DEX-2-TKA - DEXamethasone twice for pain treatment after Total Knee Arthroplasty. A protocol for a randomized, blinded, three-group multicentre clinical trial

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

Published in:
Acta Anaesthesiologica Scandinavica

DOI:
10.1111/aas.13481

Publication date:
2020

Document version:
Accepted manuscript

Citation for published version (APA):

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use
This work is brought to you by the University of Southern Denmark. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk

Download date: 30. May. 2021
This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/AAS.13481

This article is protected by copyright. All rights reserved

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

Article type : Clinical investigation

Title page:
DEX-2-TKA - DEXamethasone twice for pain treatment after Total Knee Arthroplasty. A protocol for a randomized, blinded, three-group multicentre clinical trial

Author list:
Kasper Smidt Gasbjerg¹, Daniel Hägi-Pedersen¹,², Troels Haxholdt Lunn³,⁴, Janus Christian Jakobsen²,⁵, Søren Overgaard⁶,⁷, Niels Anker Pedersen⁸, Jens Bagger⁹, Peter Lindholm¹⁰, Stig Brorson⁴,¹¹, Henrik Morville Schröder⁷,¹², Kasper Højgaard Thybo¹³, Ole Mathiesen⁶,¹³

Affiliation:
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
⁵Department of Cardiology, Holbæk Hospital, Holbæk, Denmark
⁶Orthopedic Research Unit, Department of Orthopaedic Surgery and Traumatology, Odense University Hospital, Odense, Denmark
⁷Department of Clinical Research, University of Southern Denmark, Odense, Denmark
⁸Department of Anaesthesia, Gildhøj Private Hospital, Brøndby, Denmark
⁹Department of Orthopaedics, Bispebjerg and Frederiksberg University Hospital, Denmark
Abstract

Background: Multimodal analgesia is considered the leading principle for postoperative pain treatment, but no gold standard after total knee arthroplasty (TKA) exists.

Aim: To investigate the beneficial and harmful effects of one or two doses of 24 mg intravenous dexamethasone as part of a multimodal analgesic regimen (paracetamol, NSAID and perioperative local infiltration analgesia) after TKA. We hypothesise that addition of dexamethasone will reduce postoperative opioid consumption.

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 groups: placebo,
single dose of dexamethasone, or two consecutive doses of dexamethasone. Participants, treatment providers, and investigators will be blinded to the allocated intervention. The primary outcome is total opioid consumption (units of morphine equivalents) 0-48 h postoperatively. Inclusion criteria: unilateral, primary TKA; age ≥18 years; American Society of Anesthesiologists (ASA)-Score 1-3; Body Mass Index ≥18 and ≤40; for women – not pregnant; and written informed consent. Exclusion criteria: allergy or contraindications against trial medication; daily use of high dose opioid and/or use of methadone/transdermal opioids; daily use of systemic glucocorticoids; dysregulated diabetes; and patients suffering from alcohol and/or drug abuse. Four-hundred-and-eighty-six eligible participants are needed to detect or discard a difference of 10 mg morphine equivalents 0-48 h postoperatively maintaining a family-wise error rate of 0.05 and a power of 90% for the three possible pairwise comparisons.

Discussion: Recruiting is planned to commence September 2018 and expected to finish March 2020. Trial registration: EudraCT: 2018-001099-39 (08/06-18); ClinicalTrials.gov: NCT03506789 (24/04-2019)
Background

Effective postoperative pain management is crucial for the recovery of patients undergoing surgery.\(^1\) It facilitates early mobilisation, nutrition, and resumption of daily activities.\(^1\) Multimodal analgesia is generally considered the leading principle for postoperative pain treatment.\(^2\)

Total knee arthroplasty (TKA) is a frequent procedure. In 2015, approximately 700,000 TKAs were performed in the US alone.\(^3\) TKA is associated with severe postoperative pain\(^4\) which is a major concern among patients.\(^5\) Patients undergoing TKA are often elderly with concomitant comorbidities, and a significant number develop persistent postoperative pain\(^6,7\) which may lead to chronic opioid consumption.\(^8\) Consequently, alleviation of TKA-related pain is of utmost importance, but is a clinical challenge and often includes significant amounts of opioids with adverse effects.\(^4,9\) A multitude of different analgesics and analgesic methods have been investigated for TKA pain treatment, but currently the literature does not present a gold standard.\(^9\)

