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RESEARCH ARTICLE

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Spinal anaesthesia versus general anaesthesia (SAGA) on recovery after hip and knee arthroplasty: A study protocol for three randomized, single-blinded, multi-centre, clinical trials

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Abstract

Mobilisation difficulties, due to muscle weakness, and urinary retention are common reasons for prolonged admission following hip and knee arthroplasty procedures. Whether spinal anaesthesia is detrimental to early mobilisation is controversial. Previous studies have reported differences in post-operative recovery between spinal anaesthesia and general anaesthesia; however, up-to-date comparisons in fast-track setups are needed. Our randomized, single-blinded, multi-centre, clinical trials aim to compare the post-operative recovery after total hip (THA), total knee (TKA), and unicompartmental knee arthroplasties (UKA) respectively when using either spinal anaesthesia (SA) or general anaesthesia (GA) in a fast-track setup. Included patients (74 THA, 74 TKA, and 74 UKA patients) are randomized (1:1) to receive either SA (2 mL 0.5% Bupivacaine) or GA (Induction: Propofol 1.0–2.0 mg/kg iv with Remifentanil 3–5 mcg/kg iv. Infusion: Propofol 3–5 mg/kg/h and Remifentanil 0.5 mcg/kg/min iv). Patients undergo standard primary unilateral hip and knee arthroplasty procedures in an optimized fast-track setup with intraoperative local infiltrative analgesia in TKA and UKA, post-operative multimodal opioid sparing analgesia, immediate mobilisation with full weightbearing, no drains and in-hospital only thromboprophylaxis. Data will be collected on the day of surgery and until patients are discharged. The primary outcome is the ability to be safely mobilised during a 5-m walking test within 6 h of surgery. Secondary outcomes include fulfilment of discharge criteria, post-operative pain, dizziness, and nausea as well as patient reported recovery and opioid related side effects. Data will also be gathered on all hospital contacts within 30-days of surgery. This study will offer insights into advantages and disadvantages of anaesthetic methods used in fast-track arthroplasty surgery.

KEYWORDS
anaesthesia, arthroplasty, enhanced recovery, fast-track, hip, knee

1 | INTRODUCTION

Primary hip and knee arthroplasties are among the most frequently performed surgical procedures, and their use is expected to increase due to an increasingly elderly population.[1,2] Major improvements in perioperative setup around hip and knee arthroplasties have been made during the last decade, leading to reductions in post-operative morbidity and length of stay.[3,4] Shorter hospital stays have been associated with higher patient satisfaction and can be achieved without increasing the risk of readmissions and complications.[5,6] As a continuation of the reduced length of stay, day case surgery in hip and knee arthroplasty is now a topic of interest and is used increasingly.[7] A previous study from the centres participating in this study reported that 54% of total hip (THA) and total knee arthroplasty (TKA) patients are potential day case candidates, while discharge on the day of surgery was achieved in 13% of THA, 15% of TKA and 22% of unicompartmental knee arthroplasty (UKA) patients.[8,9]

Studies investigating reasons for failed discharge following hip and knee arthroplasty identified lack of safe mobilisation and urinary retention to be frequent issues resulting in prolonged admission.[8–10] Reduced motor function and urinary retention are known effects of spinal anaesthesia, with studies reporting that 50% of patients have not regained normal motor function within 3 h of knee surgery.[11] The average time until normal sensory, motor, and urinary function was close to 7 h. However, mobilisation within a few hours post-operatively remains a corner stone in reducing the risk of thromboembolic events, length of stay[3] and urinary retention leading to catheterization, which remains a post-operative issue.

Clinical studies comparing SA to the most prevalent alternative, general anaesthesia (GA), have found that GA resulted in slightly shorter hospital stay, earlier mobilisation, and fewer cases of urinary retention.[12,13] Immediate post-operative pain favoured SA, while pain after 24 h favoured GA.[14] Reviews of the current literature generally find that some differences in outcomes may be present between SA and GA in THA, TKA, or UKA surgery.[15,16] Despite the results of previous investigations there appears not to be a consensus among hip and knee arthroplasty surgeons.[17] The choice of anaesthetic method in patients without any direct contraindications is still dependent on centre or surgeon preference.[18] Furthermore, many clinical studies, providing the basis for these decisions, were published before the start of this century.[16] This indicates a need for up-to-date randomized trials comparing anaesthetic methods in hip and knee arthroplasty.

Our aim is therefore to compare the post-operative recovery after THA, TKA and UKA when using either SA or GA in a fast-track setup.

