Neuromuscular blockade during laparoscopic ventral herniotomy: protocol for a randomised controlled trial

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ABSTRACT

INTRODUCTION: Laparoscopic herniotomy is the preferred technique for some ventral hernias. Several factors may influence the surgical conditions, one being the depth of neuromuscular blockade (NMB) applied. We hypothesised that deep neuromuscular blockade defined as a post-tetanic count below eight would provide a better surgical workspace.

METHOD: This is an investigator-initiated, assessor- and patient-blinded randomised cross-over study. A total of 34 patients with planned laparoscopic umbilical, incisional and linea alba herniotomy are studied. Patients will be randomised to receive deep NMB followed by no NMB, or no NMB followed by deep NMB. Our primary outcome is improvement of the surgical workspace (rated on a five-point scale) estimated as the difference between the workspace during deep NMB and the workspace without NMB. Secondary outcomes include, among others, surgeon's rating of surgical conditions during suturing, duration of surgery and duration of the suturing of the hernia.

CONCLUSION: This randomised cross-over study investigates a potential effect on the surgical workspace in laparoscopic ventral herniotomy using deep NMB compared with no NMB. The study may provide knowledge relevant to other laparoscopic techniques.

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Herniotomy is a frequent surgical procedure worldwide, and mid-sized hernia defects are preferably treated by laparoscopic technique. The advantages of the laparoscopic approach are shorter convalescence with earlier mobilisation, and fewer wound complications [1]. Currently, the preferred approach is to close the defect by laparoscopic suturing to reduce the formation of seroma in the hernia sac [2], and then apply a mesh by intraperitoneal onlay (IPOM) technique.

Tension in the abdominal wall muscles together with the applied pneumoperitoneum may provide difficult suturing conditions, and neuromuscular blockade (NMB) may ease the surgical conditions [3-6]. Usually, neuromuscular monitoring measures the muscle strength of the adductor pollicis muscle [7]. More resistant muscles such as the abdominal wall muscles and the diaphragm are not completely paralysed at moderate-level blockade; hence, the patients may cough and their abdominal wall may feel "tight" during surgery [8, 9]. Deeper NMB allows paralysis of all muscles, including the abdominal wall muscles and diaphragm [10].

We designed this study to assess the effect of a deep neuromuscular blockade on the surgical workspace and surgical conditions during laparoscopic umbilical, incisional and linea alba herniotomy. We hypothesise that deep NMB will provide a better surgical workspace and conditions.

METHODS

Study design

This is a crossover study. The order of intervention is randomised in order to blind the surgeon.

Study population

Adult (> 18 years of age) patients scheduled for elective umbilical, incisional and linea alba herniotomy are screened for inclusion. The exclusion criteria are listed in **Figure 1**.

Randomisation

Randomisation is 1:1 and implemented just before surgery is initiated as computer randomisation. Patients are assigned to either group A or B.

Anaesthesia

General anaesthesia will be induced with propofol 2 mg/kg and remifentanil 1.0 µg/kg/min. Tracheal intubation is performed 3 min. after induction of anaesthesia to ensure that the patient has received at least 3 µg/kg remifentanil [11]. Anaesthesia will be maintained with propofol 3 mg/kg/h and remifentanil 0.25-0.5 µg/kg/min. adjusted according to depth of anaesthesia under guidance of the Bispectral Index (BIS) (Covidien, Copenhagen, Denmark) (**Table 1**). Rocuronium 0.6 mg/kg is based on ideal body weight, and calculated as follows for men and women, respectively: height (cm) – 100, and height (cm) – 105. Timing of rocuronium injection is according to the randomisation (see intervention and Figure 1).

Sugammadex is administered at the end of anaesthesia following the product information from the

