





BMJ Open Paracetamol, ibuprofen and dexamethasone for pain treatment after total hip arthroplasty: protocol for the randomised, placebo-controlled, parallel 4-group, blinded, multicentre RECIPE trial

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ABSTRACT

Introduction Multimodal analgesia with paracetamol, non-steroidal anti-inflammatory drug and glucocorticoid is recommended for hip arthroplasty, but with uncertain effects of the different combinations. We aim to investigate benefit and harm of different combinations of paracetamol, ibuprofen and dexamethasone following total hip arthroplasty.

Methods and analysis RECIPE is a randomised, placebo-controlled, parallel 4-group, blinded trial with 90-day and 1-year follow-up performed at nine Danish hospitals. Interventions are initiated preoperatively and continued for 24 hours postoperatively. Eligible participants undergoing total hip arthroplasty are randomised to: group A: oral paracetamol 1000 mg × 4+oral ibuprofen 400 mg × 4+intravenous placebo; group B: oral paracetamol 1000 mg × 4+intravenous dexamethasone 24 mg+oral placebo; group C: oral ibuprofen 400 mg × 4+intravenous dexamethasone 24 mg+oral placebo; group D: oral paracetamol 1000 mg × 4+oral ibuprofen 400 mg × 4+intravenous dexamethasone 24 mg.

Primary outcome is cumulative opioid consumption at 0–24 hours. Secondary outcomes are pain at rest, during mobilisation and during a 5 m walk and adverse events. Follow-up includes serious adverse events and patient reported outcome measures at 90 days and 1 year. A total of 1060 participants are needed to demonstrate a difference of 8 mg in 24-hour morphine consumption assuming an SD of 24.5 mg, a risk of type I errors of 0.0083 and a risk of type 2 errors of 0.2. Primary analysis will be a modified intention-to-treat analysis. With this trial we aim to verify recommendations for pain treatment after total hip arthroplasty, and investigate the role of dexamethasone as an analgesic adjuvant to paracetamol and ibuprofen.

Ethics and dissemination This trial is approved by the Region Zealand Committee on Health Research Ethics (SJ-799). Plans for dissemination include publication in peer-reviewed journals and presentation at scientific meetings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The trial is planned to be at low risk of bias.
- ⇒ Systematic investigation of the relative effects of combinations of paracetamol, ibuprofen and dexamethasone.
- ⇒ Long-term effects will be assessed on potential harms and patient reported functional outcomes.
- ⇒ Short intervention period.
- ⇒ The minimal important difference for morphine consumption is uncertain.

Trial registration number NCT04123873.

BACKGROUND

More than a million total hip arthroplasty (THA) procedures are performed annually worldwide, and numbers are increasing.^{1–3} Pain after THA is moderate to severe,⁴ causing concern among patients and delaying rehabilitation.^{5–6} No gold standard for the treatment of postoperative pain after THA has been established,⁷ but multimodal non-opioid analgesic regimens are generally recommended.^{8,9}

Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) have proven analgesic and morphine-sparing effects when used as monotherapy.^{10–14} Furthermore, the analgesic effect of their combination was recently investigated in the PANSALD trial¹⁵ that included 556 patients undergoing THA and showed significant reductions in a 24-hour morphine consumption from the combination of oral paracetamol 1000 mg × 4 and ibuprofen 400 mg × 4 compared with



Figure 1 RECIPE trial logo

each single drug. The combination also reduced pain both at rest and during mobilisation as compared with each individual drug.

Glucocorticoids reduce the surgical inflammatory response and are well-known antiemetics.^{16–19} The postoperative analgesic effects of adjunct treatment of perioperative glucocorticoids have been investigated in two large systematic reviews with meta-analyses.^{20–21} These reviews found minor but significant opioid-sparing and pain-reducing effects from perioperative dexamethasone in patients undergoing various surgical procedures. These reviews, however, mostly included trials investigating lower to moderate doses of glucocorticoids (<8–10 mg), did not evaluate risk of bias of the included trials, and, based on the AMSTAR 2 evaluation tool,²² suffered from an overall low level of confidence (unpublished evaluation). The reviews did not address the efficacy of glucocorticoids as adjunct treatment to other non-opioid analgesics.

The relative effects of different combinations of paracetamol, NSAID and glucocorticoids are sparsely investigated in the literature.¹⁰ In a recent, preliminary and unpublished literature search we identified only one trial investigating the adjunct effects of glucocorticoids combined with paracetamol and NSAID in 50 patients following THA.²³ The recently published guideline for procedure-specific postoperative pain management (PROSPECT) for THA recommends an intraoperative dose of 8–10 mg dexamethasone as a standard component in addition to paracetamol and NSAID.⁸ This recommendation is based on results from six randomised clinical trials (RCTs) and three meta-analyses with relatively low numbers of included patients. The included trials differed markedly in designs, size and number of interventional doses, outcome measures, and types and doses of concomitant analgesic medication, making firm recommendations difficult.