2 | PATIENTS AND METHODS

2.1 | Study management

This study will be conducted in accordance with Good Clinical Practice guidelines and overseen by Good Clinical Practice monitors. Data management will be handled in confidence and in line with current legislation, including the General Data Protection Regulation (GDPR—Regulation (EU) 2016/679) and the Danish Data Protection Act. The conduction of this study was approved by the Danish Medicines Agency and the Medical Research Ethics Committees via the Clinical Trials Information System (CTIS), EUCT number: 2022-501221-21-00 (approved November 17th, 2022). Data approval for this study was acquired from the Knowledge Centre on Data Protection Compliance, Capital Region of Denmark (ref. nr. = P-2022-348 and P-2022-240). The trial is registered at euclinicaltrial.eu (2022-501221-21-00) and at clinicaltrials.gov (NCT05706844). Any changes to the protocol will be submitted to the above institutions for review, and online protocol databases will be updated accordingly.

2.2 | Study design

This study comprises three randomized, single-blinded, multi-centre, clinical trials, each within THA, TKA and UKA surgery, respectively. Participants will be included from the Department of Orthopaedic Surgery at Copenhagen University Hospital Hvidovre, Capital Region of Denmark and from the Department of Orthopaedic Surgery at Lillebaelt Hospital—Vejle, Region of Southern Denmark.

2.3 | Study population

Patients scheduled for primary THA, TKA or UKA will be pre-screened for eligibility according to the inclusion and exclusion criteria (Table 1)

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Clinical and radiological hip or knee osteoarthritis meeting the indications for primary THA, TKA or UKA • ≥18 years of age • Able to speak and understand Danish • Able to give informed consent and must be cognitively intact	• Lives in an institution • Uses walking aids, such as walker or a wheelchair. • Terminal illness • Has contraindications for either SA or GA • Has objections to receiving either GA or SA • Requires anxiolytics as premedication prior to anaesthesia • Traumatic aetiology as a basis for surgical indication • Altered pain perception and/or neurologic affection due to diabetes or other disorders • Daily pre-operative use of opioids >30 mg of morphine milligram equivalents (MME) • Standard primary arthroplasty procedure is evaluated not to be suitable • Women considered fertile but without sufficient birth control

Abbreviations: GA, general anaesthesia; SA, spinal anaesthesia; THA, total hip arthroplasty; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty.