PROTOCOL ARTICLE

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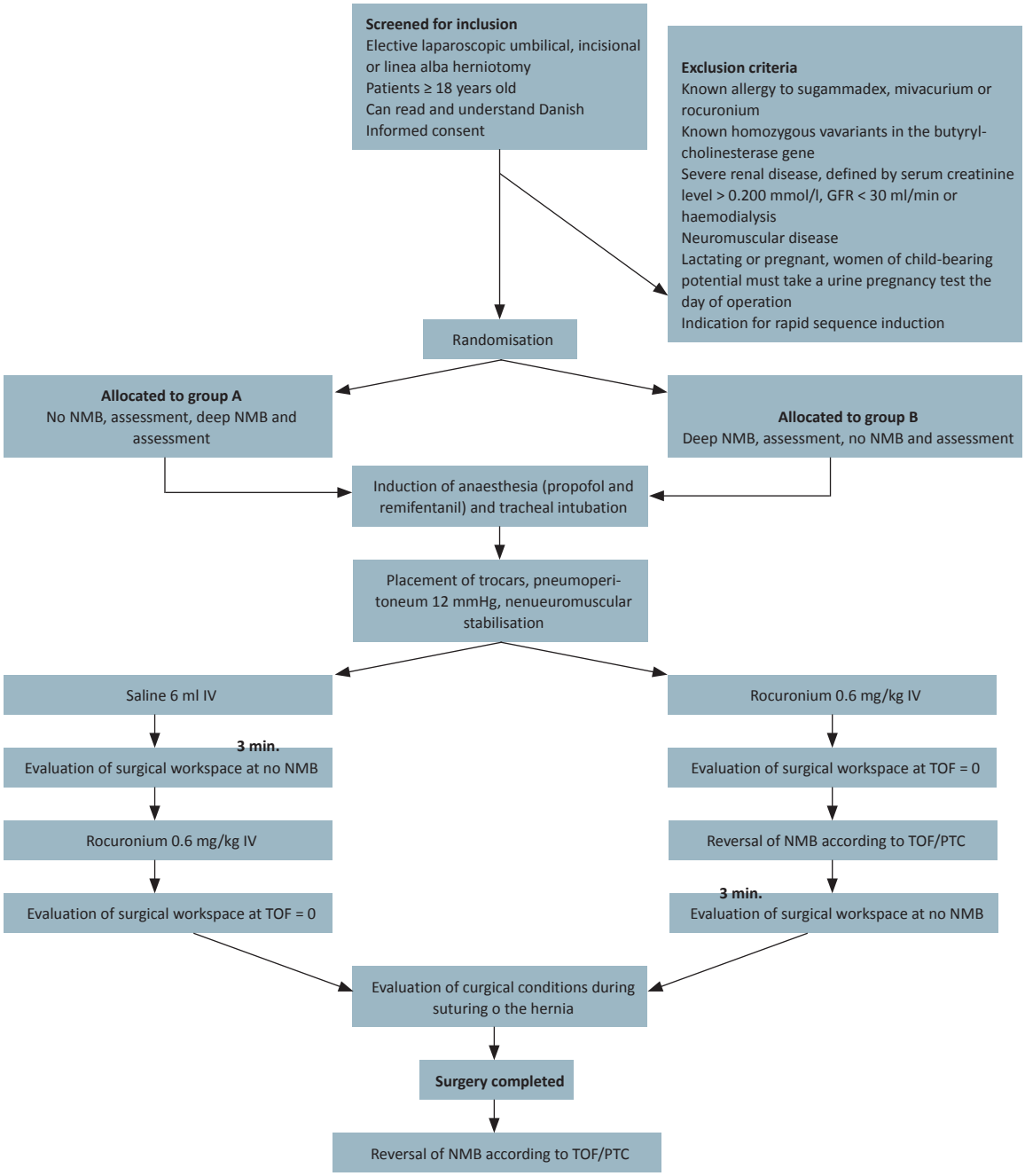
European Medicines Agency. Neuromuscular monitoring continues until the train-of-four (TOF) ratio is above 0.90 and the value is stable during a minimum of 2 min.

Neuromuscular monitoring will be done in accordance with GCRP [7] with TOF-Watch SX (MSD, Ballerup, Denmark) connected to a computer for collection of neuromuscular data (Version 2.5 INT 2007, Organon, The Netherlands). Small electrocardiography (ECG) electrodes are placed on the wrist over the ulnar nerve. The acceleration transducer is placed in a hand adaptor on the thumb. The TOF-Watch SX will be calibrated (CAL2). Measurements will be taken every 15 sec. When stable neuromuscular monitoring is assured during 2 min., the first intervention will be administered. When TOF = 0, post-tetanic count (PTC) will be measured every 3 min.

FIGURE 1

Flow diagram for patients undergoing laparoscopic ventral herniotomy.



GFR = glomerular filtration rate; IV = intravenously; NMB = neuromuscular blockade; PTC = post-tetanic count; TOF = train-of-four.

Intervention

Assessment of surgical workspace is done by the surgeon using a five-point subjective rating scale (**Table 2**). The five-point rating scale was designed in close cooperation with the surgeon to make sure that the descriptions are adequate. The applicability of the rating scale was tested by the surgeon on a number of patients prior to inclusion. The same scale is used when the surgical conditions are evaluated during hernia suturing.