Glucocorticoids (GCCs) have been used for treatment of inflammatory diseases for more than 60 years\(^10\) and have several potential beneficial effects, as well as potential adverse effects, the latter especially when administered in higher doses and for longer term.\(^11\) However, in contrast to previous concerns, based on the available literature, perioperative administration of GCC does not seem to increase the incidence of infection or symptomatic hyperglycaemia.\(^12\) In a meta-analysis of 56 trials with 5607 patients undergoing non-cardiac surgery and receiving a wide dose range of GCC but with a varying follow-up period (7-30 days or not reported), the incidences of any infection, deep wound infection, symptomatic hyperglycaemia or other serious adverse events (SAE) were similar compared with the placebo group.\(^13\)

Recent trials, including a variety of surgical procedures, indicated postoperative opioid sparing and analgesic effects of dexamethasone (DXM), which is a GCC frequently used for anti-emetic treatment.\(^13–15\) In a systematic review including 24 randomized clinical trials (RCTs) and 2751 patients, DXM at doses up to 0.2 mg/kg, resulted in smaller but significant reductions of both postoperative opioid usage and pain scores for the first 24-hours, but with no further advantage of doses >0.2 mg/kg.\(^15\) Only a limited number of trials with higher doses of GCC was, however, included in that review. Moreover, a single high preoperative dose of methylprednisolone 125 mg (equivalent to 25 mg DXM) compared with placebo\(^11\) demonstrated significantly reduced opioid requirements, pain levels, C-reactive protein (CRP) levels, postoperative nausea and vomiting (PONV), and fatigue.\(^16\) This trial, however, only included 48 patients
and needs confirmation. Thus, it is presently unknown if patients will benefit from a higher perioperative
dose of GCC. Table 1 offers an overview of the most recent systematic reviews on the subject.

Thus, the present study is motivated by that, GCCs have indicated some analgesic effects in the surgical
setting but the effects are unclear based on current evidence. Furthermore, it is unknown if higher, or
repeated doses, will demonstrate an improved effect. Finally, long-term effects are insufficiently assessed.

Aim

The purpose of this RCT is to investigate the beneficial and harmful effects of one or two doses of 24 mg
intravenous (i.v.) dexamethasone as part of a multimodal analgesic regimen after TKA.
Methods/design

‘DEXamethasone twice for pain treatment after TKA’ (DEX-2-TKA) is a randomized, blinded, three-group multicentre clinical trial (figure 1)(figure 2). Participants will be randomized to one of three groups receiving either: placebo, a single dose of DXM, or two consecutive doses of DXM. All three groups will additionally receive a standard regimen of paracetamol, NSAID (ibuprofen), and local infiltration analgesia (LIA).

Hypothesis

Our primary hypotheses are that the addition of DXM to the standard regimen will reduce postoperative opioid consumption, and that two doses of DXM will further reduce postoperative opioid consumption.

Inclusion criteria

Patients meeting all the following criteria are eligible for inclusion in the trial:

- scheduled for unilateral, primary TKA
- age ≥18 years
- American Society of Anesthesiologists (ASA)-Score 1-3
- body Mass Index ≥18 and ≤40
- for women in the fertile age, negative urine human chorionic gonadotropin (hCG) test (pregnancy test) and use of anti-conception
- written informed consent

Exclusion criteria

Patients meeting one or more of the following criteria are not eligible for inclusion in this trial:

- patients who cannot cooperate with the trial
- concomitant participation in another trial 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 oxycodone 30 mg/day or tramadol 150 mg/day) or any use of other opioids including methadone and transdermal opioids
- patients with daily use of systemic GCC (within three months before the surgery)
contraindications against ibuprofen or paracetamol, including previous gastric ulcer, known heart failure, liver failure, renal failure (eGRF <60 ml/kg/1.73m²), or thrombocytopenia (<100 × 10⁹/l); or against GCC treatment.

- dysregulated diabetes (investigator’s judgement)
- patients suffering from alcohol and/or drug abuse (investigator’s judgement)

Randomization

Participants will be randomized in a 1:1:1 ratio. The randomization will be performed by Skanderborg Pharmacy (Region of Central Denmark) using randomization.com with varying (unknown) blocks of 3*6, 2*9 or 1*18. Allocation numbers in varying blocks of 18 in total, will be distributed to the sites via the clinical trial management database software EasyTrial.net. Each participant entering the trial will be given a unique allocation number identifying the trial drug.