Consequently, there is an urgent need for a sufficiently powered, high quality randomised trial with both short and long-term follow-up systematically evaluating the relative benefits and harms of the different combinations of paracetamol, NSAID and glucocorticoid for treatment of postoperative pain after THA.

Aim

The aim of the RECIPE trial is to investigate the relative benefit and harm of the different combinations of paracetamol, NSAID (ibuprofen) and the analgesic adjuvant dexamethasone for treatment of postoperative pain after THA.

METHODS AND ANALYSIS

Trial design

RECIPE (figure 1) is a randomised, placebo-controlled, parallel 4-group, blinded, multicentre trial performed at nine Danish hospitals (figure 2). Participants will be randomised to one of four treatment groups in a 1:1:1:1 ratio using permuted block randomisation with blocks of varying size, and stratification according to site. Interventions will consist of either: (A) paracetamol+ibuprofen+placebo; (B) paracetamol+placebo+dexamethasone; (C) placebo+ibuprofen+dexamethasone; (D) paracetamol+ibuprofen+dexamethasone (figure 3). Allocation of participants will be adequately concealed, thus participants, investigators, outcome assessors, caregivers and statisticians will all be blinded to the allocation.

Hypotheses

The present trial has four intervention arms enabling six comparisons (A vs B, A vs C, A vs D, B vs C, B vs D and C vs D). We hypothesise that there will be a difference of 8 mg intravenous morphine between all pairwise comparisons in the first 24 hours after THA.

Inclusion criteria

Patients meeting the following criteria are eligible for inclusion:

- ▶ Elective, unilateral THA.
- ▶ Age ≥ 18.
- ▶ American Society of Anesthesiologists (ASA) Physical Status Classification System 1–3.
- ▶ Body mass index (BMI) > 18 and ≤ 40 kg/m²*
- ▶ Negative urine human chorionic gonadotropin pregnancy test and use of anti-conception for women in the fertile age.
- ▶ Written informed consent to participate in the trial after having fully understood the contents of the protocol and restrictions.

*Exclusions due to out-of-range BMI are expected to be very low, and the criterion is chosen to avoid extremes in pharmacokinetics.

Exclusion criteria

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

- ▶ Patients who cannot cooperate with the trial or incapable of communicating in Danish.
- ▶ Patients with concomitant participation in another trial involving analgesic medication.
- ▶ Patients with allergy to trial medication.

