DEX-2-TKA - DEXamethasone twice for pain treatment after Total Knee Arthroplasty. Detailed statistical analysis plan for a randomized, blinded, three-group multicentre clinical trial

Gasbjerg, Kasper Smidt; Hägi-Pedersen, Daniel; Lunn, Troels Haxholdt; Overgaard, Søren; Pedersen, Niels Anker; Bagger, Jens; Lindholm, Peter; Brorson, Stig; Schrøder, Henrik Morville; Thybo, Kasper Højgaard; Mathiesen, Ole; Jakobsen, Janus Christian

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MR KASPER SMIDT GASBJERG (Orcid ID : 0000-0003-1484-483X)
MR KASPER HØJGAARD THYBO (Orcid ID : 0000-0002-4727-3132)

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DEX-2-TKA - DEXamethasone twice for pain treatment after Total Knee Arthroplasty. Detailed statistical analysis plan for a randomized, blinded, three-group multicentre clinical trial

Author list:
Kasper Smidt Gasbjerg1, Daniel Hägi-Pedersen1,2, Troels Haxholdt Lunn3,4, Søren Overgaard5,6, Niels Anker Pedersen7, Jens Bagger8, Peter Lindholm10, Stig Brorson4,10, Henrik Morville Schröder6,11, Kasper Højgaard Thybo3, Ole Mathiesen4,12, Janus Christian Jakobsen2,13

1Department of Anaesthesiology, Næstved-Slagelse-Ringsted Hospitals, Næstved, Denmark
2Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark
3Department of Anaesthesiology, Bispebjerg and Frederiksberg University Hospital, Denmark
4Department of Clinical Medicine, Faculty of Health and Medical Sciences, Copenhagen University, Copenhagen, Denmark
5Orthopedic Research Unit, Department of Orthopaedic Surgery and Traumatology, Odense University Hospital, Odense, Denmark
6Department of Clinical Research, University of Southern Denmark, Odense, Denmark
7Department of Anaesthesia, Gildhøj Private Hospital, Brøndby, Denmark
8Department of Orthopaedics, Bispebjerg and Frederiksberg University Hospital, Denmark
9Department of Anaesthesiology and Intensive Care, Odense University Hospital, Odense, Denmark
10Department of Orthopaedic Surgery, Zealand University Hospital, Køge

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Corresponding author: Kasper Smidt Gasbjerg, MD, Department of Anaesthesiology, Næstved-Slagelse-Ringsted Hospital, Næstved, Denmark, Ringstedgade 41, 4700 Næstved; gasbjerg@gmail.com; +45 27 57 05 71

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Abstract

Background: Optimization of postoperative pain treatment is of upmost importance. Multimodal analgesia is the main postoperative pain treatment principle, but the evidence on optimal analgesic combinations is unclear. With the ‘DEXamethasone twice for pain treatment after TKA’ trial, we aim to investigate the role of one or two doses of glucocorticoid for postoperative pain treatment after total knee arthroplasty. To ensure transparency and minimization of bias, we present this article with a detailed statistical analysis plan, to be published before the last participant is enrolled.

Methods: ‘DEXamethasone twice for pain treatment after TKA’ (DEX-2-TKA) is a randomized, blinded, three-group multicentre clinical trial. Participants will be randomized to one of three intervention groups: single dose of intravenous dexamethasone 24 mg, two consecutive doses of intravenous 24 mg dexamethasone, or matching intravenous placebo. All three intervention groups will receive paracetamol, ibuprofen, and local infiltration analgesia. Participants, treatment providers, outcome assessors, data managers, statisticians, and conclusion drawers will be blinded to the allocated intervention. The primary outcome is total opioid consumption (intravenous morphine milligram equivalents) 0-48 hours postoperatively. Secondary outcomes are 1) visual analogue scale pain levels: a) during active 45 degrees flexion of the knee at 24 and 48 hours postoperatively, b) at rest at 24 and 48 hours postoperatively, and c) during 0-24 hours (highest score) and 24-48 hours postoperatively (highest score); and 2) the proportion of participants with one or more adverse events within 48 hours postoperatively.