Outcome measures

**Primary outcome**

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

**Secondary outcomes**

- visual analogue scale (VAS)-pain scores
  - during active 45 degrees flexion of the knee at 24 and 48 h postoperatively
  - at rest at 24 and 48 h postoperatively
  - highest score during 0-24 h and 24-48 h
- proportion of participants with one or more adverse event in the period 0-48 h postoperatively

**Exploratory outcomes**

- proportion of participants with one or more severe adverse event (SAE), including death, within 90 days after surgery (SAE defined according to ICH-GCP-guidelines, except ‘prolongation of hospitalisation’).
- total i.v. morphine consumption 0-24 h
- total oral morphine consumption 24-48 h
- VAS-pain scores
  - with active 45 degrees flexion of the knee at 6 h postoperatively

This article is protected by copyright. All rights reserved
o at rest at 6 h postoperatively
o average score during 0-24 h and 24-48 h
- timed up and go (TUG) test at 24 and 48 h including maximum pain during the TUG test
- opioid related adverse events (AE)
o level of nausea, sedation and dizziness at 6, 24 and 48 h
o number of vomiting episodes 0-24 and 24-48 h
o consumption of anti-emetics 0-24 h and 24-48 h
- quality of sleep assessed at 24 h and at 48 h
- level of fatigue at 24 h and 48 h
- questionnaire on pain, sleep and overall satisfaction for postoperative day (POD) 3-7
- proportion of participants with permanent use of opioids 90 days after surgery
- 90 days follow-up with EQ-5D-5L
- 90-days follow-up with Oxford-Knee-Score

Methods of measurements are as seen in the Appendix 1

**Trial interventions**

Trial period: from randomization to 90 days postoperatively.

Intervention period: from the participant receives the first intervention to 48 h postoperatively.

Treatments (three groups A-C)

- **Intervention A:** dexamethasone 24 mg i.v. given after induction of anaesthesia and repeated at 24 h postoperatively (±1 h)
- **Intervention B:** dexamethasone 24 mg i.v. given after induction of anaesthesia and placebo (isotonic saline) i.v. at 24 h postoperatively (±1 h)
- **Intervention C:** placebo (isotonic saline) i.v. given after induction of anaesthesia and repeated at 24 h postoperatively (±1 h)

**Concomitant medication**

Standard premedication: paracetamol (PCM) 1 g + ibuprofen (IBU) 400 mg orally 1 hour before surgery

Standard anaesthesia: spinal anaesthesia is preferred

- For spinal anaesthesia, bupivacaine 0.5% HEAVY 10 – 15 mg without opioids is used. If sedation is needed, propofol infusion is preferred.
• For general anaesthesia, propofol- and remifentanil infusions are preferred. Alternatively, sevoflurane-based anaesthesia is allowed. Fifteen minutes before end of surgery sufentanil i.v. 0.3 micrograms/kg is given.

All participants, regardless of method of anaesthesia, will receive ondansetron 4 mg intraoperatively as PONV prophylaxis.

Standard postoperative pain and nausea management

• PCM 1 g + IBU 400 mg orally four times daily
• Local infiltration analgesia (LIA) intraoperatively 150 ml ropivacaine injected by surgeon into rear and front capsule and intraarticular. No NSAIDs added in the mixture.
• PCA-morphine (0-24 h), bolus 2 mg, lockout time 10 min. Mixture: morphine 1 mg/ml
• Morphine 10 mg tablet (24-48 h) on-demand
• If there is need for morphine in addition to the PCA pump in the first 1 h after the anaesthesia has ceased, at the postanaesthesia care unit (PACU), additional bolus doses of 2 mg morphine i.v. may be given on participants’ request
• If participants experience moderate to severe nausea, ondansetron 1 mg may be given up to a maximum of 16 mg/day. If symptoms persist, droperidol (DHB) 0.625 mg i.v. may be used to a max of 1.25 mg/day

Other medications

Treatment of pain after the intervention period will follow local departments’ guidelines. Analgesic medications other than those stated above are not permitted from the participant receives the first intervention to 48 h postoperatively. This includes other opioids, chlorzoxazone, antidepressants, steroids, and gabapentinoids. Morphine, oxycodone, or tramadol in non-excluding doses as well as gabapentinoids and antidepressants are only permitted if the participant continues an already instituted treatment from before surgery. All non-analgesic medications are permitted at the discretion of the attending physician.