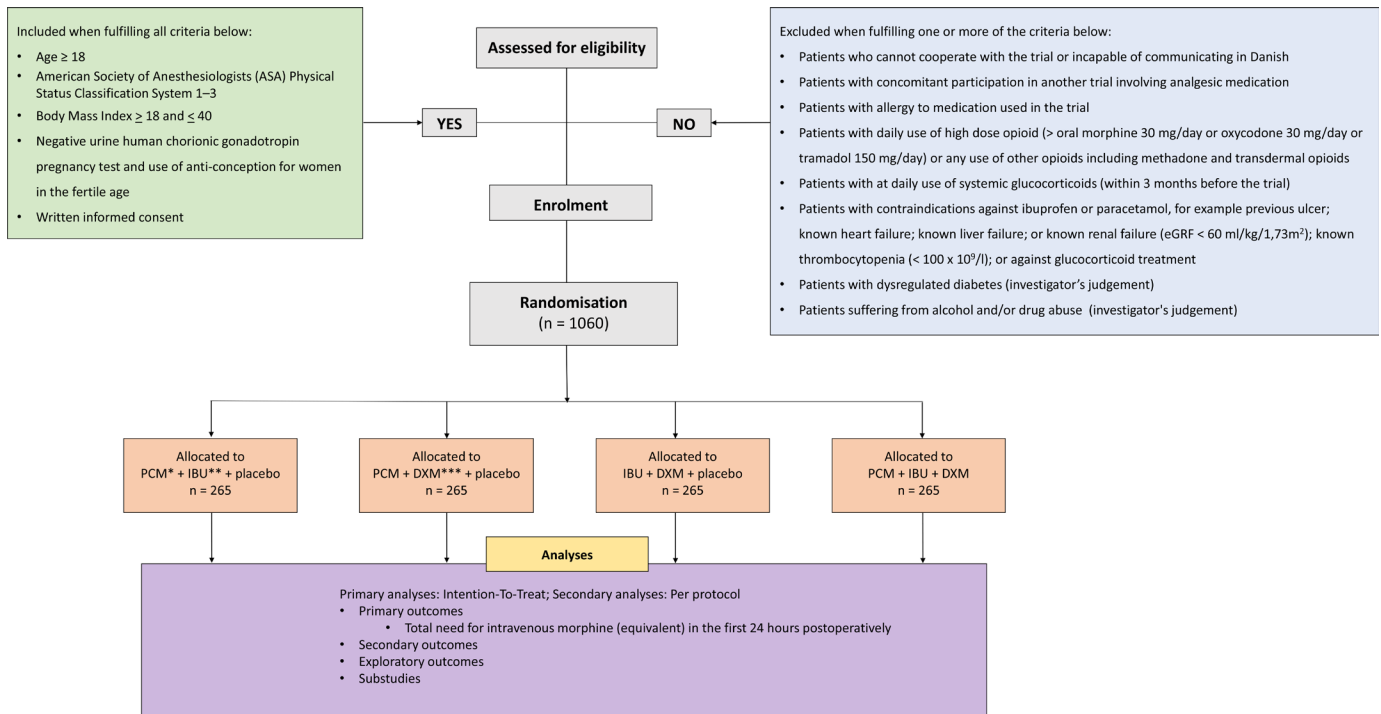


Figure 2 Trial flowchart. *PCM, paracetamol; **IBU, ibuprofen; ***DXM, dexamethasone; eGFR, estimated Glomerular Filtration Rate

- ▶ Patients with daily use of high-dose opioid (>oral morphine 30 mg/day or oxycodone 30 mg/day or tramadol 150 mg/day) or any use of other opioids including methadone and transdermal opioids.**
- ▶ Patients with at daily use of systemic glucocorticoids (within 3 months before surgery).
- ▶ Patients with contraindications against ibuprofen or paracetamol, including previous ulcer; known heart failure; known liver failure; known renal failure (eGFR <60 mL/kg/1.73 m²); known thrombocytopenia (<100 × 10⁹/L); or against glucocorticoid treatment.
- ▶ Patients with dysregulated diabetes (investigator's judgement).
- ▶ Patients suffering from alcohol and/or drug abuse (investigator's judgement).

**Patients regularly using high-dose opioids are likely to develop some tolerance. By including patients with a low/moderate opioid use, the study population will be representative of the majority of the true surgical population, and by excluding patients with high opioid use, the risk of a tolerance-related increase in opioid consumption is minimised. Additionally, in the DEX-2-TKA trial,²⁴ applying the exact same limits of daily opioid consumption, only 2.1% were excluded due to this criterion.

Allocation sequence generation

Patients will be randomised into four groups at a 1:1:1:1 ratio with block sizes of either 4, 8 or 16 distributed in overall blocks of 16. Thus, the size of an overall block will be unknown to participants and all trial personnel.

Two external pharmacies working together provide the randomisation and the blinded medication. The

randomisation sequence for trial medication is performed using designated software from the website www.randomization.com by Skanderborg Pharmacy (producing and blinding dexamethasone/placebo). The randomisation list is then passed to the Pharmacy of the Capital Denmark Region (producing and blinding paracetamol/placebo and ibuprofen/placebo) who completes packing of the trial medication. The pharmacies dispense blinded trial medication to the coordinating investigator who is unaware of both allocation sequence and contents within each drug-container marked with a unique allocation number. Trial medication is then distributed to the participating hospitals in blocks of 16 (ie, 16, 32, 48), consequently stratifying randomisation according to site.

The allocation numbers are exported to the clinical trial management software EasyTrial.net (EasyTrial ApS, Aalborg, Denmark). Every participant is then assigned a unique baseline and allocation number, enabling identification of allocated trial medication for data analysis.

Allocation concealment

Skanderborg Pharmacy provides sponsor with enclosed assignments in sequentially numbered, opaque, sealed envelopes to enable code break in case of emergency or immediate hazard to a trial participant. Furthermore, the pharmacies retain the non-blinded randomised allocation sequence list. Envelopes and allocation sequence list will not be revealed for investigators until data has been completely analysed and abstracts and conclusions covering the different possibilities for interpreting the trial results have been compiled and agreed on by the steering committee.