Discussion: The DEX-2-TKA trial will provide high quality data regarding benefits and harms of adding one or two high-doses of dexamethasone to a multimodal analgesic regimen.

Trial registration: EudraCT: 2018-001099-39 (08/06-18); ClinicalTrials.gov: NCT03506789 (24/04-2019)
Background

Although widely used and recommended, recent reviews have demonstrated that most often, no solid evidence for a procedure-specific gold standard of multimodal analgesia exists. Evidence is also lacking regarding multimodal analgesia for total knee arthroplasty. Current evidence arises from trials with: a large degree of heterogeneity, high risks of bias, small sample sizes, short follow-up, and various use of basic multimodal analgesia, and choice of outcomes. Consequently, non-effective or harmful combinations of drugs might be widely used, which may result in insufficient pain treatment and/or increased risk of adverse events.

Glucocorticoids have anti-inflammatory properties and are used daily in the clinical setting as an anti-emetic and are also used to decrease fatigue in certain patients. Recent preliminary trials have indicated that higher doses of glucocorticoids may have analgesic properties, both for one and two consecutive doses, but further evidence from adequately powered trials with appropriate follow-up is needed. The ‘DEXamethasone twice for pain treatment after Total Knee Arthroplasty’ trial (DEX-2-TKA) investigates the effect of one or two doses of 24 mg intravenous dexamethasone for total knee arthroplasty in combination with a multimodal analgesic treatment regime of paracetamol, NSAID and local infiltration analgesia.

In adherence to the International Conference on Harmonization of Good Clinical Practice, the protocol for DEX-2-TKA has been published. In recognition of the influence of statistical decisions on trial conclusions, publication of a detailed statistical analyses plan (DSAP) is important to ensure reproducibility and transparency and to reduce the risk of selective outcome reporting bias and erroneous data-driven analyses.

A DSAP exceeds that of a trial protocol article, and according to the ICH E9 should “contain a more technical and detailed elaboration of the principal features of the analyses described in the protocol, and include detailed procedures for executing the statistical analyses of the primary and secondary variables and other data”.

The present article presents the DSAP for the DEX-2-TKA trial.
Methods/design

Trial overview

DEX-2-TKA is a randomized, blinded, three-group multicentre clinical trial (figure 1) investigating the beneficial and harmful effects of one or two doses of 24 mg intravenous dexamethasone (DXM) as part of a multimodal analgesic regimen after total knee arthroplasty (TKA). Participants are randomized to one of three groups in a 1:1:1 ratio receiving either: DXM + placebo, DXM + DXM, or matching placebo + placebo (figure 2). All three groups will in addition to the trial interventions receive a standard regimen of paracetamol, NSAID (ibuprofen), and local infiltration analgesia (LIA).

Participants, outcome assessors, administrators of the intervention, treatment providers (i.e. perioperative personnel and care providers), investigators, and statisticians will be blinded to both the intervention and the allocation sequence. Participants are only enrolled after informed consent is obtained. The trial is conducted at five centres (Næstved-Slagelse-Ringsted Hospitals; Bispebjerg and Frederiksberg University Hospitals; Odense University Hospital; Gildhøj Private Hospital; and Zealand University Hospital).

The trial is conducted in accordance with the Helsinki Declaration and registered at ClinicalTrials.org (NCT03506789) and EudraCT (2018-001099-39). Before enrolment, the trial was approved by the Regional Health Research Ethics Committee of Region Zealand (SJ-695), Danish Medicine Agency (EudraCT 2018-001099-39), and the Danish Data Protection Agency (REG-34-2018). As DEX-2-TKA progresses, status and milestones can be viewed on the website: http://appraz.dk/projects/dex-2-tka/index.html (figure 3).