Blinding

Trial medication is masked by Skanderborg Pharmacy (Region of Central Denmark) and is packed and labelled by the pharmacy in accordance with the good manufacturing practice (GMP). DMX and placebo will be matching and will be indistinguishable. Participants, administrators of the intervention, treatment providers, outcome assessors, investigators, and conclusion drawers will be blinded to both the
intervention and the allocation sequence. Statistical analyses will be performed with the three intervention groups coded as ‘1’, ‘2’ and ‘3’ by two independent blinded statisticians. Three blinded conclusions will be drawn by the Steering Committee assuming that either ‘1’, ‘2’ or ‘3’ is the placebo group. Based on these three blinded conclusions, three abstracts will be written and published along with the main publication.

Skanderborg Pharmacy retains the non-blinded block randomized allocation sequence list, which will remain unrevealed until the data has been analysed and abstracts and conclusions covering the different interpretations of the trial results have been agreed upon by the Steering Committee.

Safety

AE, adverse reactions (AR), SAEs, serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs) will be recorded in the intervention period and reported to the relevant authorities according to guidelines from ICH-GCP and the Danish Medicines Agency.

Withdrawal of participants

Discontinuation of individual participants

If a SAE occurs in the intervention period, the investigator will consult the principal investigator/sponsor, to determine whether it is feasible for the participant to continue. If the participant is withdrawn, we will ask whether we may record data.

Blinding of the intervention can be broken if the treatment of the participant requires knowledge of the randomization code. This can be done by the investigator without restrictions. Breaking of the code can be done by accessing the sealed opaque envelope of the investigator and the date and reason must be recorded. The investigator will ensure the necessary procedures and expertise to handle any emergency situation that may arise during the trial.

Participant withdrawal

A participant who has not completed the trial is a participant who has received the first intervention and does not allow for continued data recording. If a participant does not complete the trial, an account will be given as to whether and how this participant and data is followed in the trial.

Statistics

Sample size estimation and power calculation
To maintain an overall familywise error rate of 0.05, the sample size estimation is based on pairwise comparisons of the primary outcome between three groups (three comparisons: ‘A’ vs. ‘B’, ‘A’ vs. ‘C’ and ‘B’ vs. ‘C’) which results in a Bonferroni adjusted risk of type I error of 0.0167. To detect or discard a minimal important difference of 10 mg morphine i.v. consumed in 48 hours with a power of 90%, and with an estimated standard deviation of 22.7 mg over 48 hours (unpublished data from 46 patients at Næstved Hospital), we need to randomize a total of 423 participants (141 in each group). We have chosen 10 mg morphine as our minimal clinically important difference (MCID), which corresponds to a change of 22% and is within an often cited MCID range (20-30%) for opioid reduction. Sample size is calculated with PS Power and Sample Size Calculations (Version 3.0, January 2009, © William D. Dupont and Walton D. Plummer). As we do not expect data for our primary outcome to be normally distributed, we will add a surplus of 15%, thus 162 participants will be included in each group, for a total of 486 eligible participants.

Statistical methods

The trial will be completed when 486 participants are included in the intention-to-treat population. The primary analysis of the primary outcome, morphine consumption within 48 h, will be a pairwise comparison of the consumption of morphine between the three groups stratified for site by van Elteren test. 98.34% confidence intervals for the difference in medians will be provided by boot-strapping.

Secondary analyses include per protocols analyses of all outcomes. The per protocol population will exclude participants with major protocol violations. The definitions of the intention-to-treat population, the per protocol population, and major protocol violations are presented in Appendix 2.

A detailed statistical analysis plan will be published prior to enrolment of the last participant.

Data collection

An electronic case report form (CRF) will be completed for each participant included in the trial. Only the investigators or their assistants will enter data in the CRF. The CRF is hosted and maintained by EasyTrial Aps (Aalborg, Denmark).

