Deep versus moderate neuromuscular blockade during total hip arthroplasty to improve postoperative quality of recovery and immune function: protocol for a randomised controlled study

Veerle Bijkerk,1,2 Jetze Visser,3 Lotte M C Jacobs,1 Christiaan Keijzer,2 Michiel C Warlé

ABSTRACT

Introduction There is accumulating evidence that deep neuromuscular blockade (NMB) improves intraoperative surgical conditions during laparoscopic surgery. Studies investigating the effects of deep NMB in open surgery are scarce. In theory, by limiting surgical damage through deeper muscle relaxation, postoperative inflammation and concomitant immune suppression can be reduced. Therefore, this study will investigate the effects of deep NMB during total hip arthroplasty, which demands a relatively large exposure of the hip joint through and in between muscles.

Methods and analysis This study is a monocentre blinded randomised controlled trial in 100 patients undergoing total hip arthroplasty under general anaesthesia. Patients will be randomised in a 1:1 fashion to an intervention group of intraoperative deep NMB (a post-tetanic count of 1–2) or a control group receiving moderate NMB (a train-of-four count of 1–2). NMB will be achieved by continuous or bolus administration of rocuronium, respectively. The primary endpoint is the quality of recovery at postoperative day 1 measured by the Quality of Recovery-40 Questionnaire, analysed by Analysis of Variance. The secondary endpoint is postoperative innate immune function, measured by ex vivo production capacity of tumour necrosis factor and interleukin-1β on endotoxin stimulation of whole blood.

Ethics and dissemination Ethical approval for this study was granted by the Medical Ethics Committee ‘METC Oost-Nederland’ (reference number 2022-15754). Informed consent will be obtained prior to study participation. Study results will be published in an international peer-reviewed journal.

Trial registration numbers ClinicalTrials.gov Registry (NCT05562999) and EudraCT Registry (2022-002451-19).

INTRODUCTION

The rate of arthroplasties has been increasing over recent years as a result of the globally ageing population and increasing prevalence of obesity.1-3 Due to enormous progress in perioperative care, recovery after arthroplasties has been enhanced and infection rates have been reduced. Still, there is a challenge to further optimise the rehabilitation process and to nearly eliminate postoperative infections.4-5 Joint replacement surgery demands a relatively large exposure of the joint, as the prostheses need to be inserted and well fixed to the exposed host bone. This exposure usually poses strong traction on muscle and adjacent tissues. Intraoperative deep muscle relaxation may reduce tissue injury by reducing muscle tension during joint replacement surgery.

In laparoscopic surgery, there is accumulating evidence that deep neuromuscular blockade (NMB) (a post-tetanic count of 1–2) improves intraoperative surgical conditions and postoperative clinical outcomes. Deep NMB enables the optimisation of the surgical fields resulting in higher surgical rating scores, as confirmed in recent systematic reviews.6-8 In addition, the use of deep NMB in laparoscopic surgery is associated with enhanced postoperative recovery and lower pain scores.9 Several studies show that early postoperative pain scores are associated...
with postoperative infectious complications. However, the use of neuromuscular blocking agents has been associated with postoperative pulmonary complications. Little is known about the effects of the use of deep NMB in non-laparoscopic surgery, as literature is mainly limited to specific fields of surgery, such as head and neck surgery. Deep NMB could limit tissue damage, caused by the strong traction on muscle and adjacent tissues in arthroplasties, and thereby improve postoperative quality of recovery.

Surgical tissue injury is associated with a postoperative state of immune disbalance, consisting of a pro-inflammatory and anti-inflammatory component. The latter is responsible for postoperative immunosuppression, similar to what is seen after trauma and sepsis. Damaged cells release danger-associated molecular patterns (DAMPs) which contribute to immunosuppression of circulating innate immune cells. Potentially, deep NMB can counteract this by limiting surgical damage and the subsequent release of DAMPs.

Little is known about the effects of deep NMB in open surgery, and more specifically in orthopaedic surgery. We hypothesise that the use of deep NMB during hip arthroplasty improves the quality of recovery and enhances postoperative immune homeostasis.