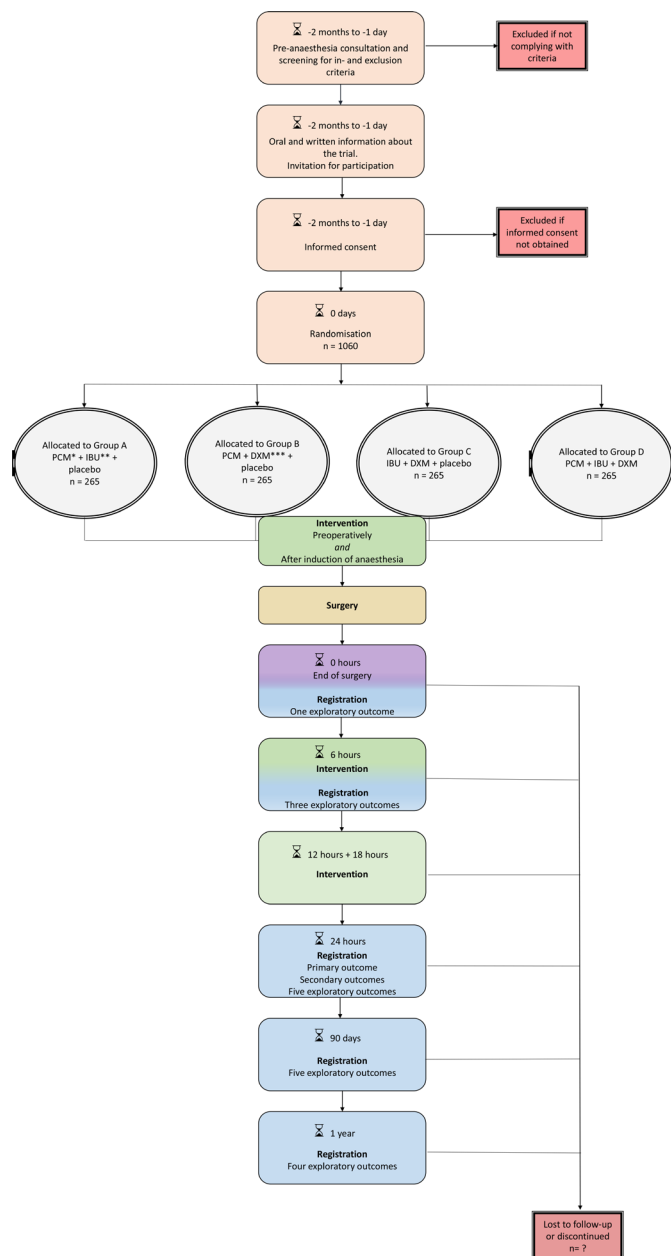


Figure 3 Flowchart for trial participants. *PCM, paracetamol; **IBU, ibuprofen; ***DXM, dexamethasone; eGFR, .

Blinding

Trial medication is packed and labelled according to the allocation numbers by the pharmacies in accordance with the Good Manufacturing Practice. All tablets, paracetamol, ibuprofen and placebo, are encapsulated with an identical and opaque capsule. Intravenous dexamethasone and the matching placebo are colourless, have identical viscosity and are supplied in identical vials. Thus, blinding of all participating parties is secured, including participants, investigators, caregivers, outcome assessors, conclusion drawers and statisticians.

Outcomes

Primary outcome

- ▶ Cumulative opioid consumption in units of intravenous morphine equivalents (according to opioid conversion table 1 in online supplemental appendix 1) in the first 24 postoperative hours. This includes opioids administered as (1) patient-controlled analgesia (PCA); (2) supplemental opioid administered at the postanesthesia care unit the first hour after end of surgery (general anaesthesia) or the first hour after ceasing of spinal anaesthesia and (3) any supplemental opioid given at the ward.

Secondary outcomes

- ▶ Visual Analogue Scale (VAS) pain scores (0–100 mm).
 - At rest at 24 hours postoperatively.
 - During active 30° flexion of the hip at 24 hours postoperatively.
 - During 5 m walk at 24 hours postoperatively (maximum pain).
- ▶ Proportion of participants with one or more adverse events in the intervention period (0–24 hours) according to ICH-Good Clinical Practice (GCP) guidelines.²⁵

Exploratory outcomes

- ▶ Proportion of participants with one or more serious adverse events, including death, within 90 days after surgery, according to ICH-GCP guidelines²⁵ (except for ‘prolongation of hospitalisation’ that has been modified to ‘hospitalisation ≥4 days’).
- ▶ Proportion of participants with one or more serious adverse events, including death, within 1 year after surgery, according to ICH-GCP guidelines²⁵ (except for ‘prolongation of hospitalisation’ that has been modified to ‘hospitalisation ≥4 days’).
- ▶ Oxford Hip Score at 90 days.
- ▶ EQ-5D-5L score at 90 days.
- ▶ Opioid use at 90 days.
- ▶ Days alive and outside hospital within 90 days after surgery.
- ▶ VAS scores
 - At rest at 6 hours postoperatively.
 - During active 30° flexion of the hip at 6 hours postoperatively.
- ▶ Prevalence of nausea at 6 and 24 hours postoperatively
- ▶ Number of vomiting episodes (0–24 hours) measured at 24 hours postoperatively.
- ▶ Consumption of ondansetron and dehydrobenzperidol (0–24 hours) measured at 24 hours postoperatively.
- ▶ Incidence of dizziness during 5 m walk at 24 hours postoperatively.
- ▶ Intraoperative blood loss during the surgical procedure.
- ▶ Quality of sleep (VAS) at 24 hours postoperatively.
- ▶ Oxford Hip Score at 1 year.
- ▶ EQ-5D-5L score at 1 year.
- ▶ Opioid use at 90 days.