Data will be collected directly from the participants by trial investigators or educated clinical personnel and from the electronic participant’s chart, the civil registration system through Statistics Denmark, the Danish National Patient Registry and the Danish National Pharmaceutical Statistic Registry. All data will be handled according to the General Data Protection Regulation. Data will be stored in five years after finishing the trial. Afterwards all paper material will be destroyed, and electronic data will be completely anonymised.
Monitoring
The trial will be externally monitored by The University of Copenhagen’s and The University of Southern Denmark’s Good Clinical Practice (GCP) units according to the latest legislation.

Ethical consideration
The trial will be conducted in accordance with the principles of the Declaration of Helsinki in compliance with the protocol, approved by the competent authority and ethics committee, and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the regulatory authorities except where it may be necessary to eliminate an immediate hazard to the trial participants.

Data analysis and publication
Before revealing the randomization list, two dedicated trial statisticians will independently perform the data analyses according to the statistical analysis plan, and the Steering Committee will agree upon written abstracts covering all possible combinations. The final manuscript will contain the correct pre-made abstracts. The protocol follow the standard protocol items: recommendations for interventional trials and the manuscript will follow consolidated standards of reporting of randomized trials (CONSORT) Statement. Authorship will be granted following the guidelines from the International Committee of Medical Journal Editors. Funding sources will have no influences on the interpretation of data. The full, anonymized dataset will be published no longer than 18 months after completion of the trial. The trial is registered at clinicaltrials.gov with identifier: NCT03506789.

Substudies
- One-year follow-up with EQ5D5L + Oxford-Knee-Score and need for medical attention and/or intervention
- Analyses of high and low pain responders
- At selected sites, troponin levels at 24 and 48 h, and cardiovascular events
- At selected sites, establishment of a bio bank (blood samples) for further research of perioperative immune function and the related effect of DXM

Timeline
2018: Application for approval from the Danish Medicines Agency, the Ethics Committee and the Danish Data Registration Agency. Development of an eCRF and randomization website
2018–2020: Enrolment of participants
2020: Data analyses, writing and submission of the manuscript
Discussion

With the present trial, we expect to be able to determine if one or two high doses of DXM has a postoperative analgesic effect in TKA, as part of a multimodal analgesic regimen including paracetamol, ibuprofen and LIA.

Our trial has several strengths. Besides being a randomized, blinded and placebo-controlled trial with low risk of bias, we expect high external validity, as the trial is both multicentre and pragmatic (i.e. the broad in- and exclusion criteria) mimicking clinical reality as much as possible. Hence, we expect the findings from this trial to be generally applicable for TKA. Furthermore, the trial has rigorous follow-up with questionnaires on day 3 to 7, an interview on day 90 and data from the comprehensive Danish public health registries.

Limitations

We chose a MCID of 10 mg morphine consumption the first 48 hours postoperatively. This is, arguably, a relatively low difference for 48-hour use. However, the analgesic effect of DXM is investigated as part of a multimodal analgesic regimen as the fourth non-opioid analgesic. Firm evidence for analgesic effect of combining more than two non-opioid analgesics is virtually none existent, and we expect that more analgesics in combination would lead to less effect of each added analgesic. We therefore chose a relatively low MCID in order not to miss any opioid-reducing effect of DXM. Another limitation of the trial is, that the expected power to detect differences in AE and SAE between the three groups is relatively low, although detected SAE in the recent PANSAID trial found an overall incidence of SAE to be 14% within 90-days of total hip arthroplasty.

It is possible that the effect of DXM may demonstrate a protracted effect lasting after the 48 h intervention period, making the difference between one and two doses of DXM difficult to distinguish until after 48 h. We have tried to count for this by a supplemental patient diary on pain for postoperative day 3-7.

We expect the results from this trial to be of high quality and with low risk of bias regarding the role of one or two doses of dexamethasone in a multimodal analgesic regimen and be able to conclude whether or not DXM is recommended for patients undergoing TKA.

Trial status
Currently, more than 290 participants have been enrolled in the trial. We expect the enrolment period to end in March 2020 at the latest. The trial status can be seen at the trial website http://appraz.dk/projects/dex-2-tka/index.html.

