General anesthesia is commonly employed for total hip replacement

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Does Deep Neuromuscular Blockade Improve Operating Conditions During Total Hip Replacements

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INTRODUCTION

During many surgeries, increased muscle tension makes it harder for the surgeon to expose the site of surgery and work within the incision. Neuromuscular blockade (NMB) drugs such as Vecuronium bind to neurotransmitter (acetyl choline) receptors at the neuromuscular junction, blocking their action and producing muscle relaxation. This muscle relaxation allows easier retraction of muscle tissues and manipulation of structures in the wound. Improved surgical conditions are likely to result in improved patient outcomes. While increased depths of NMB have been shown to optimize surgical conditions during intra-abdominal and retroperitoneal procedures, the impact of NMB depth has not been reported for orthopedic surgeries.[1] To address this, we propose to study the effect of NMB depth on surgical conditions during total hip replacement (THR).

BACKGROUND

THR is a very common surgical procedure in the US and approximately 600 cases are performed per year at MMC. The hip joint is a ball and socket joint, the head of the femur is the ball and the cup of the pelvic bone is the socket. THR requires an incision through skin and muscle with retraction of the incised muscles to expose the head of the femur which is then removed. The femoral prosthesis is inserted into the femur and next the ball of the femoral prosthesis is then inserted (reduced) into the socket. Thus, tension in the muscles can interfere with their retraction during exposure or with extracting or reducing the femoral head and patients with more developed musculature (males, younger age, physically active) could potentially present a greater challenge to the surgeon.

At MMC general anesthesia utilizing neuromuscular blockade is the routine anesthetic technique. The primary goal of NMB during THR is to facilitate retraction of muscles around the site of surgery to increase the surgeon's view of the operative site during the operation without the need for a longer incision, and to facilitate reinsertion (reduction) of the prosthesis at the end of surgery. Newer minimally invasive hip replacement techniques which use smaller incisions may theoretically require even greater depth of NMB to produce optimal surgical conditions.[2]

Until recently, the depth of NMB during surgery has been limited in practice by the time it takes to reverse the effects and allow adequate return of neuromuscular function for

safe extubation and spontaneous ventilation. The effects of NMB wear off with time; however, this process can be prolonged and in most cases NMB is reversed using medication. Older reversal medications such as Neostigmine act by increasing levels of acetylcholine at the neuromuscular junction, where it competes with the NMB agent for receptor sites. There is however a ceiling effect with this method, which limits rapid reversal of deeper NMB, especially when that deeper NMB is needed near the end of a surgery such as in THR. Thus, the constraints of reversal time limit the depth of NMB that is practical during surgery.

The FDA, however, recently approved Sugammadex for use in the US and was approved for routine use at MMC by the Pharmacy and Therapeutics Committee in May of 2016 (see appendix). In their meeting minutes, the P&T Committee noted that "in clinical trials, Sugammadex produced significantly faster reversal times for both moderate and deep blockade compared to the combination of neostigmine and glycopyrrolate. Reversal times were usually less than 5 minutes." The P&T Committee reviewed recent literature and studies, as Sugammadex has been thoroughly reviewed for patient safety and concluded that hypersensitivity reactions are mild or moderate and there is a low incidence of anaphylaxis. Sugammadex is a new NMB reversal agent which acts by sequestering rather than competing with the NMB drugs and thus has no ceiling effect, allowing timely and effective reversal of both moderate and deep degrees of NMB.[3-5] While new to the US market, this drug has been used widely and safely around the world since 2007, and has been in routine clinical use as a reversal agent at MMC since approval without incident. Sugammadex allows the anesthesiologist to maintain a deeper degree of NMB throughout THR without causing undue delay at the end of the operation. We estimate that its use reduces time to reversal from a deep block by 10 to 20 minutes.
We hypothesize that a deeper degree of NMB during THR will improve surgical conditions for the surgeon and may reduce surgical time. To explore this, we propose to perform a randomized controlled trial that will compare the effect of deep NMB versus moderate NMB, on surgical conditions during THR.