Further details can be seen in the published protocol article. The presented DSAP is published while data collection is ongoing. The DSAP has been approved by the steering committee.

Sample size

The primary outcome of DEX-2-TKA is total opioid consumption measured in units (mg) of morphine equivalents 0-48 hours postoperatively. The three groups (A, B, C) will each be compared in three comparisons: ‘A’ vs. ‘B’; ‘A’ vs. ‘C’; and ‘B’ vs. ‘C’. To maintain an overall familywise error rate of 0.05, the risk of type I error is adjusted with the “Bonferroni method” to $p = 0.05/3 = 0.0167$. To maintain a power of 90% with an estimated standard deviation of 22.7 mg over 48 hours postoperative intravenous opioid consumption (unpublished data from 46 patients at Næstved-Slagelse Ringsted Hospitals, Næstved (mean opioid consumption 45.03 mg)) a total of 423 randomized participants (141 in each group) is needed to detect or discard a minimal important difference of 10 mg of intravenous morphine equivalents. The
chosen minimal clinically important difference of 10 mg morphine corresponds to a change of 22% and is within an often used minimal important difference range (20-30%) for opioid reduction.\textsuperscript{18,19} Sample size is calculated with PS Power and Sample Size Calculations (Version 3.0, January 2009, © William D. Dupont and Walton D. Plummer) (PS). A surplus of 15% is added, as we do not expect data for our primary outcome to be normally distributed and we plan to analyse data using non-parametric statistical methods.\textsuperscript{20} Thus, a total of 486 eligible participants will be included (162 participants in each group).

Stratification and design variables

The randomization has been stratified for investigatory site and all analyses will be adjusted only for site. We will consider supplementary hypotheses-generating analyses with adjustment for sex, age, and opioid consumption prior to the TKA procedure if we observe significant baseline differences between the groups.

Any supplementary analyses will be presented as supplementary material to the main article.

For pragmatic reasons, the three sites with the lowest number of participants included (Odense University Hospital; Gildhøj Private Hospital; and Zealand University Hospital) will be merged in the statistical analyses.
Outcomes

Primary outcome

Total opioid consumption measured in units of morphine equivalents 0-48 hours postoperatively. Opioids will be administered as 1) patient controlled analgesia (PCA) morphine (0-24 hours), 2) on demand oral morphine (24-48 hours), and 3) any additional escape opioid (converted to intravenous morphine equivalents) (0-48 hours)

Secondary outcomes

- Visual analogue scale (VAS)-pain scores
  - during active 45 degrees flexion of the knee at 24 and 48 hours postoperatively
  - at rest at 24 and 48 hours postoperatively
  - highest score during 0-24 hours and 24-48 hours postoperatively
- Proportion of participants with one or more adverse events in the period 0-48 hours postoperatively (any adverse event not defined as serious (see below))

Exploratory outcomes

- Proportion of participants with one or more serious adverse events (SAE), including death, within 90 days after surgery (SAE defined according to ICH-GCP-guidelines, except ‘prolongation of hospitalisation’)
- Total intravenous morphine consumption 0-24 hours
- Total oral morphine consumption 24-48 hours
- VAS-pain scores
  - with active 45 degrees flexion of the knee at 6 hours postoperatively
  - at rest at 6 hours postoperatively
  - average score during 0-24 hours and 24-48 hours
- Timed up and go (TUG) test at 24 and 48 hours, including maximum pain during the TUG test
- Opioid related adverse events (AE)
  - levels of nausea, sedation and dizziness at 6, 24 and 48 hours (verbal ranking scale: none, mild, moderate, severe)
  - number of vomiting episodes 0-24 hours and 24-48 hours
  - consumption of anti-emetics (total dose of ondansetron and droperidol (DHB) (mg)) 0-24 hours and 24-48 hours
- Quality of sleep assessed at 24 and 48 hours (verbal ranking scale: none, mild, moderate, severe)
- Level of fatigue at 24 and 48 hours (verbal ranking scale: none, mild, moderate, severe)
- Questionnaire (patient diary) on pain (in the morning, at bedtime and average for day on numeric ranking scale: 0-10), sleep (verbal ranking scale: none, mild, moderate, severe) and overall satisfaction (numeric ranking scale: 0-10) for postoperative day 3-7
- Proportion of participants with permanent use of opioids 90 days after surgery (active prescription for opioids)
- Ninety-days follow-up with EQ-5D-5L\textsuperscript{21}
- Ninety-days follow-up with Oxford-Knee-Score\textsuperscript{22}