Primary and secondary outcomes and explorative outcomes from 0 to 90 days will be presented in the main article. Explorative outcomes on 1-year follow-up data will

be published in a separate article. The 1-year follow-up includes serious adverse events, Oxford Hip Score, EQ-5D-5L-score and opioid use.

Methods of measurements are apparent in online supplemental appendix 1.

Rational for choice of primary outcome

Measuring pain for individual patients is challenging due to the high level of subjectivity and requires many observations if a full 24-hour intervention effect is to be evaluated. Accordingly, we have chosen the cumulative patient-decided 24-hour morphine consumption as the primary outcome, as we consider this outcome to mirror the total amount of pain experienced by patients during 24 hours. Furthermore, reduction in need of postoperative opioid usage is essential for reduction of opioid-related adverse events, and most likely also for reduction of prolonged postoperative opioid use.

By investigating cumulative opioid consumption in the 24 hours immediately after surgery, effects of the interventions will be illustrated when pain intensity is expected to be highest, and the vast majority of participants will remain in hospital, enabling intravenous opioid administration.

Trial interventions

The trial period starts at randomisation and ends at 90 days postoperatively. The intervention period lasts from immediately before surgery, and the first 24 hours after surgery (T0=end of surgery). The follow-up period ends at 1 year after surgery.

After being screened for eligibility and providing the informed written consent, participants will be randomised into one of four groups receiving the experimental interventions as listed below:

Interventions

Group A

Paracetamol 1000 mg+ibuprofen 400 mg administered orally 1 hour before surgery and given with 6-hour intervals to a total of four times the first postoperative day.

Intravenous placebo (isotonic saline matching dexamethasone) administered after induction of anaesthesia.

Group B

Paracetamol 1000 mg+placebo (matching ibuprofen) orally 1 hour before surgery and given with 6-hour intervals to a total of four times the first postoperative day.

Intravenous dexamethasone 24 mg after induction of anaesthesia.

Group C

Placebo (matching paracetamol) + ibuprofen 400 mg orally 1 hour before surgery and given with 6-hour intervals to a total of four times the first postoperative day.

Intravenous dexamethasone 24 mg after induction of anaesthesia.

Group D

Paracetamol 1000 mg+ibuprofen 400 mg orally 1 hour before surgery and given with 6-hour intervals to a total of 4 times the first postoperative day.

Intravenous dexamethasone 24 mg after induction of anaesthesia.

Concomitant medication

For anaesthesia, spinal anaesthesia is preferred.

- ▶ Spinal anaesthesia is performed using bupivacaine 0.5% PLAIN 10–15 mg with no addition of opioids. If sedation is needed, propofol infusion is preferred.
- ▶ General anaesthesia is performed using propofol and remifentanyl infusions. Sevoflurane-based anaesthesia is allowed if needed according to the attending anaesthetist. Fifteen minutes before end of surgery sufentanil 0.3 µg/kg is administered.

Standard postoperative pain management

PCA-pump:

- ▶ Mixture: Morphine 1/mL; bolus: 2.0 mg; lockout time: 10 min; no background infusion.

If there is need for morphine additional to the PCA-pump in the first hour after general anaesthesia or in the first hour after ceasing of spinal anaesthesia (Bromage score 1–2), additional bolus doses of 2 mg intravenous morphine can be administered on participant request.

Standard postoperative nausea management

All patients will receive intravenous ondansetron 4 mg perioperatively. On the first indication of moderate nausea this can be supplemented by doses of 1–2 mg intravenous ondansetron to a total of 16 mg during the first 24 hours after surgery. Dehydrobenzperidole will be accessible as rescue-medication in intravenous doses of 0.625 mg to a max of 1.25 mg/day if needed.

Any other analgesic or antiemetic medications than those stated above are not permitted during the intervention period. This includes other opioids; chlorzoxazone; antidepressants; gabapentinoids; steroids; regional anaesthesia; and local infiltration analgesia. Morphine, oxycodone or tramadol in non-excluding doses as well as antidepressants and gabapentinoids are only permitted if the participant continues a treatment already instituted prior to surgery. If such treatment is implemented, the participant receives usual medication beside the trial medication. Any such already instituted opioid treatment before trial participation will not be included in the primary outcome of escape opioid consumption. All non-analgesic and non-antiemetic medications are permitted at the discretion of the attending physician. Treatment for pain and nausea after the intervention period will follow local treatment guidelines.

