ADMINISTRATIVE INFORMATION:

Title: Randomized trial on Spinal Anaesthesia vs. General Anaesthesia (SAGA) on recovery after total hip, total knee, and unicompartmental knee arthroplasty

Short title: RCT SAGA – THA, TKA, UKA

Trial registration number:

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INTRODUCTION

BACKGROUND

Optimizing the postoperative recovery of arthroplasty patients is a key factor in the fast-track protocols and day-case initiatives. Investigations of the postoperative course after hip and knee arthroplasty has identified insufficient mobilization, muscle weakness and urinary retention to be frequent postoperative challenges. Especially early mobilization is crucial in achieving timely discharge and reducing the risk of thromboembolic events. These postoperative challenges can be related to the anaesthesia methods used in hip and knee arthroplasty, however, our knowledge on this subject is lacking.

Comparative studies between spinal anaesthesia (SA) and general anaesthesia (GA) suggest that GA may result in reduced length of stay, earlier mobilization, and less pain, while SA offers quicker post-anaesthesia care unit (PACU) discharge and less immediate postoperative pain. The choice between SA and GA lacks consensus among surgeons, with preferences varying based on individual or centre preferences. This current knowledge gap highlights the necessity for contemporary, detailed studies to inform optimal anaesthesia choices for hip and knee arthroplasty patients.

OBJECTIVES

The primary objective of this study is to compare the impact of spinal anaesthesia and general anaesthesia on early mobilization after total hip (THA), total knee (TKA) and unicompartmental knee arthroplasty (UKA).

Secondary objectives are to compare fulfilment of discharge criteria, postoperative nausea and vomiting, pain, and use of opioids after THA, TKA, and UKA anaesthetized using either SA or GA.

STUDY METHODS

TRIAL DESIGN

This study consists of three individual trials. Each trial examines different hip and knee arthroplasty populations, but has identical methods for inclusion, randomization, data collection and statistical analysis. The trials are named:

- *Randomized trial on Spinal Anaesthesia vs. General Anaesthesia (SAGA) on recovery after total hip arthroplasty (RCT SAGA THA)*
- *Randomized trial on Spinal Anaesthesia vs. General Anaesthesia (SAGA) on recovery after total knee arthroplasty (RCT SAGA TKA)*
- *Randomized trial on Spinal Anaesthesia vs. General Anaesthesia (SAGA) on recovery after unicompartmental knee arthroplasty (RCT SAGA UKA)*

Each trial is conducted as a pragmatic, multicentre, randomized (1:1), single-blinded, clinical trial. Participants are randomized to receive either 1) spinal anaesthesia (SA) or 2) general anaesthesia (GA). Study data is gathered continuously during admittance. Study personnel is blinded to the allocation of the patients, but clinical personnel and the patients are not blinded, as this is not feasible given the interventions.

RCT SAGA UKA is conducted as a pilot trial exclusively at Copenhagen University Hospital Hvidovre. RCT SAGA THA and RCT TKA are conducted as multicentre trials at both Copenhagen University Hospital Hvidovre and Lillebaelt Hospital – Vejle.

RANDOMIZATION

Permutated block-randomization (4 or 6), stratified by centre for RCT SAGA THA and TKA, with allocation disclosed using non-transparent envelopes. A designated person, at Clinical Orthopaedic Research Hvidovre, Copenhagen University Hospital Hvidovre, with no other relation to the project is responsible for generating randomization sequences and preparation of the envelopes. Included patients are randomised at least three days before their planned surgery date.

SAMPLE SIZE

The primary endpoint of the study is whether patients are able to be safely mobilized during a 5-meter walking test within 6 hours of surgery. In previous studies safe mobilization was achieved after GA for 95% of THA and TKA patients, while it was only achieved for 30-45% of THA and TKA patients after SA. For this study we decided on a minimal clinically relevant difference in proportions of 30%. To detect a clinically relevant difference between 60% achieving safe mobilization in one group and 90% of achieving safe mobilization in the other group within 6 hours, would require 32 patients in each arm of each trial (95% confidence, 80% power). We aim to include 37 participants to each arm of each trial, to allow for a 15% dropout-rate in each trial.