A more in depth description of outcomes and their definition can be seen in the protocol article.\textsuperscript{15}

Measurement of outcome variables

During the intervention period (0-48 hours postoperatively), data are collected by clinical staff and local investigators at time points 6, 24 and 48 hours after surgery. 90 day follow-up data are obtained by telephone interview and/or mailing the participants questionnaires. The registration of SAEs is gathered from a combination of participant reporting, electronic patient journals, and the Danish National Patient Registry for SAE and death. A more in depth description of measurements and their definition is found in Appendix 1 of the protocol article.\textsuperscript{15}

Supplementary power calculations

Supplementary power calculations for secondary outcomes and SAE are based on data from the PANSAID trial\textsuperscript{18} (table 1 and 2).\textsuperscript{23} Power calculations were performed using PS. No power calculations for the remaining explorative outcomes have been performed.

Baseline characteristics

Participants’ baseline characteristics will be assessed after inclusion using data from the visit of which the TKA surgery was scheduled. Table 3 gives an overview of the baseline characteristics and perioperative data collected.

General analyses principles and populations

The primary conclusion from the DEX-2-TKA trial will be drawn upon the primary analysis of the primary outcome. All analysis will be performed on the “intention-to-treat population” consisting of all randomized participants who have undergone the planned TKA surgery. We will also perform a
supplementary analyses including a “per protocol population” with all randomized participants who have undergone planned TKA surgery, except those having one or more major protocol violations as defined below:

- Participants not receiving allocated trial treatment
- Participants withdrawing from the trial, allowing the use of registered data
- Participants undergoing surgery (besides the TKA) OR a procedure in the intervention period

Adherence to the trial intervention will be assessed by reporting the numbers of participants receiving zero, one, and two doses of the trial medication.
Basic principles of analysis

Results will be reported, when appropriate, as means and standard deviation, or as medians and inter-quartile values. Differences will be described with 98.34% (100 - 0.0167) confidence intervals (CI) (see ‘Sample size’).

Level of significance

Due to the three pairwise comparisons, p-values below 0.0167 will be considered statistically significant for the primary outcome (see ‘Sample size’). Results of all non-primary outcomes will only be considered hypothesis generating. Hence, for all non-primary outcomes, p-values below 0.05 will be considered statistically significant.

We will assess if the thresholds for statistical significance and clinical significance are crossed using the five-point procedure as suggested by Jakobsen and colleagues. The anticipated intervention effects used in the sample size estimation and the power estimations will be used as minimal clinically important differences (MCID) to assess the clinical significance of the trial results. We will use a Bayes factor threshold for significance of 0.1 based on the a priori anticipated intervention effect. Bayes factor results will be reported in the supplementary material.

Missing data

We will handle missing data according to the recommendation by Jakobsen and colleagues. In short, we will consider using multiple imputation if it is not valid to ignore missing data. If multiple imputation is used, then the primary result of the trial will be based on these data. To take account of the possibility that data may be ‘missing not at random’, we will use a best-worst and worst-best case scenario as sensitivity analyses, which will assess the potential impact of the missing data on the trial results. In the ‘best-worst case’ scenario it is assumed that all participants lost to follow-up in the experimental group have had a beneficial outcome; and all those with missing outcomes in the control group have had a harmful outcome. Conversely, in the ‘worst-best case’ scenario, it is assumed that all participants who were lost to follow-up in the experimental group have had a harmful outcome; and that all those lost to follow-up in the control group have had a beneficial outcome. When continuous outcomes are analysed, a ‘beneficial outcome’ will be defined as the group mean plus two SDs of the group mean, and a ‘harmful outcome’ will be defined as the group mean minus two SDs of the group mean for ‘best-worst case’ imputation.