Rational for doses and combinations

Paracetamol is the most common basic analgesic and is generally recommended after surgery.^{26 27} It is administered in doses of 4000 mg/day to secure continuous and safe 24-hour coverage and as widely advised.²⁸ Ibuprofen was already the NSAID of choice at the participating sites and is a generally used NSAID.¹⁰ A number of other

NSAIDs, including selective COX-2 inhibitors or non-selective (in particular diclofenac), are not considered due to the increased cardiovascular risks.²⁹ To secure maximal 24-hour pain coverage, ibuprofen is administered in doses of 400 mg × 4, which is also in accordance with previous trials,^{15 23 24 30} within recommended doses for anti-inflammatory use³¹ and below the maximal dose of 2400 mg/day.^{32 33}

Dexamethasone is a long-acting agent with a biological half-life of 36–54 hours and low mineralocorticoid effect.³⁴ It is comprehensively tested in trials on prevention and treatment of nausea, it is commonly used in the OR and the majority of studies investigating postoperative analgesic effects of glucocorticoid have been performed with dexamethasone.³⁵ Regarding postoperative pain treatment, the effect of dexamethasone is debateable, and, consequently, the optimal dose is unknown. The aforementioned review by De Oliveira *et al*²⁰ showed that doses >0.2 mg/kg was non-superior to doses of 0.11–0.2 mg/kg. Our dose is in concordance with recent trials investigating methylprednisolone 125 mg^{16 36–38} and two doses of dexamethasone 24 mg²⁴ on pain following lower joint arthroplasties. There is no consensus regarding the optimal timing of the administration of dexamethasone. However, the preoperative administration is reported to decrease variability in analgesic effectiveness,²⁰ and by postponing the administration to after induction of anaesthesia, participants are spared of the potential perineal pain or pruritus reported in some trials^{39 40} and the risk of unintentional unblinding is eliminated.

Safety

The incidence of adverse effects from paracetamol administration is low when used in therapeutic and short-term doses. NSAIDs have well-known adverse effects, but these often depend on dosage and duration of treatment, and, in general, adverse effects after short-term use of NSAIDs in the perioperative setting is insufficiently investigated.⁴¹

Adverse effects associated with glucocorticoid use are dependent on dosage and duration of treatment. In general, a single dose of perioperative glucocorticoid is well tolerated. Toner *et al* found no safety concerns with the administration of perioperative dexamethasone,³⁵ and Corcoran *et al* recently reported, that dexamethasone was non-inferior to placebo with respect to the incidence of surgical-site infection in non-cardiac surgery.⁴²

In this trial, all adverse events, adverse reactions, serious adverse events, serious adverse reactions, and suspected unexpected serious adverse reactions are 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 by investigator

In occurrence of a serious adverse event/serious adverse reaction in the intervention period, the investigator will consult the principal investigator or sponsor to determine whether it is feasible for the participant to continue.

If the participant is withdrawn, trial medication is discontinued but data collection is continued if permitted by the concerning participant. Unblinding of the intervention will only be done if required to prevent an impending hazard, or if optimal treatment of the participant is otherwise reliant on knowledge of the assigned allocation. This can be done by the investigator without restrictions. Breaking of the randomisation code can be done by accessing one of the designated sealed opaque envelopes. The investigator will ensure the requisite qualifications and expertise to handle any emergency that may arise during the trial.

Participant withdrawal

If a participant has undergone randomisation and surgery but subsequently decides to withdraw the consent to receive interventional drugs, this can be done at any time without restrictions. Under such circumstances interventions will be discontinued immediately. We will always enquire permission as to whether we are allowed to use data already recorded, and permission to continue recording of data in the intervention period after discontinuation of trial medication. Hence, data collection continues after any withdrawal to interventions unless explicitly disallowed by the participant in question.

Patient and public involvement

Patients were not directly involved in the design of the trial, nor was the research question influenced by public input. A panel of three participants have been asked to comment on the written participant information.

Public representatives (ie, elected regional politicians) have ethically approved the study, and patient-reported outcome measures are recorded through the EQ-5D-5L and Oxford Hip Score questionnaires, validated to detect important individual patient experiences regarding health and daily function.^{43 44}

Recruitment

As progress of the trial has experienced delays due to the COVID-19 pandemic, we have invited more hospitals for participation. Furthermore, more patients undergoing hip arthroplasty are discharged for home on the day of surgery. As a result, we also plan to include a minor number of participants, who will be discharged from hospital on the day of surgery.

Statistics

Sample size estimation and power calculation

Due to the four intervention groups in this trial, six comparisons, comparing each individual treatment group, will be of interest (A vs B, A vs C, A vs D, B vs C, B vs D and C vs D). To preserve a maximum family wise error rate of less than 0.05, the threshold for type I error rate is Bonferroni-adjusted for the pairwise comparisons to $0.05/6=0.0083$.