Pneumoperitoneum is initiated after intubation and maintained at 12 mmHg. The trocars are placed before the intervention.

In group A, patients receive a bolus of saline 6 ml (placebo), and 3 min. later the surgeon evaluates the surgical workspace on the rating scale. In group B, rocuronium 0.6 mg/kg is administered; and when TOF = 0 is reached, the surgeon evaluates the surgical workspace on the rating scale, and simultaneously PTC measurement is started. The second intervention then follows. In group A, patients are administered rocuronium 0.6 mg/kg. When TOF = 0 is reached, the surgeon re-assesses the surgical workspace and PTC measurement is started. In group B, patients are administered sugammadex according to NMB level to reverse the NMB. 3 min. later, the surgeon will re-assess the surgical workspace. In both groups, during the second assessment, the surgeon will also consider if the surgical space has improved, remains unchanged or has deteriorated. Furthermore, surgical conditions are assessed during hernia repair where group A receives rocuronium infusion targeting TOF = 0 and PTC > 1 and group B saline infusion (placebo). At the end of surgery, NMB is reversed with sugammadex in group A, and patients in group B receive saline (placebo) (Figure 1).

If surgical conditions are poor after administration of the second intervention and anaesthesia is assessed as sufficient with a normal BIS, heart rate and blood-pressure, the following interventions are allowed: in group A, bolus of saline and 3 min. waiting before surgery proceeds. In group B, mivacurium 0.2 mg/kg is administered and after 3 min., the surgery will proceed. An extra evaluation of the surgical workspace will be performed 3 min. after the additional intervention. If these interventions do not optimise the surgical conditions, propofol or remifentanil is administered at the discretion of the attending anaesthesiologist.

Blinding

Intervention medicine is prepared in the medicine room prior to surgery. This is done under double control by a nurse anaesthetist and the investigator who performs the randomisation. Randomisation group will be noted on a sheet (NMB sheet). The TOF-Watch and the arm with the neuromuscular equipment are covered. The readings from the TOF-Watch are seen on the connected computer by the nurse anaesthetist and the investigator only. The surgeon and surgical personnel are all blinded to intervention group allocation.

The group allocation, the doses of rocuronium and sugammadex administered, as well as the measurements registered with the TOF-Watch will only be noted on the NMB sheet. After conclusion of anaesthesia, the NMB sheet will be placed in an opaque envelope, which is sealed and placed in a locked drawer to which only the anaesthesia investigator of the study has access. A case will only be un-blinded if this is needed for emergency treatment. These procedures will keep the surgeon´s assessment of the primary outcome blinded to group allocation.

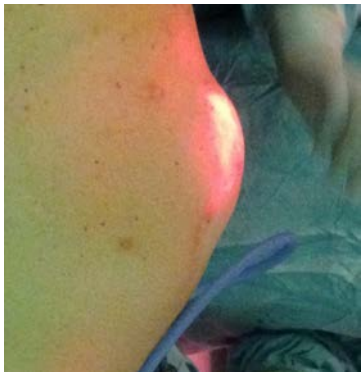
TABLE 1

Trial protocol for data collection in 34 patients undergoing laparoscopic herniotomy.

Protocol constituent	Details
Preoperative	
Fasting guideline	Allowed to eat until 6 h before and drink clear fluids until 2 h before anaesthesia
Analgesics	Ibuprofen 400 mg and paracetamol 1,000 mg
Anti-emetics	Dexamethasone 8 mg orally
Peroperative	
Anaesthesia	Induction with propofol 2 mg/kg and remifentanil 1 µg/kg/min. At least 3 µg/kg remifentanil prior to intubation Continued using propofol 3 mg/kg/h and remifentanil 0.25-0.5 µg/kg/min.
Respiratory	FiO_2 1.0 during induction, tracheal intubation and extubation FiO_2 0.4 maintained during surgery PEEP 5 cm H_2O Pressure control ventilation, tidal volume 7 ml/kg Respiration frequency 10-12 End tidal CO_2 target 4.5-5.5 kPa
Neuromuscular monitoring	In accordance with international recommendations [6]
Positioning	Supine position Arm with neuromuscular monitoring equipment placed in abducted position and concealed from surgeon
Surgical technique	Laparoscopic herniotomy, mesh placed with IPOM technique The defect will be sutured with Ethibond 0 suture with single stitches, intracorporal technique
Pneumoperitoneum	Maintained at 12 mmHg
Fluid therapy	No preoperative fluid loading Isotonic NaCl 0.9% up to 1,000 ml given intraoperatively
Blood-loss	Isotonic NaCl 0.9% is used to replace blood-loss up to 500 ml, a ratio of 1:2.5 is used Blood-loss in excess of this is replaced in accordance with the local guidelines
Temperature control	Central and skin temperatures are measured throughout the procedure, and aimed at 36-37 °C and 32 °C, respectively
Anti-emetics	Ondansetron 4 mg IV
Antibiotics	Tazocin (4 g piperacillin/0,5 g tazobactam) IV or cefuroxim 1,500 mg IV
Post-operative	
Pain treatment	Ibuprofen 400 mg orally 4 times a day for 7 days Paracetamol 1,000 mg orally 4 times a day for 7 days Morphine 10 mg orally maximum 30 mg a day for 3 days