- *RCT SAGA UKA: 74 participants (37 SA and 37 GA) all from Copenhagen University Hospital Hvidovre.*
- *RCT SAGA THA: 74 participants (37 SA and 37 GA) from Copenhagen University Hospital Hvidovre (intended nr. participants = 38) and Vejle Hospital (intended nr. participants = 36).*
- *RCT SAGA TKA: 74 participants (37 SA and 37 GA) from Copenhagen University Hospital Hvidovre (intended nr. participants = 38) and Vejle Hospital (intended nr. participants = 36).*

If one centre experiences recruitment issues, randomisation envelopes in 1 or 2 blocks will be transferred to the other centre.

FRAMEWORK

Superiority of GA over SA in achieving safe mobilization within 6 hours of surgery will be claimed if a difference in proportions of 30% is found in favour of GA.

STATISTICAL INTERIM ANALYSES AND STOPPING GUIDANCE

No interim analyses are planned. The investigators will evaluate the occurrence of serious adverse events, and if these occur in an unexpectedly high proportion of patients in relation to one of the interventions, the study will be stopped.

TIMING OF FINAL ANALYSIS

The final analysis is conducted when all included patients in the trial have passed the last follow-up (30 days after surgery).

TIMING OF OUTCOME ASSESSMENTS

Primary endpoint: safe mobilization at 5-meter walking test within 4-6 hours postoperatively. Patients will be given until 6 hours postoperatively to complete the walking test, and any early failed attempts will be redone at 6 hours postoperatively.

Secondary endpoints: fulfilment of discharge criteria, postoperative nausea and vomiting, pain, and use of opioids are evaluated at 4 and 6 hours postoperatively on the day of surgery and at 10:00 and 18:00 on any following postoperative days if the patient is still admitted.

STATISTICAL PRINCIPLES

CONFIDENCE INTERVALS AND P-VALUES

Confidence level is set at 95%, and results are presented with 95% confidence intervals. No adjustments for multiplicity are made.

ADHERENCE AND PROTOCOL DEVIATIONS

If patients are anaesthetised differently than allocated (i.e., GA instead of SA, due to technical difficulties), this is registered, and data collection continues. Reasons for cross-over are registered and reported. The overall adherence within the intervention groups will be reported.

All protocol deviations regarding sample size, eligibility, randomization, intervention, outcome definitions and statistical analyses plan will be reported.

ANALYSIS POPULATIONS

Any cases of crossover between the intervention groups will be included in their allocated treatment group as part of a modified intention-to-treat (mITT) analysis. The mITT will exclude randomised patients that did not undergo the intended arthroplasty surgery in the SAGA setup:

- Patients that after randomisation, but before being told their treatment allocation, decided not to go through with the arthroplasty surgery at the hospital.
- Patients that after randomisation, but before being told their treatment allocation, withdrew consent to participate.
- Patients that after randomisation, but before receiving treatment, were found unsuited for inclusion based on inclusion and exclusion criteria or were not able to be operated in a standard setup in accordance with the SAGA protocol.

All patients are randomised at least 72 hours before surgery but are only informed of their treatment allocation in the operating room just before surgery. The research staff remains blinded. We do therefore not consider any of the above exclusions to be related to the treatment allocation, in line with recommendations regarding unbiased mITT analyses [1].

If patients withdrew their consent or declined surgery in the operating room after being told their allocation, they will be included in the mITT as a case with missing data in the primary endpoint, as we cannot consider this to be unrelated to the treatment allocation.

If cross over cases are present in the mITT population, a secondary per-protocol (PP) analysis will be conducted on the same population according to the actual treatment received. The mITT analysis will evaluate the postoperative recovery related to a setup with intended GA or SA, while a potential PP analysis will evaluate postoperative recovery based on receiving GA or SA. The mITT analysis will be the primary analysis of the studies.