Statistical analysis

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Statistical analysis of the primary outcome

The primary analysis will be performed as a pair-wise comparison (three analyses) between the three groups’ median consumption of morphine 0-48 hours postoperative adjusted for site by using the van Elteren test. We will use bootstrapping to present 98.34% CI for the median difference.

Statistical analyses of secondary and explorative outcomes

The following outcomes will be dichotomised:

- Nausea, sedation, dizziness and fatigue – (none versus mild/moderate/severe)
- Quality of sleep and satisfaction with the overall postoperative pain treatment (very good/fairly good versus fairly bad/very bad)
- Number of vomiting episodes (none versus any)

All dichotomous outcomes (SAE, AE, chronic opioid use) will be analysed using logistic regression adjusted for ‘site’ to obtain odds ratios.

The continuous outcomes of consumption of morphine 0-24 hours and 24-48 hours, consumption of ondansetron and DHB, will be analysed using van Elteren test whereas the different pain scores, TUG test, Oxford Knee Score and EQ5D5L will be analysed using linear regression adjusted for ‘site’.

Outline of figures and tables in the primary manuscript

The first figure will be a Consolidated Standards of Reporting of Randomised Trials (CONSORT) flow diagram. The first three tables will be as follows:

1. Baseline and perioperative characteristics of the intention to treat population
2. Primary outcomes (0-48 hours morphine consumption (morphine equivalents)) according to the three groups and pair-wise comparisons
3. Secondary and exploratory outcomes

Any supplementary material will be provided in the main article appendix.

Blinding of statisticians

Two independent blinded statisticians will prior to unmasking of the randomization code perform analyses according to this present DSAP. If any disagreements between the statisticians are encountered, the statisticians will seek consensus. Remaining disagreements will be settled in conference...
with first and senior authors of the primary manuscript and subsequently be agreed upon by the Steering Committee.

The analyses will be performed with the three intervention groups coded as ‘1’, ‘2’ and ‘3’. The Steering Committee will agree upon three abstracts where either group ‘1’, ‘2’ or ‘3’ is the placebo group. The abstracts will be published along with the main publication.

Assessments of underlying statistical assumptions

We will systematically assess underlying statistical assumptions for all statistical analyses. For all regression analyses we will test for major interactions between each covariate and the intervention variable. We will, in turn, include each possible first order interaction between included covariates and the intervention variable. For each combination, we will test if the interaction term is significant and assess the effect size. We will only consider that there is evidence of an interaction if the interaction is statistically significant after Bonferroni adjusted thresholds (0.05 divided by number of possible interactions) and if the interaction shows a clinically significant effect. If it is concluded that the interaction is significant, we will consider both presenting an analysis separately for each (e.g. for each site if there is significant interaction between the trial intervention and ‘site’) and an overall analysis including the interaction term in the model.

Assessments of underlying statistical assumptions for linear regression

We will visually inspect quantile-quantile plots of the residuals to assess if the residuals are normally distributed and use residuals plotted against covariates and fitted values to assess for homogeneity of variances. If the plots show deviations from the model assumptions, we will consider transforming the outcome e.g. using log transformation or square root and/or use robust standard errors.

