actual end of surgery timepoint).

End point values	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[5]	42[6]		
Units: (n/n, %)				
VAS>30	11	18		
VAS<31	31	24		

Notes:

[5] - 2 patients excluded before intervention

[6] - 2 patients excluded before intervention

Statistical analyses

Statistical analysis title	Chi-squared
Comparison groups	Control (standard/intermediate dose (ID) v Intervention (High dose, HD)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided

Secondary: Cumulated pain day 0-2 upon rest

End point title	Cumulated pain day 0-2 upon rest

End point description:

Cumulted pain scores (VAS 0-100mm) on day 0-2, median(IQR)

End point type	Secondary

End point timeframe:

0-48 hours after surgery (prespecified timeframe of 1 hour before and after actual end of surgery timepoint).

End point values	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[7]	42[8]		
Units: mm				
median (inter-quartile range (Q1-Q3))				
Cumulated pain 0-2	80 (37 to 112)	86 (69 to 143)		

Notes:

[7] - 2 patients excluded before intervention

[8] - 2 patients excluded before intervention

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulated pain day 0-2 upon ambulation

End point title	Cumulated pain day 0-2 upon ambulation

End point description:

Cumulted pain scores (VAS 0-100mm) on day 0-2, median(IQR) upon ambulation in a 5m walk test

End point type	Secondary

End point timeframe:

0-48 hours after surgery (prespecified timeframe of 1 hour before and after actual end of surgery timepoint).

End point values	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[9]	42[10]		
Units: VAS (MM)				
median (inter-quartile range (Q1-Q3))				
Cumulated pain day 0-2 upon ambulation	82 (45 to 118)	101 (69 to 131)		

Notes:

[9] - 2 patients excluded before intervention

[10] - 2 patients excluded before intervention

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulated pain day 0-2 upon passive legg raise

End point title	Cumulated pain day 0-2 upon passive legg raise

End point description:

Cumulted pain scores (VAS 0-100mm) on day 0-2, median(IQR)

End point type	Secondary

End point timeframe:

0-48 hours after surgery (prespecified timeframe of 1 hour before and after actual end of surgery timepoint).

End point values	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[11]	42[12]		
Units: VAS (MM)				
median (inter-quartile range (Q1-Q3))				
Cumulated pain day 0-2 upon passive legg raise	23 (0 to 81)	67 (28 to 110)		

Notes:

[11] - 2 patients excluded before intervention

[12] - 2 patients excluded before intervention

Statistical analyses

No statistical analyses for this end point

Secondary: CRP after surgery

End point title	CRP after surgery

End point description:

C-reactive protein (CRP) as a measure of inflammatory response (mg/L)

End point type	Secondary

End point timeframe:

24 and 48 hour after surgery

End point values	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[13]	42[14]		
Units: mg/L				
median (inter-quartile range (Q1-Q3))				
CRP 24 hours	13 (8 to 23)	21 (9 to 34)		
CRP 48 hours	23 (12 to 35)	51 (39 to 83)		

Notes:

[13] - 2 patients excluded before intervention

[14] - 2 patients excluded before intervention

Statistical analyses

Statistical analysis title	Mann-whitney
Comparison groups	Intervention (High dose, HD) v Control (standard/intermediate dose (ID)

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - p=0.01 at 24h and p<0.01 at 48h.

Secondary: Cumulated opioid-use day 0-2

End point title	Cumulated opioid-use day 0-2

End point description:

Cumulated opioid-use presented as oral morphine in mg., cumulated day 0-2.

End point type	Secondary

End point timeframe:

Postoperative day 0-2 reported at timepoints 24h and 48h after surgery

End point values	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[16]	42[17]		
Units: mg				
median (inter-quartile range (Q1-Q3))				
Day 0-2	51 (30 to 90)	83 (46 to 111)		

Notes:

[16] - 2 patients excluded prior to randomization

[17] - 2 patients excluded prior to randomization

Statistical analyses

Statistical analysis title	Significance test

Statistical analysis description:

Mann-whitney significance test

Comparison groups	Intervention (High dose, HD) v Control (standard/intermediate dose (ID)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.06
Method	Wilcoxon (Mann-Whitney)

Secondary: Cumulated opioid-use

End point title	Cumulated opioid-use

End point description:

Cumulated opioid-use presented as oral morphine in mg., cumulated day 2-7.

End point type	Secondary

End point timeframe:

Postoperative day 2-7 reported at timepoints from evening day 2 and onto evening day 7 after surgery

End point values	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[18]	42[19]		
Units: mg				
median (inter-quartile range (Q1-Q3))				
Day 2-7	95 (18 to 185)	150 (45 to 255)		

Notes:

[18] - 2 participants excluded prior to intervention

[19] - 2 participants excluded prior to intervention

Statistical analyses

Statistical analysis title	Significance test
Statistical analysis description: Mann-whitney U test	
Comparison groups	Intervention (High dose, HD) v Control (standard/intermediate dose (ID)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.12
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Serious adverse events were reported on day 0, 1, 2, 7, 30 or 90, or when alerted via our electronic patient record-system, and all SAE were reported within 24h of alert to the Sponsor.

Adverse event reporting additional description:

Only Serious adverse events were recorded and reported in accordance with the approval of the Danish medicines agency and local ethics committee, as Dexamethasone is a broadly used and well-approved drug.
If adverse events (not serious adverse events) were reported or suspected of occurring in more than 5% of patients, the sponsor was informed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Intervention (High dose, HD)

Reporting group description:

Intervention arm, High dose Dexamethasone 1mg/kg of patient's actual bodyweight.

Reporting group title	Control (standard/intermediate dose (ID)

Reporting group description:

Intermediate dose dexamethasone 0.3mg/kg of actual bodyweight

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: No non-serious adverse events were reported, as specified in the protocol and agreed upon by the Local ethics committee and relevant authorities(DKMA)

Serious adverse events	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 42 (7.14%)	2 / 42 (4.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Patellar dislocation	Additional description: Patellar dislocation needing revision surgery		
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection	Additional description: Skin-infection, deep wound infection needing further antibiotics or Prosthetic joint infection needing revision		
subjects affected / exposed	3 / 42 (7.14%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Intervention (High dose, HD)	Control (standard/intermediate dose (ID)	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	

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? Yes

Date	Interruption	Restart date
17 March 2020	Elective surgery was shut down due to the global Covid crisis.	02 June 2020

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34749994