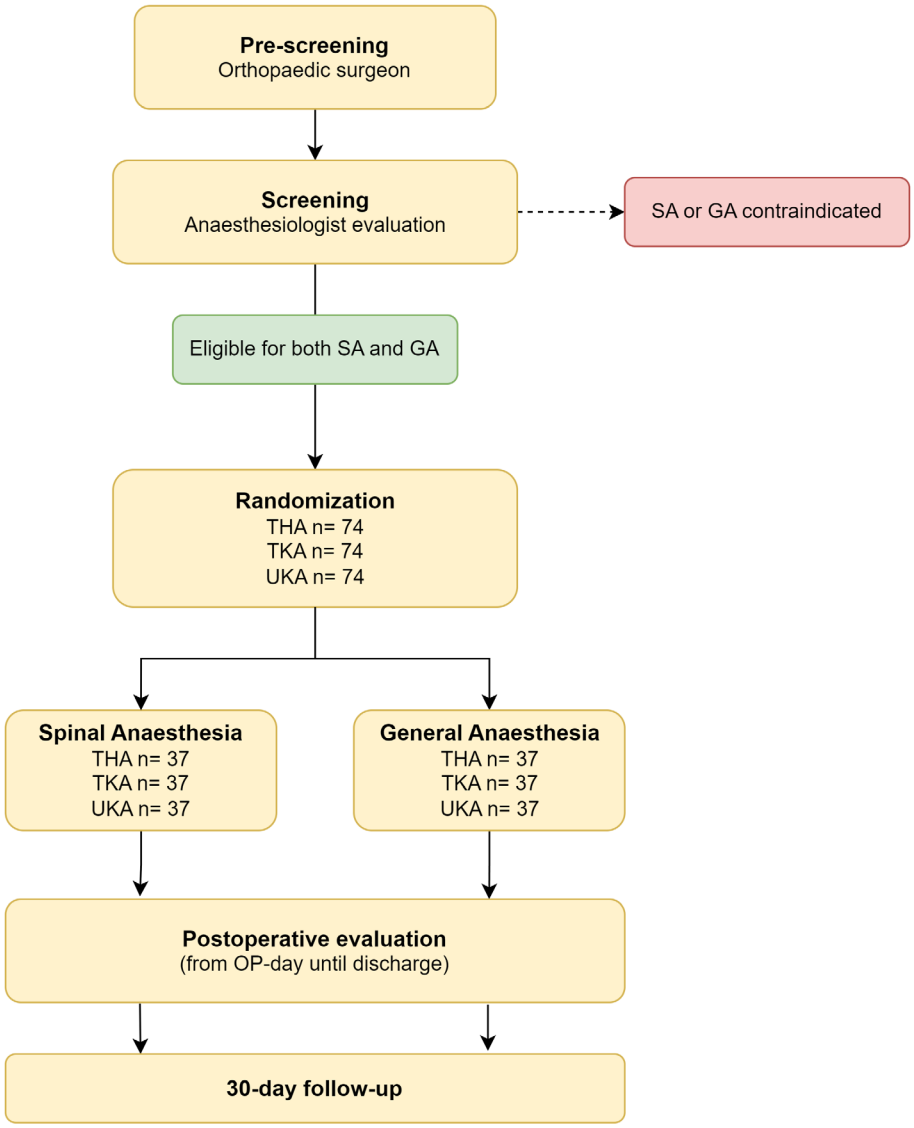

FIGURE 1 Study flow-chart: Shows the inclusion and data gathering processes of the SAGA trials. GA, general anaesthesia; OP-day, day of the operation; SA, spinal anaesthesia; THA, total hip arthroplasty; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty.

prior to surgery. Eligible patients will be contacted and given oral and written information on the study by an investigator or his/her delegates. Written consent is obtained from interested patients. Following written consent, patients are screened for any contraindications for GA or SA at the standard preoperative anaesthesiologist evaluation. If none are present, patients are considered fully included in the study (Figure 1). All patients are informed that participation is entirely voluntary and that they can withdraw their consent without any impact on current or future treatment. Patients are also informed that, if considered necessary, patients can be withdrawn by investigators.

3 | STANDARD CARE

3.1 | Surgery

Patients will be operated with either unilateral THA, TKA or UKA as treatment for primary hip and knee osteoarthritis. All participants will be operated as number 1 or 2 on the surgery schedule. THA is performed using a posterolateral approach. TKA is performed using a medial parapatellar incision. UKA is performed using a minimally invasive technique with microplasty instruments. Local infiltrative analgesia (LIA, 200 mL 0.2% Ropivacaine) is administered at the end of all knee arthroplasty procedures. No drains are used. All procedures are performed by experienced arthroplasty surgeons in accordance with recommendation from the producers of the implanted prosthesis. Region nerve blocks are not used routinely. Any use of regional nerve blocks will be registered.

3.2 | Intraoperative care

Celecoxib 400 mg and Paracetamol 1 g is administered as premedication on the morning of the surgery. SA and GA are administered per the standard regime of the departments, as described under 'Intervention'. Patients receiving SA can, based on preference, receive sedation

with Propofol 1.2–3.6 mg/kg/h iv. After induction of either SA or GA, patients will receive dexamethasone 0.3 mg/kg (1 mg/kg in case of PCS > 20) and tranexamic acid 1 g intravenously. At the end of surgery GA patients will receive Sufentanil 0.2 mcg/kg iv and Ondansetron 4 mg iv.

3.3 | Post-operative care

After surgery, patients are observed at the post-operative care unit (PACU). Patients are transferred from PACU to a dedicated fast-track arthroplasty unit, when fulfilling discharge criteria from the Danish Society of Anaesthesiology and Intensive Care Medicine (DASAIM).[19] Post-operative opioid sparing analgesia consisting of Paracetamol 1 g × 4 and Celecoxib 200 mg × 2 daily is administered for 7 days. Patients are considered ready for discharge when fulfilling functional discharge criteria:

- Steady gate with crutches (can use stairs if required by participants home environment)
- No dizziness impeding mobilisation
- Nausea is minimal and efficiently treated
- Vital parameters are within standard acceptable levels
- Pain level is acceptable to the patient (at rest numeric rating scale (NRS) < 3, and when walking 5-m NRS < 5)
- Post-operative bleeding should be consistent with expected blood loos and not require repeated dressing change
- Spontaneous urination prior to discharge (or urine volume on bladder scan < 800 mL (Copenhagen University Hospital Hvidovre)/ <600 mL (Lillebaelt Hospital – Vejle)).