SPECIFIC AIMS

1) Assess difference in surgical conditions between moderate and deep NMB groups. Enrolled patients will be randomized to receive moderate (n=58) or deep (n=58) NMB. Difference in surgical conditions will be evaluated by:
    a) The number of requests from the surgeon for additional relaxation (NMB) during the procedure. At any time during the operation if the surgeon feels the muscle tension is interfering with ease of operation he will ask for additional muscle relaxation. If the patient is moderately relaxed they will be converted to deep relaxation with additional muscle relaxants. If they are already deeply relaxed no additional relaxants will be administered (as is our current practice). All requests will be recorded.
    b) Rating by the surgeon after each surgery using an internally developed satisfaction scale. The scale was developed by modifying a scale used in a previous study of muscle relaxation in intra-abdominal surgery[1] to specify two key elements identified by our surgeon: ease of muscle retraction and femur manipulation.

2) Assess the impact of deep vs moderate NMB on time of surgery, measured from the time of incision to joint reduction.

SIGNIFICANCE

If we identify improved surgical conditions with deeper relaxation we will incorporate deep NMB into our routine anesthesia practice for THR.

METHODS

Human subjects

Eligibility

Male and female patients between 50 and 75 years old who are scheduled at MMC for elective THR by a single surgeon (Dr. Babikian) will be potentially eligible to participate in the study.

Inclusion Criteria include: ASA physical status 1-3 (the American Society of Anesthesiologists standard preoperative risk stratification assignment – add ref), age 50-75 years old, English speaking, able to provide informed consent, BMI equal to or less than 30 kg/m^2, non-emergent THR by anterolateral minimally invasive non-cemented total hip arthroplasty (ALTHA).

Exclusion criteria include: revision surgery, bilateral THR, ASA 4+, below 50 or over 75 years old, unable to provide consent, BMI greater than 30 kg/m^2, women taking oral contraceptives as Sugammadex interferes with their efficacy, contraindications to general inhalation anesthesia, such as malignant hyperthermia, or contraindications to NMB such as known allergy to NMB, and chronic kidney disease.

Sample size

Sample size calculations, performed using NQuery software (Statistical Solutions Ltd, Boston, MA), were based on a chi square test, comparing the current frequency among surgeries of surgeon requests for additional NMB (estimate, 50%) and an anticipated effect size of 50% (absolute frequency of 25% for requests for additional NMB in the deep NMB group). A sample size of n=58/group (n=116 total) would give 80% power to detect this difference at alpha = 0.05. Assuming incomplete data and cancelled surgeries among 10% of patients, we will enroll a total of 128 (64/group). Dr. Babikian performs ~400 THR surgeries per year at MMC, of which ~ 280 are among patients aged 50-70 years; thus a minimum enrollment rate of 46% would be required to achieve this sample size over a one year period.

Recruitment/Enrollment

Scheduled patients will be screened for potential eligibility by surgery office staff and the study will be introduced to identified patients during their pre-operative appointment with the surgeon (Dr. Babikian). Any patient who would like to hear more about the study will be contacted by the research coordinator for follow up. The research coordinator will provide additional information about the study and mail a copy of the informed consent form for patients to review. On the day of surgery their

anesthesiologist will elicit and answer any questions or concerns and patients who decide to enroll in the study will give informed consent at that time.

Randomization

Patients will be randomized to moderate (Group 1) or deep (Group 2) NMB using a permuted block design (blocks of n=4 and n=6) that is stratified by patient sex. The randomization plan will be developed using NQuery software (Statistical Solutions Ltd, Boston, MA). Sequentially numbered group assignments will be placed in opaque envelopes, with a separate series of envelopes for male and female patients. Immediately before each surgery, the Research Coordinator will retrieve manually the next envelope in sequence from the male or female series, as appropriate, and give this to the anesthesiologist. The surgeon will be blinded to group assignment.

Anesthesia procedures

NMB monitoring

Depth of NMB is routinely monitored during surgery using a device that applies a transcutaneous electrical stimulus over the target nerve using while the muscular contraction is observed in the target muscle group. In most surgeries the ulnar nerve is stimulated which causes contraction of the adductor pollicis longus which produces movement of the thumb. It is the movement of the thumb which is recorded. There are two modes of stimulation used to quantify depth of NMB. The first mode, train of four (TOF) measures the respective muscle contractions to nerve stimulation of four successive stimuli and is reported as the number of muscle contractions observed, for example 2 out of four contractions. The second, post tetanic count (PTC) reports the number of responses to four stimuli after a sustained (tetanic) stimulus. PTC is used when NMB completely blocks the muscular contractions to all four stimuli in the TOF. In this study we will use the TOF Watch device to stimulate and measure the neuromuscular response quantitatively. This device is in routine clinical use at the MMC.