**METHODS**

**Objectives**

The primary objective of this study is to investigate the effects of deep NMB compared with moderate NMB on the quality of recovery on postoperative day (POD) 1 in patients undergoing total hip arthroplasty (HIPPO study). The secondary objectives are to study the effects of deep NMB on postoperative innate immune function on POD 1, measured by ex vivo tumour necrosis factor (TNF) and interleukin-1β (IL-1β) production capacity on endotoxin stimulation, and on pain scores 24 hours after surgery.

**Study design**

The HIPPO study is a monocentre single-blinded randomised controlled trial performed at the Radboud University Medical Centre in Nijmegen, the Netherlands. Participants will be randomised to either a deep NMB or a moderate NMB. The aim is to include 100 patients undergoing total hip arthroplasty. All adult patients (≥18 years old) scheduled for primary or revision total hip replacement surgery under general anaesthesia are eligible for study participation and will be screened. Patients will be excluded if they meet any of the following criteria: insufficient control of the Dutch language to understand the patient information and fill out the questionnaires, known or suspected hypersensitivity to rocuronium or sugammadex, severe renal (creatinine clearance <30 mL/min) or liver disease (Child-Pugh classification C), chronic use of psychotropic drugs, more than 2 weeks use of immunomodulatory medication (such as steroids, immunosuppressants or monoclonal antibodies), women who are pregnant or currently breast feeding, deficiency of vitamin K-dependent clotting factors or coagulopathy or known or suspected neuromuscular disorders impairing neuromuscular function impairing intraoperative TOF measurements. Patients will be informed about the study by their treating orthopaedic surgeon. To avoid interference with patients’ preferences regarding their choice for the type of anaesthesia (ie, locoregional or general anaesthesia), informed consent is obtained after the type of anaesthesia has been decided. A flow chart of the study procedures is shown in figure 1.

**Study procedures**

Patients will be randomised prior to surgery in a one-to-one ratio in a deep NMB group (intervention group) and a moderate NMB group (control group). Stratification will be performed for primary or revision hip arthroplasty. Deep NMB is defined as a PTC of 1–2, and moderate NMB is defined as a TOF count of 1–2. Computer-generated randomisation will be performed by Castor EDC’s (Castor Electronic Data Capture) validated variable block randomisation model to ensure allocation concealment. After informed consent is obtained, patient baseline characteristics and medical history will be collected. The Dutch version of the validated Quality of Recovery-40 (QoR-40) Questionnaire will be completed at baseline, on POD 1 and 30. Blood samples will be obtained four times; before surgery, at the beginning of surgery (after induction but before incision), at the end of surgery (at the end of skin closure, before extubation) and one POD 1 (combined with routine laboratory assessment (24±3 hours after incision)). Blood samples will be drawn by venepuncture, a 6 mL Lithium Heparin and 10 mL EDTA tube will be collected.

**Perioperative protocol**

Participants are blinded for treatment allocation. In the operation room, the anaesthesiologist, the anaesthesiologist assistant and the attending research physician are not blinded for allocation of treatment to properly monitor the patient and ensure the correct depth of the NMB. The unblinded staff has no role in the assessment of outcomes. All other staff, including orthopaedic surgeons, scrub nurses, ward physicians and postoperative care nurses, are blinded as they are responsible for assessing and registering the outcome described below.

Patients will receive acetaminophen, ascorbic acid and pregabalin as premedication following the local protocol. Induction of anaesthesia will be achieved with total intravenous anaesthesia (TIVA) consisting of a propofol bolus of 1–3 mg/kg combined with a bolus of sufentanil bolus of 0.1–0.5 µg/kg and an esketamine bolus of 2.5–10 mg. After loss of consciousness, neuromuscular monitoring with the ToFScan (an IDMED neuromuscular monitoring; Marseille, France) is initiated. An induction dose of 0.6 mg/kg rocuronium will be administered in both the intervention and the control groups. Tracheal intubation