4 | INTERVENTION

Patients are randomized to receive either SA or GA using the standard regime at the centres. SA consists of Bupivacaine 0.5% 2 mL (10 mg) injected at levels L2–L4. In THA plain Bupivacaine is used, while hyperbaric (heavy) Bupivacaine is used in TKA and UKA. GA consists of Propofol 1.0–2.0 mg/kg iv with Remifentanil 3–5 mcg/kg iv for induction, followed by iv infusion of Propofol 3–5 mg/kg/h and Remifentanil 0.5 mcg/kg/min.

5 | RANDOMIZATION AND BLINDING

Participants are randomized using allocation sequences from https://www.sealedenvelope.com/ with random block sizes of 4 or 6 stratified for centre. Allocation is concealed in closed opaque envelopes labelled with a unique randomization-ID. The allocation sequences and envelopes were prepared by unblinded personnel at the Department of Orthopaedic Surgery, Copenhagen University Hospital Hvidovre. The unblinded personnel are not otherwise involved in the conduction of this study.

Clinical personnel performing surgical or anaesthesiologic procedures are not blinded to the allocation of the participants for safety reasons. The participants are also not blinding to their treatment allocation. However, all assessors of post-operative outcomes remain blinded, and participants are continuously instructed not to reveal their allocation the research personnel. Any unblinding of participants will be registered.

6 | STUDY SETUP AND DATA

Patients are informed and written consent is collected at the pre-operative physical examination. Patients are fully included when anaesthesiologists have determined that here are no contraindications for either SA or GA. When included, pre-operative demographic data is gathered. Demographic data includes age, sex, height, weight, Pain Catasthropizing Scale (PCS) score, and American Society of Anaesthesiologists (ASA) score. In addition, data on pre-operative medication use and comorbidity is gathered.

At least 72 h prior to surgery, patients are randomized, and the treatment allocation is revealed to the anaesthetic and surgical staff for them to prepare for surgery. Any deviations from allocation and use of sedation in SA cases are registered intraoperatively. Following surgery all patients are transferred to the PACU unit, and the time PACU, and the dose of opioids used is registered. Any use of regional nerve block will be registered. From PACU patients are transferred to a dedicated fast-track arthroplasty unit. Between 4 and 6 h of surgery a 5-m walking test, will be conducted and evaluated by a physiotherapist. Patients will be given until 6 h post-operatively to complete the walking test, so that any failed walking tests prior to the 6-h mark, will be redone at 6 h post-operatively. Data on pain, nausea, dizziness, fulfilment of discharge criteria and vital parameters will be recorded at 4 and 6 h after the end of surgery, and at 10.00 and 18.00 from post-operative day 1 until discharge. At 4 h post-operatively and at 10.00 on the following post-operative days patients will respond to the Quality of Recovery-15 questionnaire (QoR-15), the Opioid-Related Symptom Distress Scale (ORSDS) and the 3-min Diagnostic Confusion Assessment Method (3D-CAM). Before discharge, patients will also be asked whether they would like to receive similar anaesthesia at any subsequent hip or knee replacement procedure.

Following discharge, a chart-review is conducted to register any emergency departments contacts or readmission to hospital, as well as cases of mortality, within 30 days of surgery.

6.1 | Questionnaires

Pain Catastrophizing Scale (PCS) is a 13-item questionnaire, investigating pain-related rumination, exaggeration and helplessness.[20] All 13 questions have five levels scored with 0–4 points, and a total score > 20 is considered high pain catastrophizing.

Quality of Recovery-15 (QoR-15) is a 15-item questionnaire, investigating quality of recovery after surgery and anaesthesia

regarding both physical and mental well-being.[21,22] The 15 questions have 11 levels (from 0 to 10) and the total maximum score is 150 points indicating complete post-operative well-being.

Opioid-Related Symptom Distress Scale (ORSDS) investigates 12 opioid related symptoms in three dimensions; frequency, severity and bothersomeness.[23] The ORSDS results in a composite ORSDS score which is a mean of the evaluation of all present symptoms, ranging from 0 to 4 (with 4 meaning most effected by opioid related symptoms).

3-min Diagnostic Confusion Assessment Method (3D-CAM) is a 20-item diagnostic tool aimed at diagnosing cognitive delirium.[24] It investigates the presence of the following features: (1) acute change or fluctuating mental state, (2) inattention, (3) disorganised thinking and (4) altered level of consciousness. Based on the presence of features 1 and 2 as well as either 3 or 4, patients are considered delirious.