NMB administration

Vecuronium will be used as NMB drug in all study patients; this agent is currently used in over 90% of THR cases at MMC. As is currently routine Vecuronium will be given after initiation of general anesthesia with propofol to facilitate intubation and further doses of Vecuronium will be given throughout the case as noted below to maintain NMB at the desired depth until the femoral implant is reduced. After the intubating dose of Vecuronium, NMB depth will be monitored every 5 minutes and dosing will be adjusted as needed to maintain a constant depth of NMB according to our current routine practice.

Group 1: Moderate NMB: Intubating dose of Vecuronium of 0.1 mg/kg (IBW) and re-dosing with 0.0125 to 0.05 mg/kg as needed to achieve and maintain 1 to 2 TOF contractions. Redosing in this manner is a current clinical practice.

Group 2: Deep NMB: Intubating dose of Vecuronium of 0.2 mg/kg (IBW) and re-dosing with 0.025 to 0.1 mg/kg to achieve and maintain zero twitches in the TOF, and post tetanic count (PTC) of 1 to 2 contractions. This level of blockade is new to the practice since approval of the drug for use at MMC but is in common use since the advent of Sugammadex.

The surgeon may request additional relaxation at anytime for inadequate surgical conditions thought to be related to muscle tension. All requests will be recorded. Patients in the moderate NMB group will receive additional doses of vecuronium to achieve deep NMB (PTC of 1- 2). In the deep NMB group with PTC of 1-2, a saline dose without NMB will be given.

NMB reversal
Sugammadex will be given for reversal of NMB after the prosthesis has been reduced, using routine dosing of 2 mg/kg for the moderate group and 4 mg/kg for the deep group, per package insert by Merck (attached).

Surgical procedures
THR surgery will be performed by anterolateral minimally invasive non-cemented total hip arthroplasty (ALTHA); this approach is currently in routine practice at MMC and there will be no modifications for the purpose of this study.

DATA COLLECTION
Demographic and clinical data for each case will be abstracted from the medical record (EPIC) and will include age, gender, height, weight, BMI, total dose of Vecuronium, total dose of Sugammadex, time of surgery, time in the post anesthesia care unit (PACU), and maximum pain score in the PACU. Postoperatively, time to extubation will be tracked (time from the end of surgery to extubation are both points recorded in EPIC) as well as need for intubation, need for mechanical ventilation, need for additional reversal medication, and desaturation. All of these data are recorded through the existing QA database. We will confirm completion of the QA data form for each study patient.

Postoperatively the surgeon will grade the overall surgical conditions using a five point Likert scale (Figure). This scale was based on one published from a study of muscle relaxation in intra-abdominal surgery[1]; it was modified by the Investigator for use in THR, with input from Dr. Babikian. Satisfaction grading sheets will be collected by the research coordinator at the end of the procedure. The satisfaction ratings will include

patient identifiers to enable research staff to link these data with information abstracted from EPIC.

Figure: Surgical Conditions Rating Scale for THR

1	Extremely poor conditions:	Muscles resistant to retraction and obscure view, implant difficult to insert into socket, requires assist
2	Poor conditions:	Muscles resistant to retraction and obscure view, implant difficult to insert into socket not requiring assist
3	Acceptable conditions:	Muscles resistant to retraction, adequate view, difficult to insert not requiring assist
4	Good conditions:	Muscles relaxed adequate view, Easy to insert
5	Optimal conditions:	Muscles relaxed excellent view, Easy to insert

The surgical condition grading, requests for additional relaxation, time from incision to joint reduction, time to extubation and need for postoperative ventilation will be recorded on a separate data collection sheet (attached). To maintain patient confidentiality, all paper records will be stored in a locked filing cabinet in the research coordinator's office in the Anesthesia Department (card access only) and will be destroyed after data analysis is complete.

All data will be entered into a web-based, HIPAA-compliant REDCap database, to which only the PI and research coordinator have login access. De-identified data will be exported for analysis in Excel or SAS format, as necessary.

DATA ANALYSIS

Demographic and clinical data will be summarized using standard descriptive statistics, both for the overall study group and after stratification by NMB group. Continuous data will be shown as mean (standard deviation) or as median (range), as appropriate;

categorical data will be shown as frequency, n (%). Differences between treatment groups will be evaluated first using an intention-to-treat model, with subjects grouped according to the depth of NMB that they were randomized to; in post hoc analysis we will compare data between subjects grouped according to the depth of NMB that they actually received. Categorical data will be compared between groups by chi square test; continuous data will be compared using t tests or their nonparametric equivalent, as appropriate.

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