Assessments of underlying statistical assumptions for dichotomous outcomes

We will assess if the deviance divided by the degrees of freedom is significantly larger than 1 to assess for relevant overdispersion, and in this case consider using a maximum likelihood estimate of the dispersion parameter. To avoid analytical problems with either zero events or problems with all participants dying at a given site, we have only included sites planning to randomise a sufficient number of participants. However, we cannot exclude the risk that some sites might have problems with recruitment. We will, by checking if the number of participants is larger than 10 (rule of thumb) per site, consider pooling the data from small sites if the number of participants is too low.
Discussion

The DEX-2-TKA trial will provide data from a large and low risk of bias trial regarding benefits and harms of adding one or two high-doses of DXM. Furthermore, the present DSAP will ensure reproducibility of our findings, and that these findings expresses a true conclusion for future recommendations in the field of multimodal analgesia. The full, anonymized data set will be made available 18 months after 90-day-follow-up of the last enrolled participant.

Our DSAP has several strengths. First, this DSAP presents decisions concerning methods for our primary and secondary outcome analyses, eliminating the possibility of data driven analyses. Second, the plan also offers the opportunity to reproduce our results and perform a transparent and clear analysis of our data in our primary article. Third, we use validated systematised methodologies. Fourth, we increase the quality of data handling and interpretation by using two concomitant and independent statisticians for our analyses. Last, we assess our outcomes at single time points and use relatively simple statistical methods that lead to trial results that are clinically interpretable.

The chosen MCID of 10 mg intravenous morphine, can be discussed and it is difficult to decide whether it is a clinically relevant reduction of postoperative opioid use. Our MCID corresponds to a reduction of 22% and concurs with other studies in the field, however, we do not know if a lower dose would be clinically relevant. Furthermore, we recognise that it is a limitation to the study that no power calculations for explorative outcomes has been performed underlining the importance to refrain from drawing any conclusions on the base of these results.

Trial status

Currently, more than 400 participants have been enrolled in the trial, and recruiting is expected to finish March 2020.
Acknowledgements

Funding

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Conflicts of interests

Ole Mathiesen is an associate editor at Acta Anaesthesiologica Scandinavica. Otherwise, no conflicts of interest.


Table 1 Power calculations of secondary outcomes – Pain

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Standard deviation from PANSAID</th>
<th>Minimally clinically important difference</th>
<th>Power for pair-wise comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS 6 hours rest</td>
<td>23.2</td>
<td>10 mm</td>
<td>0.93</td>
</tr>
<tr>
<td>VAS 6 hours mobilization</td>
<td>25.9</td>
<td>10 mm</td>
<td>0.86</td>
</tr>
<tr>
<td>VAS 24 hours rest</td>
<td>21.7</td>
<td>10 mm</td>
<td>0.96</td>
</tr>
<tr>
<td>VAS 24 hours mobilization</td>
<td>25.3</td>
<td>10 mm</td>
<td>0.86</td>
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</tbody>
</table>
Table 2 Power calculations of adverse and serious adverse events

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Probability for control participant</th>
<th>Probability for experimental participant</th>
<th>Minimally clinically important difference</th>
<th>Power for pair-wise comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants with one or more adverse events</td>
<td>0.20</td>
<td>0.14</td>
<td>30% decrease</td>
<td>0.17</td>
</tr>
<tr>
<td>Number of participants with one or more serious adverse events</td>
<td>0.15</td>
<td>0.105</td>
<td>30% decrease</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Table 3 Baseline and perioperative characteristics. PONV = Postoperative nausea and vomiting; LIA = Local infiltration analgesia