The PANSOID trial¹⁵ reported a mean of 28 mg (SD 24.5 mg) morphine over 24 hours for the combination of paracetamol 1000 mg+ibuprofen 400 mg. Furthermore,

a recent systematic review with network meta-analysis found a mean morphine consumption of 22.8mg/24 hours when combining paracetamol and ibuprofen in major surgical procedures.⁴⁵

A persisting challenge in clinical research on postoperative pain is the fact that the quantification of a minimal important difference (MID) in morphine consumption is uncertain. A newly published systematic review of 570 RCTs on differences in MID after total knee and hip arthroplasties reported an investigator perceived median MID of 10mg intravenous morphine equivalent as absolute reduction.⁴⁶ The MID chosen for this trial is prompted by previous results and has been thoroughly debated: with a reduction of 8mg morphine/24 hours the percentage-reduction (28%–35%) in morphine consumption will be similar to those previously reported in trials investigating multimodal postoperative analgesia.^{15 45 47} In addition, this trial also investigates the addition of a third adjunct non-opioid analgesic component. Hence, it is expected that the reduction in morphine consumption will be less than with addition of a second non-opioid analgesic. In the PANSALD trial investigating two non-opioids, an MID of 10mg was chosen, and thus, the 8mg MID of the RECIPE trial corresponds to a 20% smaller MID, as would be expected for an addition of a third non-opioid analgesic.

Consequently, to detect or to discard a mean MID of 8mg in 24-hour morphine-consumption, with an SD of 24.5mg and a power of 0.80, enrolment of 920 (230 in each group) participants is needed. To adjust for a presumed non-normal distribution of data a surplus of 15% is added.⁴⁸ Hence 265 participants will be included in each group, adding up to a total of 1060 included participants. In two previous large trials with a similar setup and design, missing data on the primary outcome was limited to less than 5%.^{15 24} Furthermore, if missing data will unexpectedly occur, we plan to use multiple imputation to minimise the power loss due to missing data. Consequently, we have not adjusted our sample size per missing data. Sample size is calculated with PS Power and Sample Size Calculations (V.3.0, January 2009, William D. Dupont and Walton D. Plummer) and double controlled with Stata.⁴⁹

Statistical methods

The trial will be completed when 1060 participants are included in the trial. Statistical analyses will be performed by two independent statisticians using two different statistical programmes (Stata and R).^{49 50}

The primary analysis will be a modified intention-to-treat analysis for all outcomes. We will perform pairwise comparisons between the consumption of morphine and levels of pain between the four groups (six analyses) adjusted for site using the van Elteren test.⁵¹ To quantify the median difference between the participants in the four groups, we will report the Hodges-Lehmann median difference⁵² and associated 99.99% CIs. Adverse events will be analysed using logistic regression adjusting for

‘site’. Relative risks will be estimated using the ‘nlcom’ Stata command.

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

Adherence to interventions, surgical procedures and missing data will be reported in the final manuscript.

Missing data and sensitivity analysis to account for possible data ‘missing not at random’ will be handled according to recommendations by Jakobsen *et al.*⁵³

For non-primary outcomes regarding pain levels, we chose a MID of 10mm VAS score (0–100mm), based on results presented by Myles *et al* and Olsen *et al.*^{54 55}

A detailed statistical analysis plan will be published prior to enrolment of the final 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 from (1) the participants directly by trial investigators or educated clinical personnel; (2) the electronic participant’s chart; (3) the civil registration system through Statistics Denmark; (4) the Danish National Patient Registry and (5) the Danish National Pharmaceutical Statistic Registry. All data will be handled according to the General Data Protection Regulation. Data will be stored for 5 years after finishing the trial. Afterwards all paper material will be destroyed, and electronic data will be completely anonymised.

The coordinating investigator will perform continuous auditing of data quality through the database and audit and aid at participating sites as needed.

MONITORING

The trial will be externally monitored by The University of Copenhagen’s and The University of Southern Denmark’s GCP units according to the latest legislation. The GCP units ensure that trial conduct meets the demands set by the ethics committee, the Danish Medicines Agency and the Data Protection Agency. Furthermore, they verify blinded outcome data to ensure quality and secure absence of fraud. None of the individual monitors will have access to unblinded data before all participants are included, data-analyses are performed, and the allocation sequence is revealed.

ETHICS AND DISSEMINATION

The trial will be conducted in accordance with the principles of the Declaration of Helsinki in compliance with the protocol and according to GCP standards,²⁵ and it

is approved by the Danish Medicines Agency and the Regional Committee on Health Research Ethics (Region Zealand, Denmark. Reference SJ-799). 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.

Before revealing the randomisation list, two dedicated trial statisticians will independently perform the data analyses according to the statistical analysis plan, and the steering committee will agree on prewritten abstracts describing possible outcomes of the trial. The final manuscript will contain the correct premade abstract. The protocol follows the Standard Protocol Items: Recommendations for Interventional Trials⁵⁶ and the manuscript will follow Consolidated Standards of Reporting Trials.⁵⁷ Authorship will be granted according to the guidelines from the International Committee of Medical Journal Editors.⁵⁸ Funding sources will have no influences on the interpretation of data.