**Open access**
will be performed 2 min after the administration of rocuronium. Dexamethasone administration will be avoided intraoperatively and postoperatively to prevent any influence on the immune endpoints. During surgery, patients will be ventilated with pressure-regulated, volume-controlled ventilation through an endotracheal tube, with a mixture of oxygen in air, positive end-expiratory pressure of 5 cm H₂O and tidal volumes between 6 mL/kg and 8 mL/kg. Minute ventilation will be adjusted by changing the respiratory rate to maintain an end-tidal carbon dioxide between 31 mm Hg and 43 mm Hg. Oxygenation will be adjusted to maintain an oxygen saturation between 97% and 100% by changing the mixture of oxygen in air. Core temperature will continuously be monitored and maintained at 36–37°C, if necessary modified with a Bair Hugger temperature system.

General anaesthesia will be maintained with continuous infusion of propofol at 6–10 mg/kg/hour and esketamine at 2.5–10 mg/hour. The attending anaesthesiologist will guide intravenous anaesthesia dosage on standard clinical parameters, that is, heart rate, blood pressure, respiratory rate, sweating and movements. Remifentanil infusion at 0.25–2 µg/kg/min can be added, according to the judgement of the attending anaesthesiologist; however, this decision will be made prior to randomisation. Analgesia will be prescribed according to the local multimodal analgesia protocol. Depth of NMB will be measured by the automatic TOF PTC (ATP) function on the ToFScan at least every 5 min during surgery and will be recorded every 15-minute interval. In the moderate group (control group), the target depth is a TOF count of 1–2 throughout surgery. A bolus of 10–20 mg rocuronium will be administered when the TOF count exceeds 2. In the deep NMB group (intervention group), the target depth of NMB is a PTC of 1–2. This is achieved by continuous infusion of rocuronium, starting at 0.3 mg/kg/hour, and adjusted depending on the PTC. To maintain an adequate depth of NMB in both groups, the administration of rocuronium will be titrated by a research physician. The target depth of NMB within treatment arms is
maintained until the onset of skin closure. Intraoperative blinding of surgical personnel is assured by facing neuromuscular monitoring equipment away from the surgical team and covering these under sterile drapes. Moreover, continuous infusion of rocuronium is started only after the sterile drapes are installed and thereby not visible to the surgical team.

At the end of surgery in the deep NMB group, NMB is reversed by sugammadex 4 mg/kg. Patients in the moderate NMB group may receive sugammadex 2 mg/kg if TOF count has not recovered sufficiently. Extubation will be performed when the TOF ratio is stable at >0.9 for 2 min in at least four consecutive measurements, according to current guidelines. If the administered sugammadex dosage appears insufficient to reach a stable TOF ratio >0.9, an additional bolus of 4 mg/kg will be given.

Outcomes

The primary outcome is the QoR-10 Score on the first POD as reflected by the validated Dutch version of the QoR-40 Questionnaire. This questionnaire consists of 40 questions in which patients rate their recovery on a scale of 1–5 in several domains: physical comfort, emotional state, psychological support, physical independence and pain, resulting in a score between 40 and 200. Patients will complete the questionnaire themselves, or when their clinical condition does not allow this, with the assistance of a nurse blinded to treatment allocation.

Secondary outcomes are ex vivo production capacity of TNF and IL-1β on endotoxin stimulation of whole blood on POD 1, and pain scores (Numeric Rate Scale (NRS) 0–10) in rest and on movement 24 hours after surgery.

