Trial registration: NCT03034577

Statistical Analysis Plan

A randomized trial of deep neuromuscular blockade reversed with sugammadex versus moderate neuromuscular block reversed with neostigmine, on postoperative quality of recovery

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2. Introduction

2.1. Background and Rationale

Recovery following general anesthesia is a complex issue confounded by the type of surgery, inflammation, different anesthetic drugs and techniques, patient co-morbidities, and differing patient and clinician perceptions of what constitutes good recovery.

Recovery is not a single entity but rather covers many aspects or domains such as physiological recovery, pain and nausea, emotion and mood, return to normal life or work activities, and cognitive function. It is an entity that is difficult to quantify, which then makes it difficult to study in a systematic manner. For anesthesiologists, poor recovery is often relayed by the surgeon days or weeks after the event, and it is usually categorized as an adverse outcome.

Research tools such as the Aldrete (1) or the QoR (2, 3) scales, focus on early physiological recovery, or the immediate perioperative period. These recovery scores are not sensitive enough to measure the rate of recovery (change over time) and have not been designed for repeated measures. They are also inadequate to identify poor cognitive recovery.

In 2007, an international group of anesthesiologists and neuropsychologists formed an advisory board to create a new quality of recovery scale. The aim was to produce a tool that was simple to perform, but sensitive enough to detect change in multiple domains of recovery over time. The initial validation experiment included over 700 patients, and this work has been published in *Anesthesiology*. It is called the Postoperative Quality Recovery Scale (PostopQRS) (4). Six domains of recovery are identified: physiological, nociceptive (pain and nausea) emotive (anxiety and depression), functional recovery (return of activities of daily living), cognitive recovery, and an overall patient perspective domain including satisfaction. The scale is completed prior to surgery to provide baseline values, and then repeated at

user-defined intervals. From some of the subsequent discriminant validation studies, time points have included early and late measures such as 15 minutes, 40 minutes, 1 and 3 days, and 3 months after the completion of anesthesia (typically defined as after the last surgical stimulation). Recovery is broadly defined as return to baseline values or better, except for the cognitive domain where a tolerance factor is included to allow for normal performance variability, such that patients are allowed to perform a little worse than baseline as still be scored as recovered (5). Because repeated tests tend to have a learning effect, the cognitive domain uses parallel forms, and only a small learning has been shown (5).

One of the most important benefits of the PostopQRS scale is that it enables recovery to be quantified and measured. This makes it possible to compare different interventions with the express purpose of developing clinical interventions to improve quality of recovery. The PostopQRS offers a tool to provide the recovery process to be examined. There are no other tools in existence that provide a comprehensive, sensitive assessment of the multiple aspects or domains of recovery, and is yet relatively simple to perform. Validation studies have been performed and show good discriminative ability (5-8). Ease of use is facilitated by using a web-based data entry system and the ability to use the telephone to conduct surveys after discharge form hospital. Telephone survey has been shown to be equivalent to face to face interviews using the PostopQRS (5). Further, the PostopQRS allows users to drill down to identify which recovery domain is affected for individuals in real time as well as for group audit.

Quality of recovery after operative laparoscopy

The majority of the literature compares different operative techniques with outcome measures aimed at specific complications or length of stay. Few studies include quality of recovery or quality of life measures as secondary endpoints (9-12). However, for potential benefits relating to the use of sugammadex, there are a few studies primarily centered around deep neuromuscular block (DNB) facilitating low intraabdominal inflation pressures. Most outcomes relate to operative conditions with little data on patient

centered outcomes especially after discharge. The inclusion of sugammadex is to permit the use of DNB, and most comparative groups (of moderate block) are reversed with neostigmine.