FiO_2 = fraction of inspired oxygen; IPOM = intraperitoneal onlay; IV = intravenously; PEEP = positive end-expiratory pressure.

Umbilical herniotomy.



Data collection

A list of the data recorded is provided in **Table 3**.

Data collection is completed on the day of surgery when the patients are also discharged.

Outcome measures

The primary outcome is the improvement in surgical workspace rated on the five-point scale (Table 1), calculated as the difference between the workspace during deep NMB and the workspace without NMB. The cross-over design allows patients to serve as their own control.

The secondary outcomes are found by comparing the two groups and listed below:

- Surgeon's rating of surgical conditions while suturing the hernia (rated on the five-point scale)
- Length of surgery defined as the time from first incision to the last suturing
- Hernia suturing time (minutes from introduction of the needle until last stitch is completed)
- Assessment of whether the surgical space is better, unchanged or worse, evaluated before and after the second intervention.

The following secondary outcomes are compared according to the time period with no NMB versus the time period with deep NMB:

- Number of sudden contractions of the abdominal wall (bucking or coughing) from first incision until last stitch with corresponding level of NMB, BIS and time-point in surgery.
- Number of insufflator alarms where the pneumoperitoneum > 17 mmHg during the period when the trocars are in place with the corresponding level of NMB, BIS and time-point in surgery
- Number of episodes with continuous abdominal contractions where the abdomen feels "tight", but the operation can still proceed, from pneumoperitoneum is established until surgery is completed, with the corresponding level of NMB, BIS and time-point in surgery.

Adverse events and reactions

An investigator contacts the patients on the first and seventh post-operative day. The patients' files are screened between the 17th and 21st post-operative day. The sponsor decides whether or not there is a relationship between an adverse event and the intervention. The discrimination between an expected and unexpected adverse event is based on the product resume for rocuronium and sugammadex and the expected natural course after a laparoscopic ventral hernia repair.

We will not record side effects and events categorised as typically seen in connection with anaesthesia and surgery. The following events are found to belong to this category: changes in blood pressure or heart rate of less than ± 30% of the preoperative value, events that may be ascribed to the surgery with certainty, for example pain or infection in the surgical wound.

Serious adverse event will be recorded and relevant authorities contacted.

Major protocol violation

The intention-to-treat analysis will include all patients randomised and treated with the intervention. A need to increase pneumoperitoneum above 12 mmHg due to poor surgical conditions or conversion to laparotomy will be characterised as major protocol violations. The data will be analysed in the intention-to-treat analysis, but excluded from the per-protocol analysis.

Patients will be characterised as "drop-outs" if the

TABLE 2

The five-point scale used to assess the surgical workspace during laparoscopic herniotomy.

Scale	Description
1: extremely poor conditions	Unable to complete surgery without interventions[a]
2: poor conditions	Several minor adjustments needed to complete surgery (i.e. changes in patient-positioning, surgeon position)
3: acceptable conditions	After few minor adjustments surgery can be completed
4: good conditions	Surgical workspace is good; there is some interference, but no need for adjustments
5: optimal conditions	Surgical workspace is optimal and the procedure can be completed without any interference

a) Interventions are defined as change in depth of neuromuscular blockade and/or increased pneumoperitoneum.

surgery is cancelled or they do not receive the intervention. "Drop-out" patients will not be included in any further data analysis. Dropouts will be replaced until we have an evaluable primary outcome in 34 patients.