<table>
<thead>
<tr>
<th>Demographic characteristics:</th>
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<tbody>
<tr>
<td>Age (years)</td>
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</tr>
<tr>
<td>Sex (female/male)</td>
<td></td>
</tr>
<tr>
<td>American Society of Anaesthesiologist (ASA) physical status score</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (BMI) (kg/m²)</td>
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</tr>
<tr>
<td>Diabetes (no/yes)</td>
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</tr>
<tr>
<td>- Insulin treated (no/yes)</td>
<td></td>
</tr>
<tr>
<td>- Other antidiabetics (no/yes)</td>
<td></td>
</tr>
<tr>
<td>Prior (last month) use of analgesic medication</td>
<td></td>
</tr>
<tr>
<td>- Use of paracetamol: no use, daily use, or ‘as needed’</td>
<td></td>
</tr>
<tr>
<td>- Use of ibuprofen: no use, daily use, or ‘as needed’</td>
<td></td>
</tr>
<tr>
<td>- Use of opioids: no use, daily use, or ‘as needed’</td>
<td></td>
</tr>
<tr>
<td>- Type: Morphine, oxycodone or tramadol</td>
<td></td>
</tr>
<tr>
<td>- Amount (mg)</td>
<td></td>
</tr>
<tr>
<td>- Use of gabapentinoids: no use, daily use, or ‘as needed’</td>
<td></td>
</tr>
<tr>
<td>- Use of antidepressants: no use, daily use, or ‘as needed’</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical characteristics:</th>
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</thead>
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<tr>
<td>Duration of surgery (min):</td>
<td></td>
</tr>
<tr>
<td>Type of surgery: Uncemented, cemented, or hybrid total knee arthroplasty</td>
<td></td>
</tr>
<tr>
<td>Type of anaesthesia: General anaesthesia, spinal anaesthesia, or conversion of spinal anaesthesia to general</td>
<td></td>
</tr>
<tr>
<td>- If general anaesthesia</td>
<td></td>
</tr>
<tr>
<td>- Amount of sufentanil (μg) given 15 min before ‘end of surgery’</td>
<td></td>
</tr>
<tr>
<td>- Use of sevoflurane</td>
<td></td>
</tr>
<tr>
<td>- If spinal anaesthesia</td>
<td></td>
</tr>
<tr>
<td>- Amount of bupivacaine (mg) used</td>
<td></td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td></td>
</tr>
<tr>
<td>Administration off 4 mg ondansetron PONV-prophylaxis (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Administration off LIA (yes/no)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1 DEX-2-TKA Flowchart

Included when fulfilling all of the criteria below:
- Scheduled for unilateral, primary total knee arthroplasty
- Age ≥ 18 years
- American Society of Anesthesiologists (ASA) 1-3
- Body Mass Index ≥ 18 and ≤ 40
- For women in the fertile age, negative urine human chorionic gonadotropin (pregnancy test) and use of non-steroidal
  contraceptive
- Written informed consent

Assessed for eligibility

Yes

Enrollment

No

Randomisation

(n=486)

Allocated to:
24 mg Dexamethasone +
(n=152)

Allocated to:
24 mg Dexamethasone +
Placebo
(n=152)

Allocated to:
Placebo
(n=152)

Analysis

Primary analyses: Intent-to-Treat. Secondary analyses: Per protocol
- Primary outcome:
  - Total need for intravenous (equivalent) morphine for the first 48 h postoperatively
- Secondary outcomes
- Exploratory outcomes
- Sub studies

Excluded when fulfilling one or more of the criteria below:
- Patients who cannot cooperate with the trial
- Concomitant participation in another trial or involving medication
- Patients who cannot understand or speak Danish
- Patients with allergy to medication used in the trial
- Patients with daily use of high dose opioid (> oral morphine or oxycodeone 30 mg/day or tramadol 150 mg/day) or any use of other opioids including methadone and transdermal opioids
- Patients with at least occasional use of systemic glucocorticoids (within three months before randomisation)
- Contraindications against ibuprofen or paracetamol, including previous ulcer, known heart failure, liver failure, renal failure (eGFR < 60 ml/min/1.73 m²), or thrombocytopenia (< 100 x 10⁹/l). or against glucocorticoid treatment
- Dysregulated diabetes (investigator's judgement)
- Patients suffering from alcohol and/or drug abuse (investigator's judgement)
<table>
<thead>
<tr>
<th>Time point:</th>
<th>-2 months to -1 day</th>
<th>On the day of surgery</th>
<th>After induction of anaesthesia</th>
<th>Study period</th>
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<td></td>
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<tr>
<td>Informed consent</td>
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Figure 2 SPIRIT figure, DEX-2-TKA
Figure 3 DEX-2-TKA Logo