7 | OUTCOMES

7.1 | Primary outcome

Safe mobilisation tested by a physiotherapist during a 5-m walking test within 6 h of surgery. The walking test will be conducted between 4 and 6 h post-operatively. Any failed walking tests prior to the 6-h mark, will be redone at 6 h post-operatively.

7.2 | Secondary outcome

Pain, nausea, dizziness, fulfilment of discharge criteria and vital parameters are registered at 4 and 6 h post-operatively on the day of surgery and at 10.00 and 18.00 on following post-operative days until discharge. Pain, nausea, and dizziness is evaluated from 0 to 10 (0 being no pain/nausea/dizziness). Vital parameters include blood pressure, heart rate, respiratory frequency, blood oxygen saturation, and temperature. Discharge criteria are as listed under 'Post-operative care'.

QoR-15 and ORSDS score at 4 h post-operatively, and at 10.00 on following post-operative days until discharge.

Presence of delirium evaluated using 3D-CAM at 4 h post-operatively and at 10.00 on following post-operative days until discharge.

The occurrence of emergency department contacts or readmissions to hospital following discharge within 30-days of surgery, evaluated by chart-review.

8 | SAFETY

SA and GA are commonly used anaesthetic methods in relation to hip and knee arthroplasty and the SA and GA regimes used in this study are performed in complete agreement with current standards at the participating centres. As such included patients are not subjected to different dosages or perioperative setup, compared to patients not included in the study.

A recent clinical trial comparing spinal anaesthesia to general anaesthesia in 395 TKAs found that both methods were acceptable to use in relation to knee arthroplasty.[14] Most recent studies are large cohort or registry studies comparing many different GA regimes to a variety of neuraxial anaesthesia, including both SA and epidural anaesthesia.[25,26] Such studies have merit due to numbers but have scarce information on implementation of fast-track principles in the perioperative setup, which largely impacts the risk associated with undergoing arthroplasty surgery. A review of this literature has recommend SA in THA, as some studies have reported that using GA in comorbid THA patients result in increased risk of complications.[16] A similar recommendation for SA was not present regarding TKA.[16] Counter intuitively, a higher ASA score has been associated with the use of GA in THA patients, suggesting a selection of at-risk-patients to GA.[27] However, a study using GA in THA patients ($n = 644$) operated in a dedicated fast-track centre found that the possible risk associated with GA might be reduced in a fast-track setup,[28] and as indicated in a randomized trial of 120 THAs, GA might even have some advantages.[12]

The patients included in this study are extensively screened for any increased risk associated with receiving either SA or GA, and both centres have a long-standing involvement in a fast-track collaboration, ensuring up-to-date perioperative setups with a low risk of perioperative morbidity.

9 | STATISTICS

9.1 | Sample size calculation

The sample size needed for this study was based on previous studies comparing SA to GA in THA and TKA patients.[12,13] These studies found that, when using GA 95% of hip and knee arthroplasty patients were able to be safely mobilised during a 5-m walking test within 6 h of surgery, while this was only the case for 30%–45% when using SA. In the above studies, a higher dose of bupivacaine was used, compared to this study. Detecting a meaningful difference of 60% prevalence compared to 90% of patients being safely mobilised within each procedure (THA, TKA and UKA), with 80% power and a significance level of 0.05, requires 32 patients in each intervention arm. To allow for 15% drop-out and still have sufficient power, we intend to include 37 patients in each arm. As a result, 74 THA patients, 74 TKA patients and 74 UKA patients are to be included. UKA patients will be included from Copenhagen University Hospital only, while THA and TKA patients will be included from both centres.

9.2 | Statistical analyses

The primary outcome will be presented as a proportion with 95% confidence interval (CI) and compared using logistic regression analyses presented as odd-ratios, two-sided 95% CI and p-values. p-values <.05 are considered significant. Categorical secondary outcomes will be tested using logistic regression or Fisher's-exact test, and

continuous secondary outcomes will be tested using *t*-test or Mann–Whitney *U*-test, depending on the normality of the data. Adjusted regression analyses might be performed where appropriate. Results of both crude and adjusted analyses will be presented. Any changes to the statistical plan will be reported when results are published. Analyses will be conducted using the intention-to-treat principle, with secondary per-protocol analyses in case of patients not receiving treatment as allocated.