References:


8. Franklin PD, Karbassi JA, Li W, Yang W, Ayers DC. Reduction in Narcotic Use After Primary...


33. Li X, Sun Z, Han C, He L, Wang B. A systematic review and meta-analysis of intravenous...
glucocorticoids for acute pain following total hip arthroplasty. Medicine (Baltimore) 2017; 96. doi: 10.1097/MD.00000000000006872
Table 1, Overview of the most recent systematic reviews of glucocorticoids for pain treatment in non-cardiac surgery:

<table>
<thead>
<tr>
<th>Ref</th>
<th>Drug and administration</th>
<th>n (active/placebo)</th>
<th>Surgical population</th>
<th>Pain comparison with placebo</th>
<th>Opioid consumption in control groups</th>
<th>Opioid consumption compared with placebo (95% CI)</th>
<th>Opioid related adverse effects</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Oliveira et al.</td>
<td>Single-dose perioperative intravenous dexamethasone in adult patients. Comparisons were stratified by dose into three groups: low-dose (≤ 0.10 mg/kg), intermediate-dose (0.11–0.20 mg/kg), and high-dose (≥ 0.21 mg/kg) dexamethasone.</td>
<td>2751 (24 trials)</td>
<td>Mixed minor-major surgery (not dental)</td>
<td>Overall significant reduction at rest and during movement, both at 4 h and 24 h post-operatively</td>
<td>No data</td>
<td>Opioid consumption was reduced to a similar extent with moderate-dose: SMD = −0.82 (−1.30; −0.42) and high-dose: −0.85 (−1.24; −0.46) dexamethasone, but not reduced with low-dose dexamethasone: −0.18 (−0.39;</td>
<td>Not reported</td>
<td>Glucocorticoids most often assessed in multimodal analgesia trials.</td>
</tr>
<tr>
<td>Waldran et al.\textsuperscript{28}</td>
<td>Single-dose perioperative intravenous dexamethasone</td>
<td>2997/2799 (45 trials)</td>
<td>Mixed minor-major surgery (not dental)</td>
<td>Overall significant reduction, both at 2 h and 24 h post-operatively</td>
<td>No data</td>
<td>Fourteen studies (2157 patients) recorded opioid use at 24 h after operation. Patients receiving dexamethasone used significantly less morphine equivalents in the first 24 h after surgery (MD = −2.33 (−0.26; −4.39) mg, ( P = 0.03 )). This represents a 10.3% reduction in opioid consumption compared</td>
<td>Not reported</td>
<td>Glucocorticoids most often assessed in multimodal analgesia trials.</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Dose and Methodology</td>
<td>Number of Studies and Patients</td>
<td>Type of Arthroplasty</td>
<td>Overall Reduction, Both at 6h, 12h and 24h Postoperatively</td>
<td>Data on Opioid Use</td>
<td>Risk of Nausea and Vomiting</td>
<td>Glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------</td>
<td>-------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------</td>
<td>-------------------</td>
<td>-----------------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>Shen et al.</td>
<td>Single-dose perioperative intravenous or intraarticular methylprednisolone 40-125 mg in adult patients.</td>
<td>128/121 (4 trials)</td>
<td>Total knee arthroplasty</td>
<td>Overall significant reduction</td>
<td>No data</td>
<td>Four studies (248 patients) recorded opioid use at 24 h after operation. (WMD = −3.651, 95% CI: −5.909 to −1.393, P = 0.002)</td>
<td>Glucocorticoids most often assessed in multimodal analgesia trials.</td>
<td></td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>Single-dose or two doses perioperative intravenous or periarticular dexamethasone 5-10 mg in adult patients.</td>
<td>291/285 (6 trials)</td>
<td>Total knee arthroplasty</td>
<td>Overall significant reduction, both at 12h and 48h postoperatively</td>
<td>No data</td>
<td>Six studies (576 patients) recorded opioid use at 24 h after operation. (WMD = −2.192, 95% CI: −4.484 to 0.099, P = 0.061)</td>
<td>Glucocorticoids most often assessed in multimodal analgesia trials.</td>
<td></td>
</tr>
<tr>
<td>Fan et al.</td>
<td>Single-dose or two doses perioperative intravenous dexamethasone 10-40 mg in adult patients.</td>
<td>110/107 (3 trials)</td>
<td>Total Hip arthroplasty</td>
<td>Overall significant reduction, both at 24h and 48h</td>
<td>No data</td>
<td>Three studies (217 patients) recorded opioid use at 24 h after operation. (SMD = −0.63, 95%)</td>
<td>Glucocorticoids most often assessed in multimodal analgesia trials.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>n (trials)</td>
<td>End Point</td>
<td>Data Reported</td>
<td>Results</td>
<td>Conclusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------------------------------</td>
<td>------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al.</td>
<td>Single-dose or two doses perioperative intravenous dexamethasone 5-40 mg, hydrocortisone 200 mg or methylprednisolone 125 mg in adult patients.</td>
<td>157 (5 trials)</td>
<td>Overall significant reduction, both at 6 h, 24 h, and 48 h but not at 72 h post-operatively</td>
<td>No data</td>
<td>Five studies (157 patients) recorded total opioid use postoperative (WMD = -9.36, 95% CI -12.33 to -6.38, P = .000)</td>
<td>Overall significant reduced risk of postoperative nausea and vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al.</td>
<td>Single-dose perioperative intravenous dexamethasone 8-40 mg, hydrocortisone 200 mg or methylprednisolone 125 mg in adult patients.</td>
<td>199 (4 trials)</td>
<td>Overall non-significant reduction, both at 24 h and 48 h post-operatively</td>
<td>No data</td>
<td>Four studies (199 patients) recorded total opioid use postoperative (WMD = -15.68, 95% CI -24.60 to -6.75, P = .001)</td>
<td>Overall significant reduced risk of postoperative nausea and vomiting</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cl: Confidence Interval; MD: Mean Difference; SMD: Standardized Mean Difference; WMD: Weighted Mean Difference
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 anti-conception
- Written informed consent