It has been shown that more patients can be operated on with low intraabdominal pressure with DNB, and that operative conditions are rated as better in more patients with DNB (13, 14), though it is not absolute and there are frequent crossovers. That is, there are patients with moderate block and low pressure, and equally patients with DNB requiring high inflation pressures. The very few data on patient centered outcomes show reduced pain and nausea after DNB (13, 15-17), but lack of evidence of benefit for other recovery outcomes. This paucity of data has been stressed by review articles and editorials that DNB is associated with a modest effect on improving operating conditions but very little data to identify recovery benefits (13, 18)

Sugammadex is an effective drug to reduce deep neuromuscular blockade

There is no clinical question that sugammadex is highly effective in reversing neuromuscular blockade with rocuronium or vecuronium. This has been the subject of a Cochrane review which included 18 randomized trials, showing that sugammadex can reverse blockade with rocuronium or vecuronium independent on the depth of block, and superiority to neostigmine (19). This aspect of sugammadex does not require further study. This translates to a low incidence of residual blockade in the PACU compared to neostigmine reversal. The "safety" benefit to using sugammadex has been proven, but this does not necessarily translate into better outcomes. Sugammadex, however, is an enabling drug to facilitate deep neuromuscular blockade, allowing the anesthesiologist to continue that block until the end of surgery and reliably reverse the block. This is just not possible with neostigmine reversal, as one must wait until a train of four count of at least 2 twitches (or TOF ratio > 0.7) to safely reverse the block with neostigmine.

2.2. Objectives and hypothesis

Objectives

1. To identify whether the rate/quality of recovery is affected by deep neuromuscular block (DNB) and reversal with sugammadex versus light/moderate neuromuscular block reversed with neostigmine in patients undergoing operative gynecological or abdominal laparoscopic surgery of at least 1-hour duration.

Hypothesis

1. The technique of deep neuromuscular block and reversal with sugammadex will result in improved quality of recovery, including cognition, compared to the current standard of care technique using light/moderate neuromuscular block reversed with neostigmine in patients undergoing operative gynecological or abdominal laparoscopic surgery of at least 1-hour duration.

3. Study Methods

3.1. Trial Design

Parallel randomized trial with allocation ration 1:1. The trial was registered prior to commencement and conforms to CONSORT guidelines.

The study was conducted in secondary and tertiary hospitals, which included an active laparoscopic surgery unit for gynecology and abdominal surgery.

3.2. Randomization

The randomization sequence was produced using a computer- generated randomization sequence, in unequal blocks and stratified for gynecological and abdominal surgery. Concealment was undertaken by placing the card containing the allocation information in double opaque sealed envelopes, and concealment was maintained until after recruitment and the patients was admitted to the operating theatre. The treating anesthesiologist opened the envelopes to reveal the allocation. A non-participant in any process of the study prepared the envelopes prior to recruitment. A copy of the randomization sequence was stored in a separate databank, which is password protected and not made available to the investigators until the completion of the study.

3.3. Sample Size

Sample size estimates were based on the primary outcome of cognitive recovery at 1 week after surgery, and a clinically important difference in cognitive recovery at 1 week after surgery of 15%. Estimates of cognitive recovery were based on prior PostopQRS research and using multiple ages and surgical cohorts. It was estimated that the cognitive recovery for this cohort and duration of surgery would be 85% if there was good recovery. Using a two tailed estimate and Chi-squared analysis, alpha of 0.05, and power of 90%, with 1:1 allocation ratio; the sample size required to detect an absolute difference of 15%

was 161 per group, which was rounded up to a total sample size of 350 patients to account for potential non-completion of the study

3.4. Framework

Two-center double-blind, placebo-controlled, parallel-group, randomized, phase IV study with 1:1 allocation ratio.

3.5. Statistical interim analyses and stopping guidance

Due to the small study size, there was no planned interim analyses, nor stopping rules defined.

3.6. Timing of final analyses – timeline of study

Allocation was revealed after the last data collection time point of the last participant enrolled. Analysis followed after this point.

3.7. Timing of outcome assessments

Outcome assessments were undertaken at baseline, prior to surgery, immediate recovery parameters were measured in recovery at 15 and 40 minutes following the cessation of anesthesia. Outcomes were also measured at days 1, 3, 7, 14 and 1 and 3 months.

4. Statistical Principles

4.1. Statistical significance

A two-sided P<0.05 defined significance for the primary outcome.

4.2. Adjustments to the statistical significance

P <0.01 defined significance for secondary outcomes in order to reduce the risk of type I error.

4.3. Confidence intervals

95% Confidence intervals were reported for all effects where appropriate.

4.4. Adherence and Protocol deviations

a. Adherence to protocol was defined by the correct allocation at the correct dose at the correct time.
b. Adherence was presented in the CONSORT flow chart.
c. Protocol deviations were recorded as incorrect dose or timing, or supplemental use of midazolam.