Data will be shared according to the Medical Research Council Clinical Trials Unit guidelines⁵⁹: there must be a strong scientific argument or other legitimate rationale for the data to be used for the requested purpose; no data can be released if this would compromise an ongoing trial, and investigators who have invested time and effort into developing a trial should have a period of exclusivity, before key trial data are made available to other researchers; the resources required to process requests should not be underestimated, particularly those needed to prepare data for release, thus adequate resources must be available and the scientific aims of the study must justify the use of such resources; all data exchange must comply with Information Governance and Data Protection Policies in all countries relevant to the disclosure.

Access to data for other researchers can be requested from omat@regionsjaelland.dk in the first instance.

We commit to disseminate our findings from this trial by publishing results in peer-reviewed medical journals and through presentations at scientific/academic meetings and conferences. All participants are asked to declare whether or not they want to be informed of trial results. If interested, they will be informed when the results are published.

SUBSTUDIES

- ▶ Substudy of subgroup differences. Interventional effects on the primary outcome for subgroups differing at baseline. Predictors include: age, sex, type of anaesthesia, ASA score, preoperative opioid consumption and preoperative pain levels.
- ▶ One-year follow-up including serious adverse events; EQ-5D-5L and Oxford Hip Score responses; opioid consumption and data on medical treatment and hospital admissions from the Danish National Patient Registry.

TIMELINE

2019: Application for approval from the Danish Medicines Agency, the Ethics Committee and the Danish Data Registration Agency. Development of electronic CRFs and randomisation website.

2020–2022: Enrolment of participants

Spring 2023: Data analyses, writing and submission of the manuscript.

DISCUSSION

To our knowledge, this is the first large-scale RCT to systematically investigate the analgesic effects of combinations of paracetamol, ibuprofen and dexamethasone after THA. Due to the trial design (ie, randomised, placebo-controlled, blinded) risk of bias is limited to a minimum. The multicentre setup, pragmatic approach, and up-to-date external monitoring claim reasonable expectations of high external validity, and with thorough 90-day and 1-year follow-up, potential harms and patient-reported outcomes are profoundly accounted for. Consequently, we expect results from this trial to be generally applicable for patients undergoing THA.

Limitations

The intervention period is relatively short, and paracetamol and ibuprofen are rarely used only for 24 hours after the end of surgery. However, the primary focus is on efficacy of non-opioid analgesic and adjuvant analgesic combinations, which is expected to be demonstrated within 24 hours. Furthermore, with an enhanced recovery set-up used at most trial sites, the majority of patients are discharged the day after surgery, limiting the period of intravenous opioid usage.

The chosen MID in 24-hour morphine consumption is somewhat arbitrary as the true patient-relevant value is unknown. The true minimal important reduction of opioid consumption is indeed debateable, but it is pivotal to predefine this value before conducting a large, randomised trial. First, for practical reasons, it is necessary to calculate sample size and, second, it is crucial to prevent data-driven analyses and preserve transparency. Despite the uncertainty of the true MID, any opioid reduction is probably desirable as it mirrors a reduction in pain. Especially, since the level of acute postoperative pain is associated with persistent postoperative pain, and surgery may act as a pipeline for chronic opioid use.⁶⁰ In addition, it is previously demonstrated that the association of opioid consumption and related adverse effects is linear.⁶¹

Perspective

The need for reducing opioid consumption is obvious, and improvement in postoperative pain management is a key component. Treating pain after THA is a matter of animated discussion, and as we anticipate the results of this trial to be of high quality and with low risk of bias, we expect data from the trial to permit a recommendation

for an improved basic non-opioid analgesic regimen for patients undergoing THA. Furthermore, results will provide important information to the differences in effects for use of four multimodal analgesic combinations after a major surgical procedure

Statement regarding data monitoring and safety committee

A Data Monitoring and Safety Committee will not be established. RECIPE has a short-term intervention period of 24 hours, and the interventional drugs are well-known and already used for postoperative pain. Furthermore, exclusion criteria will prevent participation of subjects at known increased risk of adverse effects of the trial medication. Consequently, we expect that the correlation between interventions and serious adverse events will be low. Likewise, the primary outcome measure is morphine consumption, which acts as a surrogate marker for pain. The true clinical important reduction in morphine consumption is, however, not known, thus making interim decisions on termination difficult if based solely on opioid consumption.

TRIAL STATUS

As for now, more than 800 participants have been enrolled. Although the COVID-19 pandemic has proven an unpredictable factor already postponing trial activity, we expect enrolment to be completed in 2022. Trial status and other information can be retrieved at the website www.recipetrials.com.

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