As an explorative outcome, innate immune function at the end of surgery and on POD 1 will be assessed by measuring ex vivo cytokine production capacity of IL-6, IL-10 and IL-1Ra on endotoxin stimulation, plasma cytokine levels (TNF, IL-6, IL-10) and circulating DAMP concentrations (HSP70, HMGB1, S100A12, S100A8/A9). Baseline values will be measured to rule out potential baseline differences between the groups. Lithium heparin (LH) anticoagulated blood will be used for ex vivo stimulation of leukocytes, and EDTA anticoagulated blood will be used to measure plasma cytokines and DAMP levels. After blood collection, LH and EDTA anticoagulated blood samples are centrifuged at 2970 x g at room temperature for 10 min. EDTA anticoagulated plasma samples for DAMP level measurements will be spun down again at 16 000 x g at room temperature for another 10 min. The resulting plasma will be stored at −80°C until further analysis. For ex vivo cytokine production capacity, whole blood is stimulated with Escherichia coli lipopolysaccharide (LPS) using an in-house developed system. LH anticoagulated blood will be added to prefilled tubes with 2 mL Roswell Park Memorial Institute (RPMI) medium as a negative control, or 2 mL RPMI culture medium supplemented with 12.5 ng/mL E. coli LPS (serotype O55:B5) to an end concentration of 10 ng/mL. Cultures will be incubated at 37°C for 24 hours. Consecutively, the samples will be centrifuged at 2970 x g at room temperature for 10 min. Supernatants will be stored at −80°C until further analysis. Ex vivo cytokine production capacity and plasma DAMPs will be determined batchwise by ELISA and plasma cytokines by Luminex assay according to the manufacturer’s instructions. All analyses will be performed by a lab technician blinded to treatment allocation.

Additional exploratory outcomes are pain scores, analgesic consumption and 30-day postoperative (infectious) complications. In addition to 24 hours after surgery, pain scores will be obtained during the stay at the post Anesthesia Care Unit (PACU) and at 48 and 72 hours after surgery or up to hospital discharge. Pain is scored at rest and on movement by the NRS (0–10) and by asking whether the pain is acceptable or not. Assessment is done by a blinded ward nurse responsible for clinical care. Analgesic and antiemetics consumption will be monitored and registered during PACU stay and at 24 hours, 48 hours and 72 hours after surgery or up to hospital discharge. Analgesic consumption will be converted to oral morphine equivalents. Postoperative complications will be scored at POD 30 by the treating orthopaedic surgeon who is blinded to treatment allocation. Postoperative complications, including postoperative pulmonary complications, will be scored by the Clavien-Dindo classification. Infectious complications will be scored according to the relevant endpoint of the Standardised Endpoint in Perioperative Medicine and Core Outcome Measures for Perioperative and Anaesthetic Care (StEP-COMPAC) group initiative.

Data management

Study participants will be coded by a numeric code to create an anonymous dataset. All data will be collected in the certified data collection platform Castor by making use of electronic case report forms (eCRFs). The subject identification log will be stored separately and securely from the source data. In accordance with national legislation, data will be saved for 25 years.

Safety and monitoring

Unblinding is done via contact with the research team, and will only occur in circumstances when knowledge of the actual treatment arm is necessary for patient treatment and safety. The reason for breaking the code will be reported with in the CRF. All adverse events, whether related to the study intervention or not, will be documented in the eCRFs and will be followed until 30 days after the surgery. In case an adverse event is considered serious, the investigator will report it to the sponsor without undue delay (within 48 hours after the SAE was identified). The sponsor will report all serious adverse events to the medical ethics committee as required by the Good Clinical Practice (GCP) guidelines. Monitoring will be conducted in accordance with negligible risk monitoring guidelines of the Dutch Federation of Academic Medical Centres. Yearly progress and safety reports will be conducted in accordance with negligible risk monitoring guidelines of the Dutch Federation of Academic Medical Centres.
be submitted to the medical research ethics committee and competent authority.

In accordance with Dutch legislation, damage to research subjects through injury caused by the study is covered by Radboudumc insurance.

**Sample size**

Regarding the primary outcome, the QoR-40 Questionnaire, Myles et al have reported a minimal clinically important difference of 6.3. Since this is a small difference on a 40–200 scale, we decided to use a 10-point difference instead. Özdemir-van Brunschot et al and Bruintjes et al have shown SD of 14.6 and 15.7. Therefore, an SD of 15 was used for the power calculation. A t-test was used for the sample size calculation. To detect a mean difference in the QoR-40 of 10 points on POD 1, with an SD of 15, an alpha of 5% and a power of 90% with equal allocation to two arms, 48 patients per group are required. To allow for ~4% dropout, 100 patients will be randomised. In case of missing values regarding the primary outcome, QoR-40 on POD 1, participants will be replaced with a maximum of 4.