4.5. Definition of analysis populations

Patients were analyzed on an intention-to-treat basis**.**

5. Trial Populations

5.1. Screening

Patient screening was performed by a researcher who was not part of the treating team. The screening log was collected and stored as an excel file on the University of Melbourne server. This includes the reasons for screening failure and date of screening.

5.2. Eligibility Criteria

Inclusion:

1. Adult participants undergoing operative gynecological or abdominal surgery under general anesthesia of at least 1 hour duration

Exclusion:

1. Participants, who are not fluent in English will be excluded, as they may be unable to answer the recovery questionnaire adequately.
2. Participants undergoing diagnostic laparoscopy only
3. Participants <18 years of age
4. Current pregnancy
5. Known allergy to rocuronium, neostigmine or sugammadex, or desflurane

5.3. Recruitment

A CONSORT flow diagram was constructed to illustrate the flow of recruitment throughout the study. Recruitment was performed by a study investigator who was not part of the treating team and remained blinded to the allocation. Written informed consent was obtained prior to allocation.

5.4. Withdrawal

Withdrawal of the patients can occur at any point from the initial baseline up to the final completion of the study for that particular participant at 3mths after surgery, this may be in the form of refusing to continue with the study. Patient are lost-to-follow up if they are not present for their follow-up assessments in their final timepoint at 3 months.

5.5. Baseline Patient Characteristics

The following characteristics was summarized in a table format as either Mean ± SD (continuous data) on (%) (discrete data): Age, Gender, ASA status, Obesity, Education, Alcoholic consumption, Smoking status, Pre-existing conditions, Problems with previous anesthesia, Employment Status..

6. Analysis

6.1. Outcome definitions

Primary outcome

The most sensitive recovery domain of the Postoperative Quality of Recovery Scale to the effects of short acting drugs and avoidance of neostigmine is cognition. The primary outcome was the cognitive domain at 1 week after surgery, where it is expected that most of the acute inflammation will have resolved, and analgesia requirements would be minimal.

Secondary outcomes

1. Recovery for all domains and within domains at the other time points of measurement (15 minutes, 40 minutes 1 day, 3 days, 1 and 2 weeks, and 3 months following cessation of anesthesia). The domains of recovery are physiological, nociceptive, emotive activities of daily living, cognitive and overall patient perspective.

2. Compliance with protocol to ensure deep block or light/moderate block, and correctly assigned anesthetic.

3. Anesthesia, surgical (first incision to last stitch), operating room, and PACU times, and hospital length of stay

4. Incidence of persistent neuromuscular block (TOF < 4 twitches or visible fade, or TOF ratio < 0.9) upon arrival in the PACU.

5. Surgical operating conditions measured by maximal inflation pressure required for surgery, and number of times that organ movement occurred (due to diaphragmatic movement or abdominal wall

tone), and overall surgical satisfaction using a 1-5 Likert scale (1 = very unacceptable, 2 = unacceptable, 3 = acceptable, 4 = good, 5 = excellent).

6.2. Analysis Methods

A Fisher's Exact test was used to analyze the primary outcome of cognitive recovery at week 1 following laparoscopic surgery. A Generalized Linear Mixed Model (GLMM) test was used to analyze the recovery within and across all domains over time, including patient satisfaction. For the secondary outcomes, GLMM was used for analysis of the recovery domains and a T test was used for continuous data.

6.3. Missing Data

Missing Data was not expected to be substantial, so it was not imputed, and incidence of recovery was analyzed using available data only.

6.4. Additional Analyses

No additional analysis was conducted. All analyses have been previously mentioned.

6.5. Harms

Harms will be defined on an incident basis, and where the trial drug is a likely contributor to the specific harm.

6.6. Statistical Software

GENSTAT V18 (VSNi International Ltd) was used to perform the GLMM test, and SPSS V21 (SPSS Inc) was used for all other analyses.

6.7. References

This survey was conducted using the online survey tool located at www.postopqrs.com. The study related information from both the centres was transferred onto the database in a non-identifiable manner. The database only allows de-identified information to be stored and only investigators have access to the data. It complies with international privacy laws. The databank is located at the City University Hospital in London, United Kingdom. This database allows us to score participants' recovery automatically and send that information back to the investigating team. This de-identified data was used as pooled data to help establish international "benchmarks" for recovery outcomes following endoscopy procedures.

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