9.3 | Current trial status

Enrolment of participants started in February 2023. Currently 21 UKA patients, 26 THA patients, and 5 TKA patients have been included and randomised in the trial. Recruitment is expected to be completed in February 2024.

10 | DISCUSSION

This study will offer insights into the occurrence of mobilisation difficulties, reasons for prolonged admission, patient reported recovery comparing two widely used anaesthetic methods in tried and tested fast-track setups. Despite optimized fast-track principles being implemented in many departments, urinary retention and insufficient mobilisation still limit the intended rapid recovery and planned short hospital stay. Urinary retention is reported to occur in a varying degree from ranging from 13% to 44% of cases.[10,29] Insufficient mobilisation due to muscle weakness or motor blockade remain a frequent reason for continued admission even in UKA surgery,[9] which is reported to have faster recovery compared to TKA.[30] Day case surgery is proposed as a possible way to meet the increased demand for arthroplasty surgery. However, for day case surgery to have any impact on bed occupancy or cost-effectiveness, the short-term post-operative period must be optimized to ensure immediate mobilisation and limited occurrence of unforeseen barriers to discharge. Utilizing choice of anaesthetic method in selected patients to optimize the first post-operative hours may be useful.

Retrospective studies comparing SA to GA are generally favouring SA, reporting less use of opioids, lower post-operative pain, and fewer complications.[31] However, as mentioned in most of the studies, investigating this topic retrospectively across a period from 2000 to 2020 has some crucial limitations. In many countries a move towards SA over time results in more GA procedures to be from the early period (e.g., 2000–2010), while most SA procedures are from 2007 to 2010 and onwards.[31] This means that not only are most SA procedures performed using contemporary SA regimes, which are then compared to older GA regimes, but SA procedures were also more likely to be performed in modern fast-track setups. The selection criteria for determining whether to offer patients SA or GA are also mostly unaccounted for. This means that different selection criteria between centres, across time, and between SA and GA, complicate the interpretation of the results as the SA and GA population are not necessarily retrospectively comparable. It is not unlikely that retrospective investigations are comparing modern SA regimes in less morbid patients operated in a fast-track setting to outdated GA regimes in comorbid patients operated without modern perioperative setups. This calls for clinical trials comparing selected patients considered suitable for both SA and GA in an updated setup.

This pragmatic clinical trial has several strengths, one being the comparison of two up-to-date anaesthetic methods in centres with a long-standing dedication to well-described fast-track principles. The anaesthetic methods and the perioperative setup correspond to the standard clinical practice at the centre, thus offering a representation of results as close to the actual clinical setting as possible. Second, patients are selected based on their eligibility to receive both SA and GA, and therefore represent the patient population in which this dilemma is relevant. Third, this study investigates short-term post-operative recovery regarding multiple aspects, for example, professional evaluation of mobilisation, validated patient reported questionnaires, objective measurements of vital parameters.

This study also has some limitations. First, a study of this size is not suitable for investigating the occurrence of rare, but important, complications. Second, anaesthetic and surgical personnel are not blinded to the allocation of the patients for safety and logistical reasons, and the overall blinding of the trial must be considered weak at best. However, evaluation of post-operative outcomes such as the 5-m walking test and questionnaires are performed by blinded personnel. Any unintentional unblinding will be registered and reported. Third, current SA practice uses bupivacaine, while short acting alternatives, such as chloroprocaine, might be preferable regarding motor blockade.[32] However, based on this study it will be possible to implement the use of such alternatives if motor blockade is found to be major contributor to limited mobilisation.

This study will offer insights into advantages and disadvantages of spinal anaesthesia compared to general anaesthesia regarding short-term recovery after fast-track hip and knee arthroplasty. Study findings will be presented in scientific journals, local hospital publications and webpages, and specifically to participants interested in the results.

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CONFLICT OF INTEREST STATEMENT

CBJ has received a Ph.D. stipend from the above-mentioned grant from Novo Nordisk Foundation. CV has received travel support from Stryker. AT and KG have received research and institutional support from Zimmer Biomet. AT has also received speaker fees from Zimmer Biomet and research support from Pfizer Denmark, where he is also a member of an advisory board. NBF has received speaker fees from Masimo Corporation and Edwards Lifesciences. The other authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

Study concept and design: CBJ, AT, HK, NBF, CV, and KG. Drafting of the manuscript: CBJ, KG and AT. Critical revision of the manuscript: all authors.

DATA AVAILABILITY STATEMENT

Research data are not shared. Due to Danish data privacy laws, research data cannot be shared beyond the purpose of this study.

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