**Statistical analysis**

All outcomes will be analysed according to the intention-to-treat principle, a mean TOF/PTC and percentage of adequate intraoperative NMB measurements will be provided per group. All analyses will be conducted using SPSS software (SPSS V.27.0, IBM, Released 2020, Armonk, New York, USA). Continuous data will be presented as mean and SD or median and IQRs for a normal and non-normal distribution, respectively. Categorical data will be presented as numbers and percentages. For the primary analysis of the primary outcome (QoR-40 at POD 1), Analysis of Variance will be used to compare deep and moderate NMB. Adjustment for covariates (ie, age, gender, body mass index and total dose of propofol per hour/per kilogram bodyweight, baseline QoR-40) will be performed by using Analysis of Covariance when, despite randomisation, a statistically significant difference between the two groups is found (p<0.05). The same will be done for the mononuclear cell response. All adjusted analyses will be exploratory. For other outcomes, Student’s t-test will be used for continuous data; or for non-normally distributed data, the Mann-Whitney U test will be used. Categorical data will be compared by χ² test or Fisher’s exact test, in case of counts below 5. P values <0.05 will be considered statistically significant.

**DISCUSSION**

Increasing evidence indicates that deep NMB has advantages compared with moderate NMB or no NMB during laparoscopic surgery. Deep NMB enables easier manipulation of muscles and adjacent tissues and provides a perfectly still patient. This advantage has been confirmed in several systematic reviews and meta-analyses with higher ratings of the quality of the surgical field and operating conditions. Moreover, deep NMB lowers early postoperative pain scores which, in a broad surgical population, are associated with 30-day postoperative complications.

Little is known about whether these findings withstand in non-laparoscopic surgery, although in some specific fields of open surgery, there is evidence that deep NMB improves intraoperative surgical conditions as well. In recent years, perioperative care in arthroplasties has improved tremendously, due to initiatives such as fast-track surgery, resulting in a quicker recovery and reduction of peri-prosthetic joint infections. However, the population of more complex (revision) arthroplasty is not suitable for fast-track recovery and remains susceptible to postoperative deterioration and infections. Deep NMB could provide a way to reduce surgical tissue damage in arthroplasties. To the best of our knowledge, only one study has evaluated the potential beneficial effects of deep NMB in arthroplasties. This study mainly focused on postoperative delirium. Therefore, this study aims to determine whether deep NMB during total hip arthroplasty has beneficial effects on the quality of recovery and postoperative immune status.

Quality of recovery as the primary outcome is derived from the StEp initiative, an initiative to establish a set of standardised endpoints in clinical trials in perioperative care. A final list of six endpoints was established to assess postoperative comfort. Quality of recovery is measured by the validated QoR-40 Questionnaire. Pain intensity and time to mobilisation, two other relevant endpoints of the initiative, will be included as well as exploratory endpoints.

The secondary aim of this study is to evaluate the effect of deep NMB on innate immune function. A recent study by our group in laparoscopic colorectal surgery showed that a deep NMB leads to improved postoperative immune homeostasis. The potential mechanism of action of deep NMB is twofold. First, by binding to various nicotinic acetylcholine receptors in the anti-inflammatory cascade, a higher dose of neuromuscular blocking agents could have anti-inflammatory effects. A second hypothesis is that a deep NMB reduces surgical tissue damage by allowing easier performance of surgeries, consequently reducing the postoperative inflammatory reaction. Surgery-induced stressed and injured cells lead to the release of DAMPs. These endogenous patterns can bind pattern recognition receptors on antigen-presenting cells, such as Toll-like receptors. This activates the innate and adaptive immune system, resulting in a pro-inflammatory and simultaneous anti-inflammatory response. After major trauma, it has been established that the release of DAMPs leads to immune tolerance of innate immune cells. By reducing surgical damage with the use of a deep NMB, cellular stress and damage are reduced. Consequently, immune homeostasis might be better preserved, potentially leading to better patient outcomes. To evaluate this hypothesis, we will measure plasma cytokines, circulating DAMPs and the ex vivo cytokine production capacity of mononuclear cells after stimulation with LPS.
To the best of our knowledge, only one study has investigated the effects of deep NMB in arthroplasties.29 Oh et al found lower postoperative plasma IL-6 levels after deep NMB as a first indication of reduced inflammation. In our opinion, this trial can provide a broader insight into the effect of deep NMB on the different aspects of the postoperative inflammatory response.