Trial conduct and monitoring

Data collection is done using paper case-report forms. The study is conducted in accordance with the Good Clinical Practise guidelines [12] and supervised by an independent inspector from the Department of Good Clinical Practice, Bispebjerg, Denmark.

Statistics

All patients, eligible as well as excluded, will be registered at a screening list. Data from randomised patients who receive the intervention will be included in the intention-to-treat analysis.

Normally distributed variables will be expressed by means and standard deviation. Variables that are not normally distributed will be expressed as medians and ranges. Student's t-test will be used for comparison of the normally distributed variables. The Mann-Whitney U test will be used to compare ordinal or continuous variables that are not normally distributed. Fisher's exact test will be used for comparison of frequencies. A p-value < 0.05 is considered significant.

Possible carry-over effect and treatment-period interaction are tested. If results are normally distributed, a two-sample t test will be used to test for both carry-over effect and treatment-period interaction. In case of non-normally distributed data, the Wilcoxon rank sum tests will be used.

Sample size

With a clinically relevant decrease of surgical workspace of 1 on the rating scale, an expected standard deviation of 2, type 1 error set at 0.05 and a power of 0.80, we calculated a sample size of 34 patients in total. We will include patients until we have an evaluable primary outcome in 34 patients.

Ethics, approvals and registration

All patients give signed written consent before surgery. The study was approved by the Research Ethics Committee of Copenhagen (Protocol No. H-4-2014-086), the Danish Health and Medicines Authority (EudraCT No. 2014-002802-19) and the Danish Data Protection Agency (Protocol No. HEH-2014-071). The study was registered with Clinicaltrials.gov (NCT02247466).

DISCUSSION

The current lack of knowledge regarding the effect of deep NMB on surgical conditions during laparoscopic ventral herniotomy makes this study relevant, and we believe that it has the potential to transform patient care for this surgical procedure.

A recent study indicated that deep NMB improved surgical conditions for laparoscopic cholecystectomy by providing a superior visibility and a reduction of involuntary movements [6], which may apply to laparoscopic herniotomy as well.

The strength of the study is that only a few experienced surgeons will perform all the procedures, which minimises inter-observer variation. We have chosen only to include experienced surgeons. If less experienced surgeons were included, we would expect a larger variation in assessment and would therefore need to include more patients.

We believe that the setup makes the blinding of the surgeon as complete as possible, including tracheal intubation and placement of the trocars without NMB.

Moreover, this study is the first to investigate a potential effect of deep NMB on the surgical workspace with patients acting as their own control. The cross-over design eliminates the risk of a skewed distribution of significant risk factors for poor surgical conditions.

The study does have potential limitations, primarily the five-step rating scale which has not been validated

TABLE 3

List of data recorded.

	Constituents
Preoperative	
Demographic	Gender, age, height, weight, BMI, ASA status
History	Previous abdominal surgery, co-morbidity, concurrent medicine, parity, tobacco consumption
Peroperative	
Surgical evaluation	Evaluation of surgical space (5-point rating scale, Table 2) before and after the intervention Assessment if the surgical space is better, unchanged or worse after intervention (5-point rating scale, Table 2) Assessment of surgical conditions during suturing of the hernia (5-point rating scale, Table 2) Number of insufflator alarms for pneumoperitoneum > 17 mmHg Number of episodes with continuous abdominal contractions where the abdomen feels "tight", but the operation can still proceed Number of sudden contractions of the abdominal wall during operation (bucking or coughing) Need for anaesthetic intervention due to poor surgical conditions (with normal pulse and BIS) Duration of surgery, from first incision to last suture Duration of suturing the hernia Size of hernia Number of recurrences of hernias by 2-year follow-up
Anaesthesia	Continuous NMB monitoring, using TOF-Watch with data collection on a computer Amount of sugammadex and rocuronium delivered Central and peripheral body temperature measured just after intubation and before tracheal extubation Blood loss and volume of crystalloids administered

ASA = American Society of Anesthesiologists physical health; BIS = Bispectral Index; BMI = body mass index; NMB = neuromuscular blockade; TOF = train-of-four.

for assessment of surgical workspace. Specifically, it may be difficult to define exactly what value to assign, especially when the workspace is not rated as either perfect or extremely poor.

In an effort to make the conditions as comparable as possible, we plan to use both continuous BIS and neuromuscular monitoring during the study. We believe that this will help minimise the risk that insufficient depth of anaesthesia interferes with the surgical workspace. This study may potentially bring further knowledge regarding our options for improving surgical workspace in laparoscopic ventral hernia surgery.

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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