Excluded when fulfilling one or more of the criteria below:
- Patients who cannot cooperate with the trial
- Concomitant participation in another trial involving medication
- Patients who cannot understand or speak Spanish
- Patients with allergy to medication used in the trial
- Patients with daily use of high dose opioid (> oral morphine or oxycodone 30 mg/day or tramadol 120 mg/day) or any use of other opioids including methadone and transdermal opioids
- Patients with an daily use of systemic glucocorticoids (within three months before randomization)
- Contraindications against ibuprofen or paracetamol, including previous side, known heart failure, liver failure, renal failure (eGFR < 60 ml/min/1.73 m²), or thrombocytopenia (platelet < 100 x 10⁹/l), or against glucocorticoid treatment
- Dysregulated diabetes (investigator’s judgement)
- Patients suffering from alcohol and/or drug abuse (investigator’s judgement)

Assessed for eligibility

Yes

No

Enrollment

Randomization
(n=486)

Allocated to:
- 24 mg Dexamethasone + Placebo (n=162)
- Dexamethasone (n=162)
- Placebo (n=162)

Allocated to:
- Placebo + Placebo (n=162)

Analysis

Primary analyses: intention-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
Appendix 1, Methods of measurements

The total amount of morphine (mg) delivered in the period 0-48 h will be recorded. This includes PCA-morphine (i.v.), oral on demand morphine, morphine administered at the PACU and any other opioid administrated. Oral opioids will be converted to i.v.-equiv. according to table 1 (from supporting information “S2 Appendix” in Karlsen et. al). 9

The following data, except medicine usage, will be collected by asking the participants:
Participants’ pain is registered on a VAS of 100 mm or a numeric ranking scale (NRS) of 0-10: 0 = no pain; 100 or 10 = worst possible pain. NRS is used if the participant answers are obtained by telephone or questionnaire.

Pain at rest, and during 45 degrees active flexion of the knee is recorded at 6, 24 and 48 h postoperatively, and also during a timed up and go (TUG) test at 24 and 48 h (see Appendix 3). Furthermore, highest and average pain score for 0-24 and 24-48 h are recorded.

Nausea, sedation, and dizziness are recorded on a VRS scale (none, mild, moderate, severe) at 6, 24, and 48 h. Quality of sleep is ranked on a VRS scale (very bad, fairly bad, fairly good, very good) and level of fatigue on a VRS scale (none, mild, moderate, severe) at 24 and 48 h. The number of productive vomiting events (volume estimated over 10 ml) is recorded 0–24 and 24-48 h. Total use of ondansetron and droperidol (DHB) (mg) is recorded 0–24 h and 24-48 h. Participant-reported adverse effects are recorded 0-48 h.