Despite the general preference for neuraxial anaesthesia in primary hip arthroplasty and the evidence for the association between lower peri-prosthetic joint infections and neuraxial anaesthesia compared with general anaesthesia, we believe it remains relevant to improve general anaesthesia techniques.33 34 First, in many countries, the use of neuraxial anaesthesia remains limited.35 Second, in longer surgeries such as complex revision surgery, general anaesthesia is the preferred technique. Especially in the more complex surgeries, it may be relevant to optimise immune homeostasis. The previously reported association between the use of neuromuscular blocking agents and postoperative pulmonary complications in the POPULAR trial reinforced the reluctance towards using high doses of rocuronium to obtain a deep NMB.11 Additional analyses of the POPULAR trial showed limited and inadequate adherence to international guidelines regarding neuromuscular monitoring.11 36 Therefore, it can be assumed that the risk of residual paralysis can be minimised by using calibrated and standardised quantitative neuromuscular monitoring. Moreover, in our study, the side effects potentially related to the use of deep NMB will be recorded (ie, postoperative pulmonary complications). A limitation of this study is that TIVA will be used, which is in line with a vast majority of studies investigating the effect of deep NMB.8 Nevertheless, this may reduce external validity, as volatile anaesthetics are still the first choice in a lot of countries. Also, as volatile anaesthetics augment the potency of NMB, controversy exists about whether the beneficial effects of deep NMB on intraoperative surgical conditions would persist with the use of volatile anaesthetics.37–39 Another limitation is that we do not use any monitoring for the depth of anaesthesia (ie, bispectral index or entropy). However, propofol will be titrated on bodyweight and intraoperative parameters, and therefore we do not expect a significant difference within treatment arms. In case a significant difference in the dose of propofol (mg/kg/hour) between the two groups occurs, we will adjust for this potential source of bias by analysing the propofol dose as a covariate in the primary analysis.

In conclusion, this trial will investigate the potential beneficial effects of deep NMB during total hip arthroplasty on the self-reported quality of recovery on POD 1. Second, the effects of deep NMB on postoperative innate immune function will be studied. We expect that deep NMB better preserves postoperative immune homeostasis with less immunosuppression. The findings of this study will increase the knowledge about the complex inflammatory response after surgery, potentially leading to a reduction in infectious complications.

**ETHICS AND DISSEMINATION**

Protocol version 4, December 2022. Ethical approval has been granted by the regional ethics committee ‘METC Oost-Nederland’ in the Netherlands (reference number 2022-15754). The Competent Authority, in this case the Central Committee on Research Involving Human Subjects performed an additional marginal review as this is a study with medicinal products and issued a ‘no-objection’ statement. Any modifications to the trial protocol will be approved by the relevant ethics committees, and the trial registries will be updated. This study will be conducted in accordance with the principles of the Declaration of Helsinki (64th version, Fortaleza, October 2013). The trial follows local GCP guidelines. Written informed consent will be obtained from participants prior to study participation. Study results will be published in an international peer-reviewed journal and through conference presentations.

**Twitter** Christiaan Keijzer @G-3247-2016

**Acknowledgements** We thank Kim Albers for her valuable feedback on the manuscript.

**Contributors** JV, LM, CJ, CK, MCW and VB have contributed to the trial design; reviewed and approved the submitted version. VB wrote the first draft of the manuscript.

**Funding** This work was supported by Merck Sharp & Dohme grant number #A22-0396. The funder has no role in the design, data collection and analysis of the study.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made are indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iDs**

Veerle Bijkerk http://orcid.org/0009-0000-2985-872X

Christiaan Keijzer http://orcid.org/0000-0002-0428-9687

**REFERENCES**


