



Clinical trial results:

Highdose steroid for total knee arthroplasty - A randomized doubleblindet controlled trial.

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2018-002634-20 |
| Trial protocol | DK |
| Global end of trial date | 01 February 2022 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 26 September 2022 |
| First version publication date | 26 September 2022 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | NBF_HK_01_2018 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03758170 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Hvidovre Hospital |
| Sponsor organisation address | Kettegaards alle 30, Hvidovre, Denmark, 2650 |
| Public contact | Research group, anaesthesia Dept., Anaesthesia Department, Hvidovre Hospital, Capital Region of Denmark, +45 38623862, Nicolai.Bang.Foss@regionH.dk |
| Scientific contact | Research group, anaesthesia Dept., Anaesthesia Department, Hvidovre Hospital, Capital Region of Denmark, +45 38623862, Nicolai.Bang.Foss@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 | 01 March 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 January 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 February 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To investigate the amount of patients with VAS >30 in a 5-meter walk test, 24 hours postoperatively after total knee arthroplasty.

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-sparing analgesia including Cox-2 inhibitors, acetaminophen(paracetamol) and rescue opioids (morphine or oxycodone).

All patients had pre- and postoperative tranexamic acid.

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.

Lunn TH, Andersen LO, Kristensen BB, Husted H, Gaarn-Larsen L, Bandholm T, Ladelund S, Kehlet H: Effect of high-dose preoperative methylprednisolone on recovery after total hip arthroplasty: A randomized, double-blind, placebo-controlled trial.

Br J Anaesth 2013; 110:66–73

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 metaanalysis

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? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Denmark: 157 |
| Worldwide total number of subjects | 157 |
| EEA total number of subjects | 157 |

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) | 40 |
| From 65 to 84 years | 113 |
| 85 years and over | 4 |

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 September 2021

Pre-assignment

Screening details:

From January 29, 2019, to september 31, 2021, a total of 1277 patients planned for hip arthroplasty were assessed for inclusion in accordance with inclusion and exclusion criteria. 75% of screened patients were eligible and 160 patients were included and 157 randomized.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall period (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:

Randomization 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 |

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 | Solution for infusion |
| Routes of administration | Infusion |

Dosage and administration details:

Dexamethasone 10mg/ml, added to a 100 ml. NaCl container in accordance with 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 | Intermediate comparator |
| 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 | Solution for infusion |
| Routes of administration | Concentrate for solution for infusion |

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 | Intermediate comparator |
|---------------------------------------|--------------|-------------------------|
| Started | 80 | 77 |
| Completed | 80 | 77 |

Baseline characteristics

Reporting groups

| | |
|--|-------------------------|
| Reporting group title | Intervention |
| Reporting group description: | |
| Intervention arm, High dose Dexamethasone 1mg/kg of patient's actual bodyweight. | |
| Reporting group title | Intermediate comparator |
| Reporting group description: | |
| Intermediate dose dexamethasone 0.3mg/kg of actual bodyweight | |

| Reporting group values | Intervention | Intermediate comparator | Total |
|--|--------------|-------------------------|-------|
| Number of subjects | 80 | 77 | 157 |
| 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 | 72 | 68 | |
| full range (min-max) | 46 to 87 | 43 to 89 | - |
| Gender categorical | | | |
| Gender, female | | | |
| Units: Subjects | | | |
| Female | 51 | 36 | 87 |
| Male | 29 | 41 | 70 |
| ASA | | | |
| ASA-score | | | |
| Units: Subjects | | | |
| ASA 1 | 5 | 11 | 16 |
| ASA 2 | 63 | 46 | 109 |
| ASA 3 | 12 | 20 | 32 |
| Body mass index | | | |
| BMI | | | |
| Units: Kg/M3 | | | |
| median | 30 | 28 | |
| inter-quartile range (Q1-Q3) | 27 to 34 | 25 to 32 | - |

End points

End points reporting groups

| | |
|--|-------------------------|
| Reporting group title | Intervention |
| Reporting group description: | |
| Intervention arm, High dose Dexamethasone 1mg/kg of patient's actual bodyweight. | |
| Reporting group title | Intermediate comparator |
| 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 | Intermediate comparator | | |
|--|-----------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 77 | | |
| Units: Number/percentage | | | | |
| Mild pain (<30 mm on VAS 0-100 mm) | 35 | 36 | | |
| Moderate to severe pain (>30 mm on VAS 0-100 mm) | 45 | 41 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Chi squared primary outcome |
| Comparison groups | Intervention v Intermediate comparator |
| Number of subjects included in analysis | 157 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.65 |
| Method | Chi-squared |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.07 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.4 |

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 | Intermediate comparator | | |
|---------------------------------------|-----------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 77 | | |
| Units: VAS score in mm | | | | |
| median (inter-quartile range (Q1-Q3)) | 34 (19 to 50) | 35 (17 to 57) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Mann whitney |
| Comparison groups | Intervention v Intermediate comparator |
| Number of subjects included in analysis | 157 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.88 |
| 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 | Intermediate comparator | | |
|-----------------------------|-----------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 77 | | |
| Units: number | | | | |
| >30 mm on 0-100 mm VAS | 26 | 20 | | |
| <30 mm on 0-100mm VAS | 54 | 57 | | |

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 | Intermediate comparator | | |
|---------------------------------------|-----------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 77 | | |
| Units: mg/L | | | | |
| median (inter-quartile range (Q1-Q3)) | 13 (6 to 25) | 16 (9 to 38) | | |

Statistical analyses

No statistical analyses for this end point

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 1mg/kg |
|-----------------------|---------------------|

Reporting group description:

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

| | |
|-----------------------|------------------------|
| Reporting group title | Intermediate 0.3 mg/kg |
|-----------------------|------------------------|

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 recorded, as accepted in the protocol by the local ethics committee and DKMA

| Serious adverse events | Intervention 1mg/kg | Intermediate 0.3 mg/kg | |
|---|---|------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 3 / 77 (3.90%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis postoperative | Additional description: Deep vein thrombosis postoperative, assessed to be due to lack of mobilization after discharge. | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 77 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | Additional description: Atrial fibrillation in a patient not formerly known to have atrial fibrillation | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 0 / 77 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | Additional description: 2. degree AV- block demanding insertion of a pacemaker. | | |

| | | | |
|---|---|----------------|--|
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 77 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Soft tissue infection | Additional description: Postoperative soft tissue infection in the area of surgery, treated by antibiotics, no revision needed. | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 2 / 77 (2.60%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| | Additional description: Postoperative wound infection including the arthroplasty and demanding revision surgery | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 77 (1.30%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| | | | |
|---|---------------------|------------------------|--|
| Non-serious adverse events | Intervention 1mg/kg | Intermediate 0.3 mg/kg | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 77 (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