TRIAL POPULATION

SCREENING DATA

Data on eligibility incl. age, sex and surgery type is collected and reported in aggregated form. This will function as a comparison between included and non-included patients. No statistical comparisons will be conducted.

ELIGIBILITY

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 preoperative 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

RECRUITMENT, WITHDRAWAL AND FOLLOW-UP

Patients are pre-screened by the orthopaedic surgeons. At a standard preoperative physical examination 2-3 week prior to surgery, patients are asked whether research personnel can contact patients to provide them with study information. If patients consent to participation, the anaesthesiologist at the following standard preoperative anaesthesiologic examination will screen the patient for any contraindications for either SA or GA. Once screened by the anaesthesiologists, patients are considered included in the studies and baseline characteristics will be recorded.

Should the investigators become aware of previously unknown conditions, making included patients ineligible for participation, the investigators will withdraw the patient. These conditions include but are not limited to worsening of known disease, newly developed diseases or health conditions, and general safety concerns regarding anaesthesia.

In a CONSORT flow diagram the following will be reported; number of screened patients, number of excluded patients, number of randomized patients, number of patients allocated to each trial arm, number of patients that received anaesthesia in accordance with the allocation, and the number of patients that, after randomization, withdrew their consent, were excluded, or lost to follow-up.

BASELINE CHARACTERISTICS

The following baseline characteristics are registered at the time of inclusion:

Age, sex, height, weight, Charlson Comorbidity Index, Pain Catastrophizing Scale score, FRAIL-scale, ASA-score, preoperative blood sample results.

The baseline characteristics will be presented by intervention group using descriptive statistics. No statistical testing will be performed for baseline differences as suggested by the CONSORT-group [2].

ANALYSIS

OUTCOME DEFINITIONS

PRIMARY OUTCOME:

Ability to walk 5 meters 6 hours postoperatively:

Whether or not the participant is able to walk 5 meters safely and independently (also when using walking aid) within 6 hours of surgery evaluated by physiotherapists postoperatively.

Primary goal: Stable and safe 2-point gait with two crutches.

Secondary goal: Stable and safe 3-point gait with two crutches.

- Negative criteria:
    - Orthostatic: Dizziness, nausea, vomiting, fainting.
    - Motor control criteria: Poor muscle control or strength, insecure foot placement, impaired sensibility.

Stepwise mobilization course:

- Orthostatic test: from lying to sitting position.
- Motor control test: ability to move toes and lower limbs, firmly and securely planting the feet in the ground.
- Mobilization test: a few steps with a high walking frame.
- 5-Meter walking test using two crutches.

KEY SECONDARY OUTCOMES:

The key secondary outcomes are based on the first public registration of the study on https://euclinicaltrials.eu/ (2022-501221-21-00). Any erroneous disagreement between this first registration and the following registrations are corrected to coincide with the first registration.

Fulfilment of discharge criteria at 6 hours postoperatively:

Fulfilment of functional discharge criteria is evaluated at both 4 and 6 hours postoperatively. This will be a dichotomous outcome where patients are either ready for discharge (fulfil all criteria) or are not ready for discharge (fail at least one criteria).

Pain levels at 4 and 6 hours postoperatively:

Pain levels (numerical relation scale (NRS) 0-10) during rest and activity (walking 5 meters) at 4 and 6 hours are registered through a nurse-assisted questionnaire.

Opioid use in Morphine Milligram Equivalents within the first 6 hours of surgery:

A cumulated amount of opioid in Morphine Milligram Equivalents within the first 6 hours postoperatively. Data on opioid use at the postoperative care unit and the bed ward is collected until 6 hours postoperatively.

Postoperative Nausea and Vomiting (PONV) at 4 and 6 hours postoperatively:

Nausea and vomiting levels (NRS 0-10) during rest and activity (walking 5 meters) at 4 and 6 hours are registered through a nurse-assisted questionnaire.