If participants are discharged after 24 h, but before 48 h, a telephone interview will be conducted at 48 h in order to retrieve data as stated above. Instead of TUG, participants will report pain when supporting their own weight on the knee.

Participants are given a questionnaire (checkmarks) on pain, sleep, and satisfaction with the overall pain treatment for POD 3-7 (see Appendix 5). Pain is recorded in the morning and in the evening including an average score for the day with NRS. Sleep is scored on a VRS scale each morning.

The 90-day mortality rate will be retrieved from the Civil Registration System, “CPR-registret”, and SAEs are recorded from the Danish National Patient Registry, “Landspatientregisteret”. SAEs are defined as modified SAEs. A modified SAE is defined as SAE, according to the ICH-GCP guidelines excluding “prolongation of hospitalisation”, as we recognise that it will be impossible to adjudicate such events.
Permanent use of opioids 90 days after surgery will be retrieved from the Danish National Pharmaceutical Statistic Registry, “Lægemiddelstatistikregisteret”.

The 90-day follow-up will be performed by telephone and mail, and the participants will fill out questionnaires on quality of life and knee function (EQ5D5L and Oxford-Knee-Score, respectively (see Appendix 5)). Furthermore, participants will be asked about the need for medical attention, anti-biotics, intervention, and/or re-operation.
Appendix 2, Definition of populations and violations

**Intention-to-treat population**: All randomized participants who have undergone the planned total knee arthroplasty surgery

**Per protocol population**: All randomized participants who have undergone planned total knee arthroplasty surgery except participants having one or more protocol violations as defined below.

**Major protocol violations**:

- 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
Appendix 3, **Timed Up and Go (TUG) test**

**Purpose:** Assessment of participant mobility

Investigator instructions: The participant must wear firm footwear and can use walking aid of their need. The TUG starts with the participant placed in a chair and a clear identified line on the floor 3 meters in front of the chair.

Participant instructions: “When I say WALK you will do as follows”:

1. Stand up
2. Walk to the line 3 meters in front of you at your preferred pace
3. Turn 180 degrees at the line
4. Walk back to the chair at your preferred pace
5. Sit down again

Timing:

Starts at the command “walk”

 Stops when the participant sits in the chair again
Appendix 4, Trial organisation
DEX-2-TKA trial organisation

Steering Committee - Members
- Daniel Hjøg Pedersen, Head of Research Consultant, MD, PhD, Department of Anaesthesiology, Næstved Hospital
- Ole Mathiesen, Professor, MD, PhD, Head of Centre of Anaesthesiological Research, Department of Anaesthesiology, University Hospital Zealand, Køge
- Kasper Smidt Gadbjerg, MD, Department of Anaesthesiology, Næstved Hospital
- Jens Bagger, MD, Department of Orthopaedic Surgery, Bispebjerg Hospital
- Henrik Morville Schrøder, Head of Research Consultant, MD, Department of Orthopaedic Surgery, Næstved Hospital
- Søren Overgaard, MD, DMsc, Professor, Head of Research, Department of Orthopaedic Surgery and Traumatology, Odense University Hospital
- Troels Hanoldt Lunn, MD, PhD, DMsc, Associate Professor, Department of Anaesthesiology, Bispebjerg Hospital
- Peter Lindholm, MD, Department of Anaesthesiology and Intensive Care, Odense University Hospital
- Stig Bronson, Professor, MD, PhD, DMsc, Department of Orthopaedic Surgery, University Hospital Zealand, Køge
- Niels Anker Pedersen, MD, consultant, Department of Anaesthesiology, Private Hospital – Gildhøj

Local Principal Investigators
- Næstved-Søborg-Kristians Hospitals, Næstved
- Kasper Smidt Gadbjerg
- Bispebjerg Hospital
- Troels Hanoldt Lunn
- Odense University Hospital
- Søren Overgaard
- Zealand University Hospital
- Ole Mathiesen
- Private Hospital – Gildhøj
- Niels Anker Pedersen
Appendix 5, Questionnaires (in Danish): Questionnaire postoperative day 3-7, EQ5D5L, Oxford Knee Score

Questionnaire postoperative day 3-7