OTHER SECONDARY OUTCOMES:

Urinary retention: no spontaneous urination and bladder scan with >800 mL (>600 mL at Vejle) prior to discharge.

Vital signs: systolic and diastolic blood pressure, pulse, blood oxygen saturation, temperature.

Postoperative blood sample results: Haemoglobin, serum-creatinine, and C-reactive protein.

Opioid-Related Symptom Distress Scale – questionnaire (ORSDS): A score based on 20 opioid related symptoms evaluating the burden of these symptoms.

Quality of Recovery – 15 score (QoR-15): a score based on 15 questions evaluating postoperative recovery.

3-minute Diagnostic Interview – Confusion Assessment Method (3D-CAM):

Attitude towards anaesthesia type: Whether patients would like to receive similar anaesthesia for any following arthroplasty surgery.

Blood transfusions: Whether patients received blood transfusion.

Emergency room contacts, complications, readmission or mortality within 30 days of surgery.

ANALYSIS METHODS

The primary analysis aim is to assess whether the ability to be safely mobilized within 6 hours of hip and knee arthroplasty is different between the two anesthetic methods, GA and SA. The main hypothesis to be tested is that GA patients are more likely to be safely mobilized compared to SA patients within 6 hours of arthroplasty surgery. This will be assessed in the (mITT) population, defined as all patients having undergone the intended arthroplasty surgery, between the comparison groups (GA and SA) as allocated. Superiority of GA over SA in achieving safe mobilization within 6 hours of surgery will be claimed if a difference in proportions of 30% is found in favour of GA.

Main analysis of primary outcome: The proportion of patients able to be safely mobilized within 6 hours of surgery will be compared between intervention groups using a logistic regression model. A supporting model adjusted, including possible confounders such as age and sex, will also be conducted. Estimates from the analysis will be presented as odd-ratios and 95% confidence intervals, for both crude and adjusted models.

In case of cross-over cases, a per-protocol analysis with similar statistical methods will be conducted.

Key secondary continuous outcomes will be analysed using t-test or Wilcoxon rank-sum test depending on normality. Results from t-tests will be presented as differences in means and 95%

confidence interval. Results from Wilcoxon rank-sum tests will be presented as differences in medians and p-values. Key secondary dichotomous outcomes will be compared using fisher's exact test. A mixed-effect model accounting for repeated measures using patient ID as a random effect will be used to compare both 4 and 6 hours NRS scores for pain and PONV between the intervention groups.

Normality will be evaluated using quantile-quantile plots and histograms.

MISSING DATA

Missing data will be reported for all outcomes and presented data. For the primary endpoint in the mITT and PP analysis, 3 analyses with different handling of missing data will be performed: 1) using available data only. 2) assigning missing data in SA patients with an approved mobilization attempt and missing data in GA patients with a failed mobilization attempted. 3) assigning missing data in SA patients with a failed mobilization attempt and missing data in GA patients with an approved mobilization attempted. This will serve as a sensitivity analysis, and differences in conclusion based on the three analyses will be discussed and reported. If no difference in the conclusion is present between the 3 analyses, the analysis on available data will be the main result discussed, while all 3 will be reported. Data from randomised patients excluded from the mITT will not be imputed or analysed.

HARMS

Included patients are under standard surveillance during admittance at the bed ward. If patients are discharged on the day-of-surgery, research staff will contact the patients over the phone on postoperative day 1 to enquire whether any symptoms have occurred since discharge.

Serious adverse events occurring during this timeframe will be reported stratified for intervention groups, with an evaluation of probable relationships with the interventions.

STATISTICAL SOFTWARE

Analysis will be conducted using R (R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.)

1. Kahan B C, White I R, Edwards M, Harhay M O. Using modified intention-to-treat as a principal stratum estimator for failure to initiate treatment. Clin. Trials 2023; 20(3): 269. doi: 10.1177/17407745231160074.

2. Schulz K F, Altman D G, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340(7748): 698–702. doi: 10.1136/BMJ.C332.